Drug Class Review

Beta Adrenergic Blockers

Final Report
Update 4

July 2009

Update 3: September 2007
Update 2: May 2005
Update 1: September 2004
Original Report: September 2003

The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Mark Helfand, MD, MPH
Kim Peterson, MS
Vivian Christensen, PhD
Tracy Dana, MLS
Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

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Published in a separate document.

The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

Beta blockers inhibit the chronotropic, inotropic, and vasoconstrictor responses to the catecholamines, epinephrine, and norepinephrine. Most beta blockers have half-lives of over 6 hours (Table 1). The shortest acting are pindolol (3 to 4 hours) and propranolol (3 to 5 hours). Most of the included beta blockers are metabolized in combination by the liver and kidneys, with the exception of atenolol, which is metabolized primarily by the kidneys while the liver has little to no involvement.

The beta blockers listed in Table 1 are approved for the treatment of hypertension. Other US Food and Drug Administration-approved uses are specific to each beta blocker and include stable and unstable angina, arrhythmias, bleeding esophageal varices, coronary artery disease, asymptomatic and symptomatic heart failure, hypertension migraine, and secondary prevention post-myocardial infarction (Table 2).

Beta blockers differ in their effects on the 3 adrenergic receptors (β_1, β_2, and α) and in their duration of effect (Table 1). Cardioselective beta blockers preferentially inhibit β_1 receptors that are principally found in the myocardium. Non-cardioselective beta blockers also inhibit β_2 receptor sites, which are found in smooth muscle in the lungs, blood vessels, and other organs. Beta blockers with intrinsic sympathomimetic activity act as partial adrenergic agonists and would be expected to have less bradycardic and bronchoconstriction effects than other beta blockers. Finally, carvedilol and labetalol block α-adrenergic receptors and would be expected to reduce peripheral vascular resistance more than other beta blockers.

Table 1. Beta blockers included in the review

Drug	Usual hypertension dose	Daily dosing frequency	Half-life (hours)	Cardio-selective	Partial agonist activity (ISA)	Alpha antagonist effect
Acebutolol	200-1200 mg/d	Twice	3-4	Yes	Yes	No
Atenolol	50-100 mg/d	Once	6-9	Yes	No	No
Betaxolol	5-40 mg/d	Once	14-22	Yes	No	No
Bisoprolol	5-20 mg/d	Once	9-12	Yes	No	No
Carteolol	2.5-10 mg/d	Once	6	No	Yes	No
Carvedilol	12.5-50 mg/d	Twice	7-10	No	No	Yes
Carvedilol phosphate (controlled release)	20-80 mg/d	Once	10.6-11.5	No	No	Yes
Labetalol	200-1200 mg/d	Twice	3-6	No	No	Yes
Metoprolol tartrate	50-200 mg/d	Twice	3-7	Yes	No	No
Metoprolol succinate (extended release)	50-400 mg/d	Once	3-7	Yes	No	No
Nadolol	20-240 mg/d	Once	10-20	No	No	No
Nebivolol	5-40 mg/d	Once	12-19	Yes	No	No
Penbutolol	20 mg/d	Once	5	No	Yes	No
Pindolol	10-60 mg/d	Twice	3-4	No	Yes	No
Propranolol	40-240 mg/d	Twice	3-4	No	No	No
Propranolol long-acting	60-240 mg/d	Once	8-11	No	No	No
Timolol	10-40 mg/d	Twice	4-5	No	No	No

Abbreviations: d, day; ISA, intrinsic sympathomimetic activity.

Table 2. Approved indications

Drug	Hyper-tension	Chronic stable angina	Atrial arrythmia	Migraine	Bleeding esophageal varices	Heart failure	Post-myocardial infarction	Decreased left ventricular function after recent myocardial infarction
Acebutolol	Yes	Yes						
Atenolol	Yes	Yes					Yes	
Betaxolol	Yes							
Bisoprolol	Yes							
Carteolol	Yes							
Carvedilol (immediate release)	Yes					Mild to severe		Yes
Carvedilol phosphate (extended release)	Yes					Mild to severe		Yes
Labetalol	Yes							
Metoprolol tartrate	Yes	Yes					Yes	
Metoprolol succinate (extended release)	Yes	Yes				Stable, symptomatic Class II-III		
Nadolol	Yes	Yes						
Nebivolol	Yes							
Penbutolol	Yes							
Pindolol	Yes							
Propranolol	Yes	Yes	Yes	Yes				
Propranolol long-acting	Yes	Yes	Yes	Yes				
Timolol	Yes			Yes			Yes	

Adapted from Drug Facts and Comparisons®

Purpose and Limitations of Evidence Reports

Systematic reviews, or evidence reports, are the building blocks underlying evidence-based practice. An evidence report focuses attention on the strength and limits of evidence from published studies about the effectiveness of a clinical intervention. The development of an evidence report begins with a careful formulation of the problem. The goal is to select questions that are important to patients and clinicians, then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

An evidence report emphasizes the patient's perspective in the choice of outcome measures. Studies that measure health outcomes (events or conditions that the patient can feel, such as quality of life, functional status, and fractures) are emphasized over studies of

intermediate outcomes (such as changes in bone density). Such a report also emphasizes measures that are easily interpreted in a clinical context. Specifically, measures of absolute risk or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions is dependent on the numbers of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another measure useful in applying the results of a study is the number needed to treat (or harm), the NNT (or NNH). The NNT represents the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the NNT.

An evidence report also emphasizes the quality of the evidence, giving more weight to studies that meet high methodological standards that reduce the likelihood of biased results. In general, for questions about the relative benefits of a drug, the results of well-done, randomized controlled trials are regarded as better evidence than results of cohort, case-control, or cross-sectional studies. In turn, these studies are considered better evidence than uncontrolled trials or case series. For questions about tolerability and harms, controlled trials typically provide limited information. For these questions, observational study designs may provide important information that is not available from trials. Within this hierarchy, cohort designs are preferred when well conducted and assessing a relatively common outcome. Case control studies are preferred only when the outcome measure is rare, and the study is well conducted.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting that allows for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes, including antipsychotics, unstable or severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have comorbid diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that in practice are used for much longer periods of time. Finally, efficacy studies tend to use objective measures of effects that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

An evidence report also highlights studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. *Effectiveness* studies conducted in primary care or office-based settings use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, hospitalizations, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it is neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as an efficacy or effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice, or, in the clinical setting, how relevant they are to a particular patient.

Studies across the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard to determine whether the characteristics of different drugs are related to their effects on disease. An evidence report reviews the efficacy data thoroughly to ensure that decision-makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how much there is of it, may have limited applicability to practice. Clinicians can judge the relevance of the study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies. As a result, clinicians must make decisions about treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. An evidence report indicates whether or not there is evidence that drugs differ in their effects in various subgroups of patients, but it does not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these are decisions that must be informed by clinical judgment.

In the context of developing recommendations for practice, evidence reports are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. By themselves, they do not tell you what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is not true. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policies. Additional criteria include acceptability to physicians or patients, the potential for unrecognized harms, the applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. Initially, the Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest,

and based on these, the eligibility criteria for studies. These were reviewed, revised, and approved by representatives of organizations participating in the Drug Effectiveness Review Project. It is the representatives' responsibility to ensure that the questions reflect public input or input from their members. The participating organizations approved the following key questions to guide this review.

Key Question 1. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in effectiveness/efficacy?

Key Question 2. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine prophylaxis or bleeding esophageal varices, do beta blocker drugs differ in harms?

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

This review includes beta blockers that are available in the United States in an oral form and are indicated for hypertension. We excluded esmolol, an ultra-short acting beta blocker available only in intravenous form. Esmolol is used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias. We also excluded sotalol, a nonselective beta blocker with Class III antiarrhythmic activity that is used exclusively for arrhythmias. Beta blockers that are unavailable in the United States are bopindolol, bucindolol, medroxalol, and oxprenolol.

METHODS

To identify relevant citations, we searched Ovid MEDLINE (1966 to January Week 4 2009), the Cochrane Database of Systematic Reviews (Second Quarter 2008), Database of Abstracts of Reviews of Effects (Third Quarter 2008) and the Cochrane Central Register of Controlled Trials (Third Quarter 2008), using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). In addition, pharmaceutical manufacturers were invited to submit dossiers, including citations, using a protocol issued by the Center for Evidence-based Policy (available at: http://www.ohsu.edu/drugeffectiveness/pharma/index.htm). All citations were imported into an electronic database (EndNote® X2).

Study Selection

One reviewer assessed all citations and selected full articles for inclusion, with consultation from a second reviewer where necessary. All disagreements were resolved by consensus.

We included English-language reports of studies of the patient populations and efficacy outcomes listed in Table 3. For studies of hypertension, we excluded studies in which blood

pressure lowering was the only endpoint; most of these studies sought to identify equivalent doses of beta blockers rather than differences in clinical effectiveness. Instead, we sought evidence of long-term effects on mortality, cardiovascular events, and quality of life. We only included studies in stable angina patients with duration of 2 months or longer. We only included studies of long-term treatment in post-coronary artery bypass graft patients, excluding studies of the short-term use of beta blockers to suppress atrial arrhythmias. With regard to placebo-controlled trials of recent myocardial infarction or heart failure, we only included studies with sample sizes of 100 patients or more.

Table 3. Included outcome measures

Population	Outcomes
Hypertension	1. All-cause and cardiovascular mortality 2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure) 3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance) 4. Quality of life
Stable angina (treatment ≥ 2 month's duration)	1. Exercise tolerance 2. Attack frequency 3. Nitrate use
Post-coronary artery bypass graft (long-term treatment)	1. All-cause mortality 2. Ischemic events (myocardial infarction, unstable angina, need for repeat coronary artery bypass graft, and percutaneous transluminal coronary angioplasty)
Recent myocardial infarction (with and without left ventricular dysfunction)	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually development of heart failure)
Symptomatic chronic heart failure	1. All-cause or cardiovascular mortality 2. Symptomatic improvement (heart failure class, functional status, visual analogue scores) 3. Hospitalizations for heart failure
Asymptomatic left ventricular dysfunction	1. All-cause and cardiovascular mortality 2. Cardiovascular events (usually development of heart failure)
Atrial fibrillation/flutter	1. Rate control 2. Relapse into atrial fibrillation
Migraine	1. Attack frequency 2. Attack intensity/severity 3. Attack duration 4. Use of abortive treatment
Bleeding esophageal varices	1. All-cause mortality 2. Fatal/non-fatal rebleeding

We included the following safety outcomes: overall adverse event incidence, withdrawals due to adverse events, and frequency of important adverse events associated with beta blockers including bradycardia, heart failure, and hypotension. In some studies, only "serious" or "clinically significant" adverse events are reported. Some studies do not define these terms, and in other studies, the definitions vary between studies.

To evaluate efficacy, we included randomized controlled trials and good-quality systematic reviews. To evaluate effectiveness and safety, we included trials as well as good observational studies.

Data Abstraction

From included trials we abstracted information about the study design; setting; population characteristics (including sex, age, race, and diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria.[1, 2] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failing to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

Appendix C also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix C); clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment, and adequacy of detail provided for included studies; and appropriateness of the methods of synthesis. Again, these studies were categorized as good when all criteria were met.

The overall strength of evidence for a particular key question or outcome reflects the risk of bias of the study (based on quality and study design), consistency, directness, and precision of the set of studies relevant to the question. The overall strength of evidence was graded as good, fair, and poor.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one beta blocker against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. As such, direct comparisons were preferred over indirect comparisons. Similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

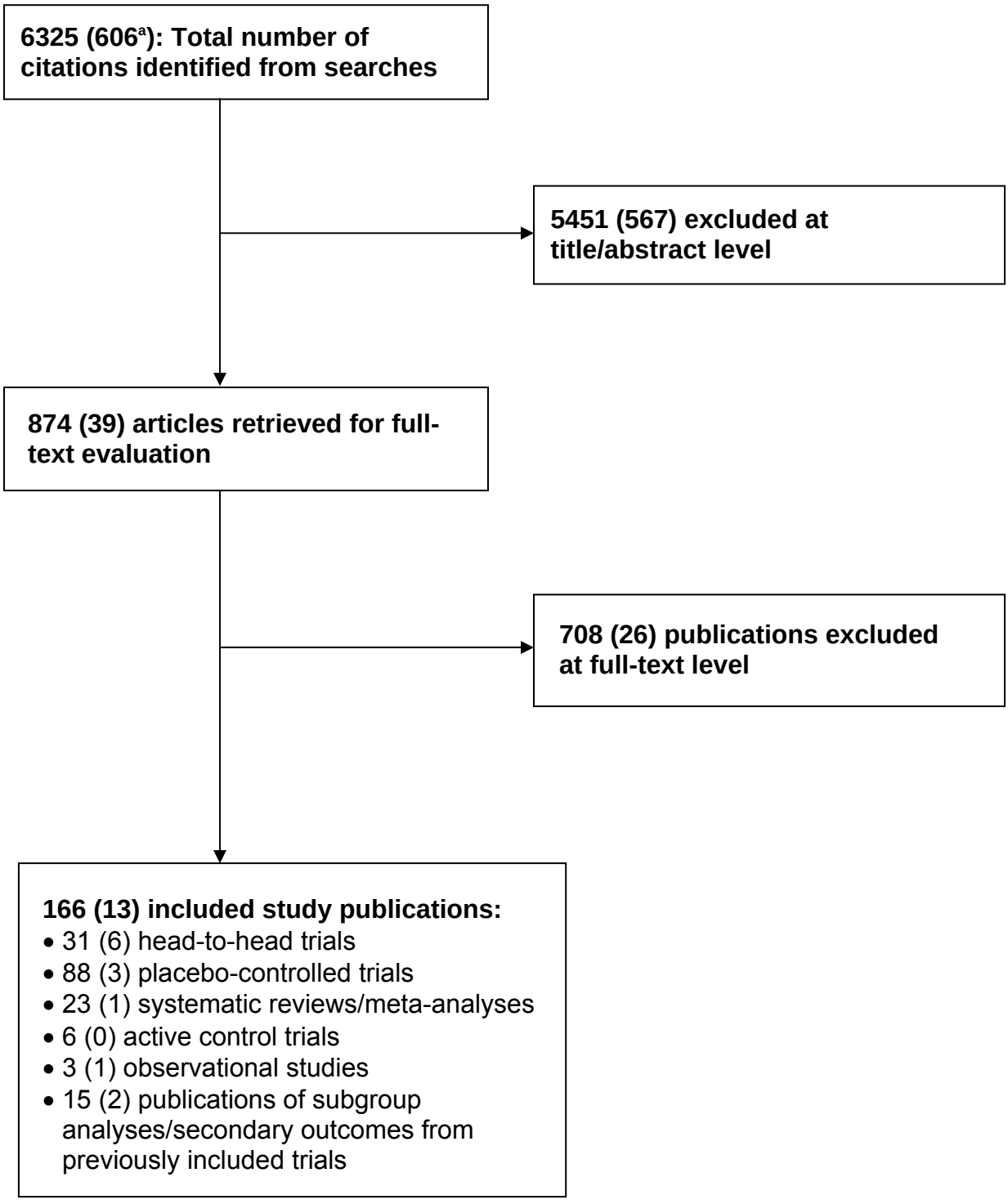
In theory, trials that compared beta blockers to other drug classes or placebos could also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Data from indirect comparisons were used to support direct comparisons, where they exist, and were also used as the primary comparison where no direct comparisons existed. Such indirect comparisons should be interpreted with caution.

RESULTS

Overview

Searches identified 6325 citations, with 606 new in Update 4. The results of study selection are outlined in Figure 1. Dossiers were received for Update 4 from the manufacturers of carvedilol, carvedilol controlled release, and nebivolol. Studies excluded at the full text level are listed in Appendix D.

Figure 1. Results of study selection



[a] Numbers in parentheses are results of the literature search new to Update 4.

Summary of Findings

Efficacy/effectiveness

Hypertension

- Direct comparisons
  - There were no head-to-head trials of different beta blockers on long-term (≥6 months) health or quality-of-life outcomes.
  - No consistent differences between beta blockers in quality-of-life outcomes were found in shorter-term, head-to-head trials of beta blockers.
- Placebo-controlled trials
  - Long-term placebo-controlled trials of propranolol and atenolol were found, however no reliable indirect comparisons can be made from them.
- Gaps: Long-term effectiveness; quality of life

Angina

- Direct comparisons
  - There were no significant differences in exercise tolerance or attack frequency in 6 head-to-head trials of carvedilol compared with metoprolol, pindolol compared with propranolol, betaxolol and propranolol, or betaxolol compared with metoprolol in patients with stable angina.
  - Atenolol and bisoprolol were equivalent in angina patients with chronic obstructive pulmonary disease.
  - Atenolol and labetalol (when combined with chlorthalidone) were equivalent in angina patients with hypertension.
- Placebo-controlled trials
  - One short-term, placebo-controlled trial of propranolol did not add any meaningful evidence of comparative efficacy in attack frequency or exercise parameters.

After coronary artery bypass graft

- Direct comparisons
  - There were no head-to-head trials of beta blockers in adults following coronary artery bypass graft.
- Placebo-controlled trials
  - Two placebo-controlled trials suggested that long-term use of a beta blocker after coronary artery bypass graft does not improve mortality or other outcomes. For example, the MACB Study Group conducted a fair-quality trial that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5 to 21 days following coronary artery bypass graft and measured the effects of treatment on death and cardiac events. No differences between metoprolol and placebo were found in mortality (3.3% compared with 1.8%; P=0.16) or in ischemic events (myocardial infarction, unstable angina, need for additional coronary artery bypass graft, or percutaneous transluminal coronary angioplasty).

- Gaps: long-term direct comparisons

Recent myocardial infarction

- Direct comparisons
  - One fair-quality head-to-head trial found no differences in mortality after 1 year between atenolol and propranolol, but this was a relatively small trial.
  - One fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol.
  - One fair-quality head-to-head trial found no differences in time to first cardiac adverse event or all-cause mortality between carvedilol and metoprolol tartrate.
- Placebo-controlled trials
  - In placebo-controlled trials, similar mortality reductions were reported for acebutolol, metoprolol tartrate, propranolol, and timolol for patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. Carvedilol is the only beta blocker shown to reduce mortality in post-myocardial infarction patients who are already taking an ACE (angiotensin-converting enzyme) inhibitor. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent myocardial infarction were identified. Carvedilol reduced mortality and reinfarction in 1 placebo-controlled trial of patients with a mean left ventricular ejection fraction of greater than 32.8% (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction [CAPRICORN] trial).

Heart failure

- Direct comparisons
  - There were no direct comparator trials comparing 2 or more of the drugs proven to reduce mortality (bisoprolol, carvedilol, and sustained release metoprolol succinate).
  - In the Carvedilol or Metoprolol European Trial (COMET) trial, carvedilol was superior to metoprolol tartrate reducing all-cause mortality (number needed to treat, 18) after a mean follow-up of 58 months in patients with mild to moderate heart failure.
  - No differences were found between carvedilol and metoprolol tartrate in improving symptoms (quality of life; New York Heart Association classification) or exercise capacity in 4 smaller head-to-head trials.
  - Improvements in New York Heart Association function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol.
- Placebo-controlled trials
  - Bisoprolol, metoprolol succinate, and carvedilol have each reduced total mortality, as a planned primary endpoint, by approximately 35%.
  - Based on findings from the COPERNICUS trial (N=2289), carvedilol is designated as the beta blocker with the most direct, strongest evidence of having a mortality benefit in patients with severe heart failure. In a post-hoc subgroup

analysis of 795 patients from the good-quality MERIT-HF trial, metoprolol succinate has also demonstrated a mortality reduction relative to placebo similar to that for carvedilol in patients who had a similar mortality risk.
    - In the SENIORS trial (N=2128), which involved patients who were, overall, older (mean age of 76 years) and healthier than in the prior major trials (higher mean left ventricular ejection factor, lower annual placebo mortality rate), nebivolol was superior to placebo in reducing the risk of the primary composite outcome of all-cause mortality or cardiovascular hospital admission (31.1% compared with 35.3%; hazard ratio, 0.86; 95% CI, 0.74 to 0.99). When components of the primary outcome were examined individually as secondary outcome measures, differences between nebivolol and placebo were no longer statistically significant.
    - We found no trials that directly evaluated the effects of carvedilol phosphate, the long acting form of carvedilol, on mortality in adults with heart failure. Approval of the heart failure indication for carvedilol phosphate was based on "equivalence of pharmacokinetic and pharmacodynamic parameters between carvedilol phosphate and conventional carvedilol tablets."

Atrial arrhythmia

- Direct comparisons
    - There were no differences between bisoprolol 10 mg and carvedilol 50 mg in preventing relapse of atrial fibrillation in patients subjected to cardioversion of persistent atrial fibrillation (>7 days).
- Placebo-controlled trials
    - Atenolol, nadolol, and pindolol, but not labetalol, were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo based on findings from a good-quality systematic review examining 12 studies of rate control in patients with chronic atrial fibrillation.
    - One placebo-controlled trial found that metoprolol CR/XL 100 to 200 mg was effective in preventing relapse of atrial fibrillation/flutter after cardioversion. Over 6 months, atrial fibrillation or flutter relapse rates were significantly lower in patients taking metoprolol CR/XL. Death rates were similar. The study was not powered to examine mortality.
    - A study examining the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure found that when added to digoxin, carvedilol significantly improved mean left ventricular ejection fraction scores and reduced severity of symptoms/functional capacity when compared to digoxin alone. There were no differences between monotherapies of carvedilol or digoxin.

Migraine

- Direct comparisons
    - Head-to-head trials showed no difference in efficacy in reduction of attack frequency, severity, headache days, or acute tablet consumption, or in improvement in any subjective or composite index in any of the comparisons made (atenolol, metoprolol durules, metoprolol, or timolol compared with propranolol or nebivolol compared with metoprolol).

- Placebo-controlled trials
    - In placebo-controlled trials atenolol, metoprolol durules, and propranolol had similar results as was observed in head-to-head trials. Placebo-controlled trial results also showed that bisoprolol reduced effect attack frequency significantly and that pindolol had no appreciable effects.

Bleeding esophageal varices

- Direct comparisons
    - One small head-to-head trial showed no difference between atenolol 100 mg and propranolol 40 to 160 mg in rates of non-fatal/fatal rebleeding and all-cause mortality.
- Placebo-controlled trials
    - Results of 1 trial of nadolol and 8 small placebo-controlled trials of immediate-release and 2 formulations of extended-release propranolol for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis did not provide any additional indirect evidence of the comparative efficacy across beta blockers in these clinical outcomes. The somewhat mixed results across the placebo-controlled trials of propranolol suggest that treatment initiation interval may have an effect on rebleeding rates.

Harms

- There were no consistent significant differences between beta blockers in head-to-head trials in overall adverse events, withdrawals due to adverse events, or individual adverse events.

Subgroups

- A meta-analysis (see Table 16) suggested that beta blockers are equally effective in reducing mortality in subpopulations stratified by gender and race.
- There is insufficient evidence to draw conclusions about the effects of beta blockers on perinatal mortality or preterm birth.

Key Question 1. Do beta blocker drugs differ in efficacy or effectiveness?

Key Question 1a. For adult patients with hypertension, do beta blockers differ in efficacy or effectiveness?

Summary

Beta blockers are equally efficacious in controlling blood pressure in patients with hypertension. No beta blocker has been demonstrated to be more efficacious or to result in better quality of life than other beta blockers, either as initial therapy or when added to a diuretic, ACE inhibitor, or angiotensin receptor blocker. Evidence from long-term trials is mixed; overall, beta blockers are generally less effective than diuretics, and are usually no better than placebo, in reducing cardiovascular events. The exception was 1 large trial in which treatment with metoprolol resulted in lower all-cause mortality than treatment with a thiazide diuretic.

Detailed Assessment

Primary or initial therapy

Beta blockers have been used as initial therapy in patients with hypertension and as additional therapy in patients whose blood pressure is not well controlled with a diuretic. In several head-to-head trials, beta blockers have similar effects on blood pressure control.[3-11] No trials have examined whether beta blockers have different effects on all-cause mortality, cardiovascular mortality, or cardiovascular events among patients with hypertension.

By the time beta blockers became available, diuretics had already been shown to prevent cardiovascular events, primarily strokes. It was considered unethical to compare a beta blocker to placebo in patients who were likely to benefit from a diuretic. For this reason, most large, long-term trials of beta blocker therapy for hypertension used a comparison group taking a diuretic rather than a placebo. Unlike diuretics, then, beta blockers have not been clearly demonstrated to be more effective than placebo in reducing cardiovascular events when used as initial therapy in the general population of patients with hypertension.

The Medical Research Council trials, the International Prospective Primary Prevention Study in Hypertension, the Heart Attack Primary Prevention in Hypertension study, and the Metoprolol Atherosclerosis Prevention in Hypertensives study compared a beta blocker to a thiazide diuretic. Of these trials, only the 2 Medical Research Council trials compared a beta blocker to placebo. In 1 Medical Research Council trial, atenolol 50 mg daily was not better than placebo and less effective than a diuretic in adults ages 65 to 74 who had baseline blood pressures of 160/115 mm Hg or higher.[12] In the other Medical Research Council trial, which recruited 17 361 patients with mild diastolic hypertension (90 to 109 mm Hg), beta blocker therapy (atenolol) reduced the odds for stroke, but only in nonsmokers and to a smaller degree than a low dose of a thiazide diuretic (bendrofluazide).[13]

Of the trials that compared a beta blocker with a diuretic, only 1 (Metoprolol Atherosclerosis Prevention in Hypertensives study) had any suggestion that the beta blocker was more effective. In that trial, deaths from heart attacks and strokes as well as total mortality were lower in the metoprolol treated group than in those treated with a diuretic (hydrochlorothiazide or bendroflumethiazide).[14] The trial continues to be cited as strong evidence that beta blockers reduce mortality when used as primary treatment for hypertension. However, it must be weighed against the mixed results of the Medical Research Council trials and other trials of beta blockers compared with diuretics. In a good-quality meta-analysis of 10 trials published in 1998 or earlier, beta blockers were ineffective, or less effective than comparator drugs, in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality (odds ratios 1.01, 0.98, and 1.05, respectively).[15]

Secondary treatment

The Systolic Hypertension in the Elderly Program (SHEP) trial examined a stepped approach for treating isolated systolic hypertension in the elderly.[16] Chlorthalidone was the first step. Atenolol was prescribed if the blood pressure goal could not be achieved with chlorthalidone 25 mg daily. Compared to placebo, stepped treatment prevented 55 cardiovascular events per 1000 patients over 5 years. The contribution of beta blocker therapy with atenolol to the overall benefit is not clear; most of the benefit was attributed to chlorthalidone.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002) did not include a beta blocker arm.[17] Based on the results of this trial, the Joint National

Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) recommends a diuretic as the first-line treatment for most patients who have Stage 1 hypertension without compelling indications.[18]

Quality of life

There was no definitive evidence that 1 beta blocker yields a better quality of life than another for patients who have hypertension. Eight trials directly compared different beta blockers[19] on changes of quality of life-associated measures. We excluded 2 trials of atenolol compared with propranolol based on poor-quality ratings.[7, 20] The methods described in these publications were insufficient to rule out the possibilities that results were biased by inadequate randomization procedures (methods weren't described and baseline characteristics weren't reported) and/or by mishandling of missing data (attrition reasons not described and proportion of patients included in analyses not reported). Table 4 below summarizes the results of the fair-quality trials.

The strongest evidence of any differences between beta blockers came from a 4 week trial of captopril, enalapril, propranolol, and atenolol that used a larger sample size (N=360) and a parallel design.[8] This was the only trial that is clearly industry-funded. Patients were all men that were "at least 21 years of age, employed or retired, educated at high-school level or equivalent, and married or living with a significant other." Self-ratings of improvements were greater for atenolol than propranolol in Psychologic General Well-Being-measured self-control, distress overall and that caused by obsessions and hostility symptoms (Symptom Check List-90-R), and on global and social satisfaction indices from the Life Satisfaction Index. It remains unclear, however, as to whether these short-term results in men can be generalized to a broader population over a longer period of time.

The strength of the evidence from the remaining trials was limited by smaller sample sizes and, in the crossover trials, results that were averaged across treatment periods.[5, 19, 21-23] Improvement in self-rated sexual interest (Minor Symptom Evaluation profile) was greater for atenolol than metoprolol CR in 1 trial of 60 patients (mean age 58 years; 43.3% male).[5]

Two trials of metoprolol succinate compared to nebivolol examined quality of life measures. One trial was conducted in Germany and compared nebivolol 5 mg to metoprolol succinate 95 mg. After 12 weeks of treatment, 48 men (ages 40 to 55) with newly diagnosed hypertension experienced decreased sexual function on metoprolol 95 mg, but not nebivolol 5 mg.[23] However, the article provides insufficient detail to determine how the metoprolol succinate 95 mg product compares to the metoprolol succinate product available in the United States and Canada. In another trial, after 6 weeks of treatment of 46 adults with mild hypertension, sleep quality, as measured by scores on the Pittsburgh Sleep Quality Index, was improved by treatment with nebivolol 5 mg, but declined following treatment with metoprolol CR 100 mg.[19]

Table 4. Quality-of-life outcomes in head-to-head trials of hypertensives

Trial (quality)	Comparison Design Sample size	Duration (weeks)	Washout (weeks)	Results
Steiner 1990[8] (Fair)	Atenolol vs. propranolol Parallel N=360	4	NA	Atenolol superior to propranolol on *some* Psychologic General Well-Being, SCL-90-R, and Life Satisfaction indices and no differences on Insomnia Symptom Questionnaire or Sexual Function Questionnaire
Walle 1994[5] (Fair)	Atenolol vs. metoprolol CR Crossover N=16	6	NR	Atenolol superior to propranolol on 1 Minor Symptom Evaluation item; no differences in all other Minor Symptom Evaluation and Psychologic General Well-Being scores
Buhler 1986[21] (Fair)	Atenolol vs. bisoprolol Crossover N=104	8	2-6	No differences on unspecified self-assessment questionnaire
Dahlof 1988[22] (Fair)	Atenolol vs. metoprolol CR Crossover N=74	6	NR	No differences on Minor Symptom Evaluation or Jern's quality-of-life questionnaires
Yilmaz 2008 (Fair)	Nebivolol vs. Metoprolol ER Parallel N=46	6	NR	Nebivolol superior to metoprolol ER at end of treatment. Nebivolol (32% poor sleepers) compared with metoprolol (76% poor sleepers) (*P*=0.006). Mean global PSQI score decreased (5.77 to 4.55) for nebivolol arm; increased (5.11 to 6.53) for metoprolol arm. Higher score indicated worse sleep.
Brixius 2007 (Fair)	Nebivolol vs. Metoprolol Crossover N=48	28	NR	Metoprolol 95 mg (–0.92 points), but not nebivolol (+0.13 points) decreased erectile function (*P*=0.04).

Abbreviations: NA, not applicable; NR, not reported; PSQI, Pittsburgh Sleep Quality Index.

Two placebo-controlled trials reported the effect of long-term beta blocker therapy on quality of life in otherwise healthy patients who have hypertension (Evidence Tables 1 and 2). The Trial of Antihypertensive Interventions and Management[24-26] had a serious flaw: only patients who were available for the 6-month blood pressure readings (79.4%) were included in the quality-of-life analysis. After 6 months, atenolol and placebo were similar on several dimensions from the Life Satisfaction Scale, the Physical Complaints Inventory, and the Symptoms Checklist, including *summary* ("total physical problems", "overall psychological functioning", "overall life satisfaction"), *distress* ("sexual physical problems", "depression", "anxiety", "sleep disturbances", "fatigue"), and *well-being* ("satisfaction with physical health", "sexual satisfaction"). In the second trial,[27] there were no differences between propranolol and placebo in cognitive or psychological measures after 1 year of treatment.

Key Question 1b. For adult patients with angina, do beta blockers differ in efficacy or effectiveness?

Summary

There were no differences in exercise tolerance or attack frequency in head-to-head trials of carvedilol compared with metoprolol, pindolol compared with propranolol, betaxolol compared with propranolol, and betaxolol compared with metoprolol tartrate in patients with chronic stable angina. Atenolol and bisoprolol were equivalent in angina patients with chronic obstructive pulmonary disease. Atenolol and labetalol (when combined with chlorthalidone) were equivalent in angina patients with hypertension.

Beta blockers that had intrinsic sympathomimetic activity reduced the resting heart rate less than other beta blockers, a potential disadvantage in patients suffering from angina pectoris. For this reason, experts recommend against using beta blockers with intrinsic sympathomimetic activity in patients with angina.

Detailed Assessment

In 1966 the first beta blocker, propranolol, was shown in a multicenter controlled trial to improve symptoms in patients with angina pectoris.[28] Several other beta blockers (acebutolol, atenolol, metoprolol tartrate, metoprolol succinate, nadolol, propranolol, and propranolol long-acting) have been demonstrated to reduce symptoms of angina in placebo-controlled trials.

Most head-to-head trials of beta blockers in patients with angina pectoris observe patients for only 2 to 4 weeks of treatment.[29-36] In these trials, exercise tolerance, attack frequency, or nitroglycerin use were generally similar at comparable doses.

Six fair-quality head-to-head trials evaluated angina symptoms after 2 or more months of treatment with beta blockers (Table 5, Evidence Tables 3 and 4). Mean ages ranged from 55 to 61.5 years and most subjects were men (71.5% to 100%), with the exception of 1 study, which included 40% male subjects.[37] Exercise parameters were measured using bicycle ergometric testing in all but 2 trials,[38, 39] which used a treadmill. One study, however, did not include exercise parameters in its study design.[37] There were no significant differences in exercise tolerance or attack frequency. No significant differences were found between betaxolol 20 mg and metoprolol tartrate 100 mg on 5 of 6 health-related quality-of-life parameters. Compared with metoprolol tartrate (15%), however, significantly greater numbers of patients on betaxolol improved on the 'Physical Function' parameter (43%; $P<0.01$).[37]

Table 5. Results of head-to-head trials in patients with angina

Trial Sample size	Interventions	Results	
		Exercise parameters	Attack frequency and/or nitroglycerine use (% reduction)
Van der Does 1999 N=368	Carvedilol 100 mg Metoprolol 200 mg	No difference	Not reported
Frishman 1979 N=40	Pindolol 10-40 mg Propranolol 40-240 mg	No difference	No difference
Narahara 1990 N=112	Betaxolol 20 and 40 mg Propranolol 160 and 320 mg	No difference	No difference
Dorow 1990 N=40 (comorbid chronic obstructive pulmonary disease patients)	Atenolol 50 mg Bisoprolol 5 mg	Not reported	82.8% compared with 64.3% (not significant)
Chieffo 1986 N=10 (comorbid hypertension)	Labetalol 200 mg +chlorthalidone 20 mg Atenolol 100 mg +chlorthalidone 25 mg	Not reported	60% compared with 80% (not significant)
Kardas 2007 N=112	Betaxolol 20 mg once daily Metoprolol tartrate 50 mg twice daily	Not reported	0.42/week compared with 0.46/week[a] (not significant)

[a] Decrease in number of chest pain episodes per week compared with baseline.

Over the long term, beta blockers may differ in their ability to prevent or reduce the severity of anginal attacks. In 1 fair-quality 2-year multicenter European trial, propranolol was better than placebo after 8 weeks but not after 24 weeks of treatment.[40] Specifically, after 8 weeks propranolol 60 to 240 mg reduced the proportion of patients using nitroglycerin (57% compared with 73% in the placebo group; P=0.04) and increased the mean total work time by 48% compared with 13% (P=0.04). These effects were transient, however, and propranolol was equivalent to placebo on those parameters after 24 weeks of treatment. Propranolol and placebo had similar effects on the number of weekly angina attacks, the number of attack-free days, maximum workload, and exercise duration at 8- and 24-week endpoints. The relevance of this trial was limited because since the time it was conducted, the rate of progression of angina may have been altered by advances in treatment of atherosclerosis (for example statin therapy).

A good-quality meta-analysis identified 72 randomized controlled trials of a beta blocker compared with a calcium channel blocker and 6 trials comparing a beta blocker to a nitrate.[41] This meta-analysis found that, in general, beta blockers had similar efficacy but fewer discontinuations due to adverse events than calcium channel blockers, but the authors did not report results for each beta blocker separately.

Key Question 1c. For adult patients who have undergone coronary artery bypass grafting, do beta blockers differ in efficacy or effectiveness?

We did not examine the short-term (4 to 10 days) use of beta blockers to prevent or control atrial tachyarrhythmias after coronary artery bypass graft.[42-46] In addition to the beta blockers included in our review, esmolol, a very short-acting, intravenous beta blocker, is used postoperatively to control tachyarrhythmias.

In 7 trials, long-term use of a beta blocker after coronary artery bypass graft did not improve mortality or other outcomes (Evidence Tables 5 and 6). For example, the MACB Study Group conducted a fair-quality trial[47] that randomized 967 patients (85.5% male, median age 64 years) to metoprolol 200 mg once daily or placebo within 5 to 21 days following coronary artery bypass graft and measured the effects of treatment on death and cardiac events. No differences between metoprolol and placebo were found in mortality (3.3% compared with 1.8%; P=0.16) or in ischemic events (myocardial infarction, unstable angina, need for additional coronary artery bypass graft or percutaneous transluminal coronary angioplasty).

Key Question 1d. For adult patients with recent myocardial infarction, do beta blockers differ in efficacy or effectiveness?

Summary

Table 6 summarizes evidence from meta-analyses and major trials of beta blockers in patients with recent myocardial infarction. Timolol was the first beta blocker shown to reduce total mortality, sudden death, and reinfarction outcomes in the Norwegian Multicenter Study.[48] Subsequently, similar total mortality reductions were reported across trials of acebutolol,[49] metoprolol tartrate (Goteborg), and propranolol (Beta Blocker Heart Attack Trial) in comparable populations. In addition, similar benefits in sudden death were reported for propranolol[50] and metoprolol tartrate[51, 52] and in reinfarction for metoprolol tartrate.[52]

Carvedilol reduced reinfarction rates in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, which recruited stable inpatients with recent myocardial infarction and a left ventricular ejection fraction of 40% or less. Carvedilol is the only beta blocker shown to reduce mortality in post-myocardial infarction patients who are already taking an ACE inhibitor. An extended-release form of carvedilol (carvedilol phosphate) was approved by the US Food and Drug Administration in October 2006. No studies of carvedilol phosphate in patients following myocardial infarction were identified through literature searches. Approval of the left ventricular dysfunction following myocardial infarction indication for carvedilol phosphate was based on pharmacokinetic and pharmacodynamic data that demonstrated bioequivalence with carvedilol.

Indirect comparisons of beta blockers across these trials must be done with caution because the study populations differed in duration, the presence or absence of left ventricular dysfunction, the dose and timing of therapy, and the use of other medications.

Table 6. Comparison of outcomes of mortality-reducing beta blockers in patients following myocardial infarction

Beta blocker	Mortality reduction in general population of post-myocardial infarction patients	Mortality reduction in post-myocardial infarction patients with left ventricular dysfunction	Sudden death reduction	Reinfarction reduction
Acebutolol	Effective	Uncertain	Insignificant effect	Insignificant effect
Carvedilol	Not established	Effective	Uncertain (trend)	Effective
Carvedilol phosphate	No evidence	No evidence	No evidence	No evidence
Metoprolol tartrate	Effective	Probable	Effective	Effective
Propranolol	Effective	Probable	Effective	Insignificant effect (BHAT, Hansteen 1982)
Timolol	Effective	Uncertain	Effective	Effective

Head-to-Head Trials

No consistent differences between beta blockers were found in 3 head-to-head trials in post-myocardial infarction patients.[53-55] A 6-week trial comparing atenolol 100 mg to propranolol 120 mg had inconclusive results.[53] The second trial, an open-label study with a median follow-up of 1.6 years, compared carvedilol to atenolol. Patients in this study had mean left ventricular ejection fraction 53.9% at baseline. The primary outcome of the study was the change in left ventricular ejection fraction at 1 year; time to first serious cardiovascular event was a secondary endpoint. No significant difference was found between the 2 interventions in either change in left ventricular ejection fraction (P=NR) or time to occurrence of a serious cardiovascular event (P=0.524), which remained when controlling for use of diuretics (P=0.990).[56] However, these results are not conclusive, as the study's authors acknowledge that the study was underpowered to detect such a difference for this secondary outcome. A study of 313 patients comparing metoprolol tartrate 100 mg twice daily to carvedilol 25 mg twice daily for a mean of 13.4 months found no differences in time to first composite cardiac adverse event (all-cause death, postinfarction angina, heart failure, rehospitalization, and revascularization) or time to composite hard event (cardiovascular death and nonfatal reinfarction).[55] There were statistically significant differences in 5 of 8 health-related quality-of-life domains measured using the Short Form-36 questionnaire (adjusted for age and baseline differences) favoring the carvedilol group.[55]

Placebo-controlled Trials

Because there are so few comparative trials, inferences about the comparative effectiveness of beta blockers in post-myocardial infarction patients must be made on other grounds. The criteria for making these comparisons might include:

1. Demonstration of reduced mortality in large, multicenter placebo-controlled trials
2. Degree of mortality reduction compared with other beta blockers
3. Improvements in other outcomes

4. Tolerability
5. Effectiveness studies and applicability of efficacy studies to current practice.

Mortality

Three systematic reviews have analyzed over 60 trials of beta blockers after myocardial infarction.[57-59] The first (Yusuf, 1985) analyzed 22 long-term trials of beta blockers in acute myocardial infarction. Overall beta blockers reduced mortality by 23%, from an average of 10% to 8%. The second (Hjalmarson, 1997) found an average 20% mortality reduction in 24 trials of a total of 25000 patients.

A more recent review (Freemantle, 1999) used meta-regression to examine the relationship of characteristics of different beta blockers with the outcome of treatment.[59] In their analysis of 24 long-term trials, cardioselectivity had no effect, but there was a near significant trend towards decreased benefit in drugs with intrinsic sympathomimetic activity. Individually, acebutolol (0.49; 0.25-0.93), metoprolol tartrate (0.80; 0.66-0.96), propranolol (0.71; 0.59-0.85), and timolol (0.59; 0.46-0.77) significantly reduced mortality, but there was insufficient data to distinguish among them. The analysis included just 1 trial of carvedilol, a pilot study in 151 post-myocardial infarction patients.[60]

Table 7 summarizes placebo-controlled trials that enrolled over 100 patients, had long-term follow-up (greater than 6 weeks), and met our other inclusion criteria. All of these trials were analyzed in the 1999 systematic review except for CAPRICORN, which was conducted from 1997 to 2000 at 163 sites in 17 countries and published in 2001.[61] Unlike the other trials, CAPRICORN included only patients who had reduced left ventricular function (≤ 40%) after acute myocardial infarction as determined by echocardiography or cardiac catheterization. Patients with uncontrolled heart failure, such as those requiring intravenous diuretics, were excluded. Of 1959 subjects randomized to either carvedilol or placebo at an average of 10 days following a confirmed myocardial infarction, 1289 had no clinical signs of heart failure (Killip Class I), 593 had Killip Class II heart failure, and 65 had Killip Class III failure. The mean ejection fraction was 32.8%.

The original primary endpoint was all-cause mortality. Subsequently, following a masked interim analysis in which the data and safety monitoring board found that overall mortality rates were lower than predicted, the CAPRICORN steering committee decided to adopt the co-primary endpoints of all-cause mortality together with all-cause mortality *plus* cardiovascular hospital admissions. There was no difference between carvedilol and placebo for the primary endpoint of mortality plus cardiovascular admissions (35% compared with 37% for placebo over 1.3 years, P=0.299). However, carvedilol reduced the *original* primary endpoint of total mortality in the first 30 days (19% compared with 33%; hazard ratio, 0.58; 95% CI, 0.33 to 1.02) [62] and over 1.3 years (12% compared with 15% for placebo over 1.3 years; number needed to treat, 30 or number needed to treat for 1 year, 43). The P value was 0.03, which, although nominally significant, did not meet the higher level of significance specified when the combined primary outcome measure was adopted.

CAPRICORN was the only trial to demonstrate the added benefit of a beta blocker in post-myocardial infarction patients taking ACE inhibitors or having undergone thrombolytic therapy or angioplasty. It was also the only trial specifically designed to evaluate a beta blocker in post-myocardial infarction patients who have asymptomatic left ventricular dysfunction. Based on CAPRICORN, the United States Food and Drug Administration gave carvedilol an indication to reduce mortality in "left ventricular failure after a myocardial infarction."

The use of ACE inhibitors, thrombolytics, and angioplasty support the relevance of CAPRICORN to current care in the United States and Canada. However, the case for relevance could be strengthened if data were available to compare other practices and the quality of care between sites that recruited successfully and those that did not. Additional information about the recruitment of patients and the centers at which the CAPRICORN was conducted might provide additional insight into its relevance to current practice in the United States and Canada. Of the 1949 subjects in the trial, 83 were enrolled in the United States and 5 were from Canada. Five of the 6 top recruiting sites were in Russia, which enrolled the most subjects of any country (600). Of the 163 study sites, 24 enrolled only 1 subject. In their *Lancet* paper, the authors of CAPRICORN noted that "recruitment was slow in some countries where it was widely perceived that the case for beta blockers in all patients with myocardial infarction was proven." The statement leaves open the possibility that, in North America, the subjects in CAPRICORN would already have been taking beta blockers.

Is the mortality reduction in CAPRICORN different from what would be expected from older trials of beta blockers in post-myocardial infarction patients or in patients with heart failure? The authors of the *Lancet* paper raised this question, noting that the 23% mortality reduction in CAPRICORN is identical to that found in meta-analyses of the older beta blocker trials.

Mortality was higher in CAPRICORN than in previous trials of beta blockers in post-myocardial infarction patients. The likeliest explanation is that many earlier trials included a broader mix of patients, including many who had normal left ventricular function and a better prognosis. Unlike many major trials, the CAPRICORN publication did not say how many patients with myocardial infarction were seen at the participating centers during the period of recruitment. It was also not clear what proportion of potentially eligible patients were excluded because they had an ejection fraction greater than 40%. These statistics would be useful in comparing the CAPRICORN subjects to the subjects of previous trials of beta blockers in post-myocardial infarction patients.

There was no direct evidence that other beta blockers shown to reduce mortality in post-myocardial infarction patients or in patients with heart failure worked as well as carvedilol in post-myocardial infarction patients with decreased left ventricular function and few or no symptoms of heart failure. While the older trials undoubtedly included some subjects with left ventricular dysfunction, it is difficult to determine how many, or how this subset did compared with post-myocardial infarction patients with normal left ventricular function.

Indirect evidence came from a good-quality meta-analysis.[63] This analysis examined the relationship between the mortality reduction reported in each trial and the proportion of patients in the trial who had heart failure. There were few data on the effects of beta blockers after myocardial infarction in patients with documented left ventricular systolic dysfunction, but some studies included subjects with clinical findings of heart failure and reported the proportion of subjects that had these findings. As expected, studies that included patients with heart failure had higher mortality rates. The relative benefit of beta blockers on mortality after a myocardial infarction was similar in the presence or absence of heart failure.

Two retrospective subgroup analyses in heart failure patients from individual trials included in this meta analysis provided additional details supporting this hypothesis. One is from the Beta Blocker Heart Attack Trial (BHAT), a large, 3-month trial of propranolol published in 1980. In BHAT, 710 of 1916 subjects had a history of congestive heart failure prior to randomization. Propranolol lowered total mortality from 18.4% to 13.3% (a 27% reduction) in

patients with a history of heart failure and from 7.8% to 5.9% (25% reduction) in patients who did not have a history of heart failure.[64]

The other retrospective subgroup analysis was from a 1980 placebo-controlled trial of metoprolol. At the time of randomization, 262 (19%) of the 1395 subjects had signs or symptoms of mild heart failure.[65] Metoprolol or placebo was administered intravenously once, followed by oral metoprolol or placebo for 3 months, followed by open treatment with metoprolol for up to 2 years in all patients who had signs of ischemia. For patients with heart failure, mortality during the first year of the study was 28%, compared with 10% in subjects without signs of heart failure ($P<0.0001$). Among the subjects with heart failure at the time of randomization, metoprolol reduced mortality during the 3-month double-blind phase of the trial (14% compared with 27%, $P<0.0009$, number needed to treat=8).

Sudden death

Significant reductions in sudden death were reported in 2 of 3 trials of metoprolol tartrate,[51, 52] 1 trial of propranolol,[50] and in 1 trial of timolol.[48]

Reinfarction

Significant reductions in reinfarction rates were reported in 1 of 2 trials of metoprolol tartrate[52] and in 1 trial of timolol.[48] Carvedilol was also associated with significantly reduced reinfarction rates in the CAPRICORN trial.

Arrhythmias

Evidence on the effect of beta blockers on post-myocardial infarction arrhythmias is unclear based on the available evidence. No significant difference in occurrence of post-myocardial infarction arrhythmia (defined as cardiac arrhythmia, fibrillation, or tachycardia) was found in placebo-controlled trials of acebutolol (1 trial)[66] or propranolol (1 trial),[50] while 1 placebo-controlled trial of propranolol found a small, but significantly higher, percentage of withdrawals due to serious ventricular arrhythmia in the placebo group (0.3% propanolol compared with 1.0% placebo; $P<0.025$).[67] One trial of timolol found a significantly higher proportion of patients experiencing ventricular tachycardia with placebo use (20% placebo compared with 8.5% timolol; $P=0.05$) while the number of episodes of ventricular tachycardia (55 placebo compared with 10 timolol) was not statistically significant (data not provided).[68]

Two publications comparing carvedilol to placebo presented mixed results. One older trial found no significant difference between the 2 drugs in the rate of cardiac arrhythmias among all enrolled patients.[60] In a subgroup analysis of patients (N=49/151; 32%) with baseline left ventricular ejection fraction <45%, carvedilol was associated with a significant decrease in serious cardiac events, a combined endpoint that included death, reinfarction, unstable angina, congestive heart failure, and ventricular tachycardia ($P=0.04$). The second publication, a post-hoc analysis of data from the CAPRICORN trial, compared rates of atrial and ventricular arrhythmias.[69] As stated above, patients enrolled in the CAPRICORN trial had baseline left ventricular ejection fraction ≤40%. Atrial and ventricular arrhythmias were found to be less common with carvedilol use relative to placebo (hazard ratio, 0.48; 95% CI, 0.30 to 0.76; $P=0.0015$ and hazard ratio, 0.37; 95% CI, 0.24 to 0.58; $P<0.0001$, respectively. These values remained significant when controlling for history of arrhythmias. Carvedilol was also found to reduce the risk of all analyzed combinations of death and arrhythmia outcomes.

Withdrawals

Among the major trials, rates of withdrawal ranged from 9.3% to 36.6%, probably indicating differences in patient characteristics. Within studies, rates of withdrawal were generally similar for the beta blocker and placebo groups, with 3 exceptions. Rates of withdrawal were greater for metoprolol tartrate in 1[70] of 5 trials, pindolol in 1 trial,[71] and propranolol in 1 trial.[67]

Table 7. Summary of results from placebo-controlled trials of beta blocker therapy following myocardial infarction

Study Year	Interventions	Duration	Number enrolled	Total mortality	Sudden death	Reinfarction	Withdrawals
Acebutolol							
Boissel 1990	A: Acebutolol B: Placebo	271 days	607	A: 5.7% (17/298) B: 11% (34/309) *P*=0.019; NNT=19	NR	A: 3% B: 3.6% NS	A: 33% B: 36.6% NS
Carvedilol							
Basu[a] 1997	A: Carvedilol B: Placebo	6 months	151 (146 analyzed)	A: 2.7% (2/75) B: 4.2% (3/71) *P*=NS	NR	A: 5.3% B: 11.3% NS	NR
CAPRICORN 2001	A: Carvedilol B: Placebo	1.3 years (mean)	1959	A: 12% (116/975) B: 15% (151/984) *P*=0.031; NNT=30	A: 5% B: 7% NS	A: 3% B: 6% *P*=0.014	A: 20% B: 18% NS
Metoprolol tartrate							
Stockholm 1983	A: Metoprolol tartrate B: Placebo	3 years	301	A: 16.2% (25/154) B: 21% (31/147) *P*=NS	A: 5.9% B: 14.3% *P*<0.05	A: 11.7% B: 21.1% *P*<0.05	A: 24.7% B: 23.8% NS
Amsterdam 1985	A: Metoprolol tartrate B: Placebo	1 year	553	A: 3.3% (9/273) B: 5.7% (16/280) *P*=NS	A: 0.3% B: 2.5% NS	A: 5.9% B: 7.1% NS	A: 32% B: 24% *P*=0.02
Belfast 1985	A: Metoprolol tartrate B: Placebo	1 year	764	A: 11.8% (49/416) B: 14.9% (52/348) *P*=NS	A: 1.9% B: 4.7% *P*<0.05	NR	A: 22.8% B: 19% NS
Lopressor 1987	A: Metoprolol tartrate B: Placebo	1.5 years	2395	A: 7.2% (86/1195) B: 7.7% (93/1200) *P*=NS	NR	NR	A: 31.9% B: 29.6% NS
Goteborg 1981	A: Metoprolol tartrate B: Placebo	2 years	1395	A: 5.7% (40/698) B: 8.9% (62/697) *P*=0.024; NNT=32	NR	A: 5% B: 7.7% NS	A: 19.1% B: 19.1% NS
Pindolol							
Australian & Swedish Study 1983	A: Pindolol B: Placebo	2 years	529	A: 17.1% (45/263) B: 17.7% (47/266) *P*=NS	A: 10.6% B: 11.7% NS	NR	A: 28.8% B: 18.8% *P*=0.0078
Propranolol							
Baber 1980	A: Propranolol B: Placebo	9 months	720	A: 7.9% (28/355) B: 7.4% (27/365) *P*=NS	NR	A: 4.8% B: 7.4% NS	A: 23% B: 24.1% NS

Study Year	Interventions	Duration	Number enrolled	Total mortality	Sudden death	Reinfarction	Withdrawals
Hansteen 1982	A: Propranolol B: Placebo	1 year	560	A: 8.9% (25/278) B: 13.1% (37/282) *P*=NS	A: 3.9% B: 8.1% *P*=0.038	A: 3.9% B: 3.5% *P*=NS	A: 25% B: 25% *P*=NS
BHAT 1982	A: Propranolol B: Placebo	25 months	3837	A: 7.2% (138/1916) B: 9.8% (188/1921) *P*=0.0045; NNT=39	NR	A: 5.4% B: 6.3% NS	A: 12.7% B: 9.3% *P*=0.0009
Timolol							
Roque 1987	A: Timolol B: Placebo	24 months	200	A: 6.7% (7/102) B: 12.2% (12/98) *P*=NS	NR	NR	NR
Norwegian Multicenter Study 1981	A: Timolol B: Placebo	17 months	1884	A: 10.4% (98/945) B: 16.2% (152/939) *P*=0.0002; NNT=18	A: 5% B: 10.1% *P*<0.0001	A: 9.3% B: 15% *P*=0.0002	A: 24% B: 23.3% NS

Abbreviations: NNT, number needed to treat; NR, not reported; NS, not significant.
[a] Primary endpoint was occurrence of combined cardiac events (cardiac death, re-infarction, unstable angina, heart failure, emergency revascularization, ventricular arrhythmia, stroke, or additional cardiovascular therapy).

Key Question 1e. For adult patients with heart failure, do beta blockers differ in efficacy or effectiveness?

Summary

The United States Food and Drug Administration approval of metoprolol succinate for mild to moderate heart failure (New York Heart Association Class II or III) is based on MERIT-HF. United States Food and Drug Administration approval of carvedilol for severe heart failure is based on COPERNICUS. Its approval for mild to moderate heart failure is based on 5 other trials, 4 of which constitute the United States Carvedilol Study plus the Australian-New Zealand Heart failure study (see Table 10). Heart failure is not a United States Food and Drug Administration-approved indication for nebivolol or bisoprolol, which is a generic drug.

The main findings from placebo-controlled trials in patients with mild to moderate heart failure are summarized in Table 8. Reductions in mortality, sudden death, cardiovascular deaths, and death due to heart failure were similar for bisoprolol, metoprolol succinate, and carvedilol. Because several carvedilol trials performed in the United States had significant mortality reductions, the evidence for carvedilol may be more relevant to a United States population. When titrated gradually in stable patients, there is no difference in tolerability among these drugs.

No studies of carvedilol phosphate (extended-release carvedilol) in patients with heart failure were identified through literature searches. Approval of the heart failure indication for carvedilol phosphate was based on pharmacokinetic and pharmacodynamic data that demonstrated bioequivalence with carvedilol.

In 2289 patients with severe heart failure (COPERNICUS), carvedilol clearly reduced mortality and the combined endpoint of mortality and hospitalizations. Carvedilol had the most direct, strongest evidence. In a post-hoc subgroup analysis of 795 patients from the good-quality MERIT-HF trial, metoprolol succinate demonstrated a mortality reduction relative to placebo similar to that for carvedilol in patients who had a similar mortality risk. This was a weaker level

of evidence than that for carvedilol, but the lack of a direct comparator and the difficulty of comparing subjects from the different trials makes it uncertain whether one of these drugs is superior in patients with the various degrees of heart failure.

Table 8. Main findings in placebo-controlled trials of patients with mild to moderate heart failure

Beta blocker	Mortality reduction	Reduction in sudden death	Reduction in progressive heart failure	Improvement in New York Heart Association class	Improvement in exercise parameters	Improvement in quality of life
Bisoprolol	Yes	Yes	Not proven	Yes	Not significant	Not significant
Carvedilol	Yes	Yes	Mixed results	Not proven	Not significant	Not significant
Carvedilol phosphate	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Metoprolol Succinate	Yes	Yes	Yes	Not proven	Not significant	Yes
Nebivolol	Not significant	Not significant	No evidence	Not significant	No evidence	No evidence

In the Carvedilol or Metoprolol European Trial (COMET) trial, a head-to-head trial conducted in patients with mild to moderate failure, carvedilol reduced mortality compared with metoprolol tartrate, the immediate-release form of metoprolol. In previous trials, however, metoprolol tartrate had not been proven to reduce mortality. The COMET trial does not resolve the question of whether carvedilol is superior to metoprolol succinate or bisoprolol, the preparations that have been shown to reduce mortality.

Detailed Assessment

Placebo-controlled trials

Mortality

Eight meta-analyses of placebo-controlled trials of various beta blockers in heart failure were published in the mid-1990's through 2000 (Evidence Tables 9 and 10).[73-80] In general, these meta-analyses found that beta blockers reduce mortality by about 30%, preventing 3.8 deaths per 100 patients in the first year of treatment. Nevertheless, the authors of the meta-analyses agreed that larger trials were needed before beta blockers could be recommended routinely for patients with heart failure.

The mortality benefits of seven beta blockers (atenolol, bisoprolol, bucindolol, carvedilol, metoprolol tartrate, metoprolol succinate, and nebivolol) have been evaluated in placebo-controlled trials in adults with heart failure. Five of these beta blockers (bisoprolol, bucindolol, carvedilol, metoprolol succinate, and nebivolol) have been evaluated in major trials that enrolled 1000 to almost 4000 patients (Table 9). Bisoprolol, in the Cardiac Insufficiency Bisoprolol Study II trial (CIBIS-II); carvedilol, in the Carvedilol Prospective Randomized Cumulative Survival trial COPERNICUS; and metoprolol succinate, in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure trial (MERIT-HF); but not bucindolol, in the

BEST trial, reduced total mortality (as planned primary endpoint) by approximately 35%. The nonsignificant result for bucindolol suggest that individual beta blockers may differ in their effectiveness to reduce mortality in heart failure patients (bucindolol is not available in the United States, but is included in Table 9 for comparison).

Two trials evaluated nebivolol in relation to all-cause mortality or cardiovascular hospitalization, New York Heart Association class reduction, and quality of life.[72, 98] Mortality was included as a secondary outcome measure in both of these trials. The SENIORS study of 2128 elderly patients included patients with a history of heart failure (hospital admission for heart failure during the past 12 months or an ejection fraction of ≤35%). The mean age of patients was 76 and the mean ejection fraction was 36%. SENIORS included some patients who were similar to those included in the other trials, but a majority of patients who were older, had little or no left ventricular dysfunction, and had a lower risk of death. Thirty-five percent had an ejection fraction of >35%, and the annualized placebo mortality rate was 10%. When compared with placebo, nebivolol reduced the composite risk of all-cause mortality or cardiovascular hospital admission (31.1% compared with 35.3%; hazard ratio, 0.86; 95% CI, 0.74 to 0.99)[72] but had nonsignificant effects on the individual variables examined as secondary outcomes. A subgroup analysis demonstrated that the risk of mortality or hospitalization for patients with a left ventricular ejection fraction of either ≤35 or >35% was not significantly different (*P*=0.42). In a post-hoc analysis, researchers identified the subgroup of patients most similar to the other major outcome trials. In this subgroup, defined as patients of less than 75.2 years with an ejection fraction ≤35% (n=342 for nebivolol and n=342 for placebo), findings were similar to that seen with metoprolol-controlled release, bisoprolol, and carvedilol (hazard ratio for the primary composite variable was 0.73; 95% CI, 0.56 to 0.96). For all-cause mortality alone, the hazard ratio was 0.62 (95% CI, 0.43 to 0.89). It should be noted, however, that the older and healthier patients (those with less severe left ventricular distinction) in the SENIORS trial were not evaluated in a subgroup analysis, and therefore it is unknown as to whether nebivolol would be effective in this population.

In the ENECA trial, nebivolol was examined for 8 months as an add on therapy in 260 elderly patients with chronic heart failure.[98] Total mortality, included as a secondary outcome measure, was not significant when compared to placebo (survival rate 67.47% compared with 62.89; *P*=0.696). Results of the ENECA study are discussed below in relation to the study's primary outcome measures of New York Heart Association class reduction and quality of life.

Table 10 summarizes 16 placebo-controlled trials (including those in Table 9) that enrolled over 100 patients and met our other inclusion criteria (Evidence Tables 9 and 10). These trials evaluated atenolol 50 to 100 mg,[81] bisoprolol 5 to 10 mg,[82, 83] carvedilol 50 to 100 mg,[84-93] metoprolol tartrate 100 to 150 mg,[94, 95] metoprolol succinate (CR) 12.5 to 25 mg,[96, 97] and nebivolol 10 mg.[72, 98]

Relation of mortality reduction to severity of heart failure

The trials in Table 9 leave no doubt that, in certain patients, bisoprolol, carvedilol, and metoprolol succinate reduce mortality. The main unresolved questions are 1) whether any of these agents is superior to the others in patients with mild to moderate failure, and 2) whether, in patients with severe failure, bisoprolol or metoprolol succinate are equivalent to carvedilol, which is the only drug that has a United States Food and Drug Administration indication in this group.

Many authors have used the placebo group mortality rates to make inferences about the baseline severity of patients in the various trials. However, several factors, including New York Heart Association Class, ejection fraction, blood pressure, lifestyle, and the quality of medical care influence mortality in patients with heart failure. For this reason it has proven difficult to judge the relative severity of illness among the major trials listed in Table 9.

MERIT-HF provides interesting data about the relationship of New York Heart Association class and ejection fraction:

MERIT-HF Subgroups	EF<25%	EF>25%
New York Heart Association Class II	707 ("A")	928
New York Heart Association Class III-IV	795	1561 ("D")

The large number of Class II patients with "severe" left ventricular dysfunction (ejection fraction <25%) illustrates the hazards of inferring functional class from ejection fraction. Conversely, a significant proportion of patients with "moderate to severe" heart failure (Class III and IV) had an ejection fraction >25%. As one would expect, the subgroup with New York Heart Association Class III-IV and ejection fraction <25% had the highest mortality. It would be impossible to distinguish between patients in cells "A" and "D" based on mortality rates and entry criteria.

The 4 United States Carvedilol trials and the Australian-New Zealand trial demonstrated that in patients with New York Heart Association Class II to IV heart failure, carvedilol reduced mortality. As shown in Table 10, the severity of heart failure of patients in these trials varied substantially, suggesting that carvedilol was effective across a broad spectrum of heart failure patients. These trials used an active drug run-in period during which patients who could not tolerate a small dose of carvedilol, were noncompliant, or died were excluded prior to randomization. For this reason, the mortality reductions and rates of withdrawal and adverse events are not comparable to those of other trials. In Table 10 we summarize mortality results of these and other trials after adjusting the number of deaths in the carvedilol group by adding in deaths that occurred during the run-in period.

COPERNICUS was a well-designed, well-conducted placebo-controlled trial of carvedilol conducted in 334 Centers. Of 2289 subjects randomized, 627 were recruited from the United States and Canada; the rest were recruited in Europe (including Russia), the United States, Canada, Israel, Australia, South Africa, Argentina, and Mexico. It is difficult to compare the COPERNICUS subjects to those of other trials because COPERNICUS did not report New York Heart Association Class or exercise capacity, which were inclusion criteria in the other trials. COPERNICUS was intended to recruit a more severely ill population than the United States carvedilol trials. COPERNICUS subjects had higher mortality than 3 of the 4 trials that make up the United States Carvedilol Trial.

The mortality effect in COPERNICUS was consistent for sex, age, and other subgroups. The effect was lower, but not significantly so, for patients who had an ejection fraction <20% compared with those who had ejection fraction >20% and for those recruited in Europe, Australia, and the Middle East compared with North and South America.

MERIT-HF**,** conducted in the United States and Europe, recruited stable subjects with mild to severe heart failure. Although it had a significant proportion of subjects with New York Heart Association Class II symptoms, the mean ejection fraction was similar to that of CIBIS-II. MERIT-HF was well-designed and well-conducted and had clear-cut overall reductions in

overall mortality, death from cardiac causes, sudden death, and heart transplantation, as well as a reduction in all-cause hospitalization (RR, 0.84; CI, 0.76-0.95).

The MERIT-HF investigators defined a "high risk" group consisting of the 795 patients who had New York Heart Association class III-IV and ejection fraction <25%. This subgroup had a mean ejection fraction (19%) and placebo group mortality (18.2%) close to that of COPERNICUS.

The applicability of the results of any trial to a United States population is a major issue in all of these trials, because heart failure survival depends on other aspects of care. The United States Food and Drug Administration review of the MERIT-HF trial found "a strong suggestion of a treatment-by-region (United States compared with Europe) interaction with respect to mortality." MERIT-HF had 1071 United States subjects and 2920 European subjects. The placebo group mortality was higher in Europe (168/1462; 11.5%) than in the United States (49/539; 9.1%). Metoprolol succinate reduced all-cause mortality in Europe (hazard ratio, 0.55; *P*=0.0001) but not in the United States subgroup (hazard ratio, 1.05; *P*=0.7961). The lack of any trend toward reduced mortality in the United States subgroup is of concern.

For carvedilol, relevance to the United States population is not a concern, because the United States Carvedilol Trials were performed in the United States. Rather, the concern is what COPERNICUS adds to what was already known from the United States Carvedilol Trials. About 1 in 5 patients in COPERNICUS were from the United States; the hazard ratio was 0.80 in the United States patients and 0.60 in the rest of the world. Statistically, this difference is not meaningful, but that is not the whole story, for 2 reasons. First, the "rest of the world" is not homogeneous. Second, the proportion of United States patients in COPERNICUS was much lower than in MERIT-HF, so it is not surprising that the United States subgroup (n=482) was not a statistical outlier in COPERNICUS. Next to the United States, Russia (n=309) and Poland (n=299) recruited the most patients in COPERNICUS, and carvedilol had larger mortality reductions in these 2 countries than in 9 of 13 others.

CIBIS-II was a well-conducted multicenter European study designed to recruit stable subjects with moderate to severe heart failure (New York Heart Association Class III-IV).[83] Most patients were New York Heart Association Class III. The annual placebo mortality rate was 13%, which is higher than the rate projected by the CIBIS-II investigators based on the results of CIBIS-I. Nevertheless, this mortality rate and the average ejection fraction of 27% are closer to those of MERIT-HF, which recruited mostly Class II and III patients, than to those of COPERNICUS, which is thought to have recruited New York Heart Association Class III and IV patients.

In CIBIS-II, 752 subjects were New York Heart Association Class III or IV and had an ejection fraction less than 25%, but the results in this subgroup have not been reported completely, although the hazard ratio was said to be 0.78 (0.56 to 1.07). For the Class III patients, annual placebo group mortality was about 13%; over the entire study (averaging 1.3 years of followup), the number needed to treat to prevent 1 death was about 19. For the Class IV patients, the annual placebo mortality was about 18%, and the number needed to treat to prevent 1 death over 1.3 years was about 15. The mortality reduction for Class IV patients was of borderline statistical significance; when measured as a difference of probabilities, the confidence interval was 0.0005 to 0.127 (from that is, from 0 to 12.7 lives saved for every 100 patients).

Table 9. Comparison of major beta blocker trials in heart failure

Trial	Drug and target dose	Ejection fraction criteria (mean)	New York Heart Association class	Number of subjects	Annual placebo mortality	Mortality reduction	Withdrawal rate for active drug group[a]
CIBIS-II	Bisoprolol 10mg once daily	<35% (0.27)	III (81%) IV (19%)	2647	13%	34%	15%
MERIT-HF	Metoprolol CR 200mg once daily	<40% (0.28)	II (41%) III (56%) IV (3.6%)	3991	11%	34%	14%
BEST	Bucindolol 100mg twice daily	<35%	III-IV	2708	17%	10%[b]	23%
COPERNICUS	Carvedilol 25mg twice daily	<25% (0.20)	NR	2289	19%	35%	12.6%
US Carvedilol[c]	Carvedilol 25mg twice daily[d]	≤35%	II-IV	1094	12%	65%[e]	11%[f]
SENIORS (age ≥ 70 yrs)	Nebivolol 10 mg daily	≤35%[g] (0.36)	I 2.85% II 56.4% III 38.7% IV 2.05%	2128	10%	13%[b,h]	26.7%

[a] All values were not different from the placebo group except for COPERNICUS (placebo withdrawal rate 15.9%, *P*=0.0026).
[b] Not significant.
[c] Planned analysis of pooled results of 4 independent, double-blind placebo-controlled trials.
[d] Dosage target was 50 mg twice daily in patients whose weight was 85 kg or more.
[e] Mortality was not the primary endpoint, and the estimated mortality reduction was inflated because of the use of an active-drug run-in period before randomization. Withdrawal rates are also affected by use of an active-drug run-in phase. See Table 10.
[f] Study stopped early on recommendation of Data and Safety Monitoring Board based on finding of a significant effect of carvedilol on survival. When program was terminated, more patients were receiving or had completed treatment with carvedilol than placebo (89% compared with 83%, *P*=0.002).
[g] The SENIORS trial included patients with at least one of the following: documented hospital admission within previous 12 months with discharge diagnosis of congestive heart failure or documented left ventricular ejection fraction ≤ 35% within the previous 6 months.
[h] The composite of all-cause mortality or cardiovascular hospital admission was the primary endpoint and all-cause mortality was measured as a secondary outcome.

Table 10. Patient characteristics and annualized mortality rates adjusted for active drug run-in periods in trials of beta blockers for heart failure

Trial	Drug	Primary endpoint	New York Heart Association class	Entry criterion for ejection fraction (average)	Mortality in placebo group (per year)	Mortality in treatment group (per year)	Sample size
Sturm 2000	Atenolol	Combined worsening heart failure or death	II-III	≤25% (17%)	5.0%	8.0%	100
CIBIS	Bisoprolol	Mortality	III-IV	<40% (0.25%)	10.4%	8.3%	641
CIBIS-II	Bisoprolol	Mortality	III-IV	<35% (0.275%)	13.2%	9.0%	2647
Bristow[a]	Carvedilol	Exercise tolerance	II-IV	≤35% (0.23%)	33.8%	10.9%	345
Packer[a]	Carvedilol	Exercise tolerance	II-IV	≤35% (0.22%)	14.0%	15.3%	278
Colucci[a]	Carvedilol	Progression of heart failure	II-III	≤35% (0.23%)	6.4%	2.2%	366
Cohn[a]	Carvedilol	Quality of life	III-IV	≤35% (0.22%)	8.6%	4.3%	105
ANZ[a]	Carvedilol	Exercise tolerance, LVEF	I-III	<45% (0.29%)	7.9%	7.0%	415
Christmas	Carvedilol	LVEF	I-III	<40% (0.29%)	4.9%	6.9%	387
Copernicus	Carvedilol	Mortality	NR	< 25% (0.20%)	18.5%	11.4%	2289
MUCHA (Japanese)	Carvedilol	CHF global assessment	II-III	≤40% (30%)	NR	NR	190
Cice 2003 (dialysis)	Carvedilol	LVEF, NYHA	II-III	<35% (0.26%)	36.6%	25.8%	114
MDC	Metoprolol	Mortality+ morbidity	I-IV	<40% (0.22%)	11.0%	12.0%	383
Waagstein 2003	Metoprolol	NR	II-III	<40% (28.5%)	9.1%	7.6%	165
MERIT	Metoprolol CR	Mortality	II-IV	<40% (0.28%)	10.8%	7.3%	3991
MERIT high-risk subgroup	Metoprolol CR	Mortality	III-IV	<25% (0.19%)	18.2%	11.3%	795
RESOLVD[a]	Metoprolol CR	Exercise tolerance, neurohumoral parameters	I-IV	<40% (0.28%)	16.0%	8.4%	768

Trial	Drug	Primary endpoint	New York Heart Association class	Entry criterion for ejection fraction (average)	Mortality in placebo group (per year)	Mortality in treatment group (per year)	Sample size
Edes 2005 ENECA	Nebivolol	LVEF	II-IV	≤35% (0.259%)	5.9%	5.6%	260
Flather 2005 SENIORS	Nebivolol	Mortality and cardiovascular hospital admission	I-IV	≤35% (0.36%)	10.3%	9.0%	2128

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association classification.
[a] Studies which has an active drug run-in phase are marked with an asterisk. We added deaths during the run-in period to the total for the active drug.
[b] New York Heart Association Class not reported, but all patients had symptoms on minimal exertion or at rest.

In addition to all-cause mortality, sudden death, and cardiovascular mortality, endpoints in beta blocker trials include symptoms, progression of disease, need for hospitalization, and need for (or time to) transplantation. The major placebo-controlled trials and many smaller trials evaluated these outcomes in Table 11.

New York Heart Association class

The effect on New York Heart Association class rating was inconsistently reported. The CIBIS trial found that significantly more patients taking bisoprolol improved by at least 1 New York Heart Association class (21% compared with 15%; P=0.03) but there was no differences in patients that deteriorated by at least 1 class (13% compared with 11%). Results were mixed for carvedilol. Three trials suggest carvedilol is superior to placebo in improving the overall New York Heart Association class distribution.[85, 86, 91] This includes the MUCHA trial of Japanese patients with heart failure.[91] In 3 other trials, including a subset of dialysis patients with heart failure,[92] carvedilol had no effect.[84, 88, 92] Metoprolol tartrate did not significantly improve the New York Heart Association class in either of 2 trials. In the MERIT-HF trial, metoprolol CR increased the proportion of patients that improved by at least 1 New York Heart Association class overall (28.6% compared with 25.8%; P=0.003). A post-hoc analysis found the same effect in a subgroup of patients with baseline New York Heart Association class III-IV and left ventricular ejection fraction < 25% (46.2% compared with 36.7%; P=0.0031).[99] By contrast, carvedilol did not reduce progression of heart failure in COPERNICUS. In the ENECA study of 260 patients with chronic heart failure treated with nebivolol as an add on therapy, compared with placebo (27%), slightly fewer elderly patients (≥65 years) with heart failure taking nebivolol at an average dose of 7.4 mg improved by at least 1 New York Heart Association class overall (26%).[98]

Exercise capacity

The carvedilol trials[84-86, 88] were consistent in showing equivalency to placebo in exercise capacity improvement as measured by both the 6-minute walk and 9-minute treadmill tests. Results of treadmill testing (modified Naughton protocol) were mixed in 2 placebo-controlled trials of metoprolol.

Quality of life

Quality of life in heart failure patients was most commonly assessed using the Minnesota Living with Heart Failure Questionnaire. Overall, placebo-controlled trials provided limited evidence that beta blockers significantly improve quality of life in heart failure patients. Carvedilol was consistently associated with nonsignificant improvements in quality of life in patients with mild to moderate[84-86] or severe[87] heart failure.

In the MDC trial, patients taking immediate release metoprolol experienced significantly greater improvements in quality of life than those taking placebo, however, no data were provided and it is unclear as to which measurement instrument was used. For controlled-release metoprolol, results of quality-of-life assessments were mixed across 2 trials.[97, 100] In the ENECA study, reductions in Minnesota Living with Heart Failure Questionnaire scores were similar for nebivolol compared with placebo.[98]

Table 11. Outcomes in placebo-controlled trials of beta blockers for heart failure

Study Year	Beta blocker	All-cause mortality rates *P* value NNT	Sudden death rates *P* value NNT	Death due to heart failure *P* value NNT	New York Heart Association class improvement	Exercise capacity	Quality of life
Sturm 2002	Atenolol	10% vs. 16% NS	NR	16% vs. 39% NS	NR	NR	NR
Anonymous 1994 CIBIS	Bisoprolol	16.6% vs. 20.9% NS	4.7% vs. 5.3% NS	NR	Improvement (≥1 class) 21% vs. 15%; *P*=0.03	NR	NR
Anonymous 1999 CIBIS-II	Bisoprolol	12% vs. 17% *P*<0.0001 NNT=19	4% vs. 6% *P*=0.0011 NNT=38	NR	NR	NR	NR
Bristow 1996 US Carvedilol Heart Failure Study Group: MOCHA	Carvedilol	4.6% vs. 15.5% *P*<0.001 NNT=9	2.3% vs. 7.1% *P*=0.035 NNT=21	1.1% vs. 7.1% *P*=0.003 NNT=17	No effect (data NR)	6-minute walk test/9-minute self-activated treadmill testing: no effect (data NR)	Mean change in MLHFQ: no effect
Packer 1996 US Carvedilol Heart Failure Study Group: PRECISE	Carvedilol	4.5% vs. 7.6% NS	NR	NR	Improvement: 21.5% vs. 6.9%; *P*=0.014	Mean increase in 6-minute walk test distance (m): 17 vs. 6 (NS) 9-minute treadmill test distance: no effect	MLHFQ: no effect (original data NR)
Colucci 1996 US Carvedilol Heart Failure Study Group:	Carvedilol	0.9% vs. 4% NS	NR	Heart failure progression (deaths+hospitalizations + need for	Improvement: 12% vs. 9%; *P*=0.003	9-minute self-minute treadmill test: car=pla (data NR)	Mean change in MLHFQ: (−4.9) vs. (−2.4)

Study Year	Beta blocker	All-cause mortality rates *P* value NNT	Sudden death rates *P* value NNT	Death due to heart failure *P* value NNT	New York Heart Association class improvement	Exercise capacity	Quality of life
Mild				more medications) 25/232(11%) 28/134(20.9 %) *P*=0.008 NNT=10			NS
Cohn 1997 US Carvedilol Heart Failure Study Group	Carvedilol	2.8% vs. 5.7% NS	NR	NR	% decrease in Class III/IV patients: 20% vs. 9.5%; NS	Mean increase in 6-minute walk test distance (m): 19.0 vs. 28.4 (NS)	Mean improvement in MLHFQ: 11.6 vs. 8.8 (NS)
Anonymous 1997 Australia/New Zealand Heart Failure Research Collaborative Group	Carvedilol	9.6% vs. 12.6% NS	4.8% vs. 5.3% NS	6.7% vs. 7.2% NS	Improved: 26% vs. 28%; NS	Treadmill exercise duration/6-minute walk distance: car=pla (data NR)	NR
Packer 2001 COPERNICUS	Carvedilol	11.2% vs. 16.8% *P*=0.00013 NNT=19	6.1% vs. 3.9% *P*=0.016 NNT=46	NR	NR	NR	NR
Cleland 2003 CHRISTMAS	Carvedilol	4.3% vs. 3.2% NS	NR	NR	NR	Exercise time (method NR) (seconds): 405 vs. 427 NS	NR
Hori 2004 MUCHA (Japanese patients)	Carvedilol	NR	NR	NR	Improved 5 mg= 80.9% vs. 48.9%; *P*<0.001 20 mg= 70.8% vs. 48.9%; *P*<0.05	NR	NR
Cice 2003 (Dialysis patients)	Carvedilol	51.7% vs. 73.2% *P*<0.01 NNT=5	3.4% vs. 10.6% NS	NR	Class I: 8.3% vs. 0% Class II: 66.7% vs. 33.4% Class III: 25% vs. 44.4% Class IV: 0% vs. 22.2% All NS	NR	NR
Waagstein 1993 MDC	Metoprolol tartrate	11.8% vs. 11.1% NS	9.3% vs. 6.3% NS	2.6% vs. 2.6% NS	Improvement: effective (data NR)	Mean increase in exercise capacity (sec): 76 vs. 15; *P*=0.046	met>pla *P*=0.01 (original data NR)

Study Year	Beta blocker	All-cause mortality rates *P* value NNT	Sudden death rates *P* value NNT	Death due to heart failure *P* value NNT	New York Heart Association class improvement	Exercise capacity	Quality of life
Waagstein 2003	Metoprolol tartrate	4.6% vs. 3.8% NS	NR	NR	Improved: 42% vs. 33% NS	Bicycle test: met=pla (data NR)	NR
Anonymous 1999 MERIT-HF	Metoprolol succinate	7.3% vs. 10.8% *P*=0.00009 NNT=29	3.9% vs. 6.5% *P*=0.0002 NNT=39	1.5% vs. 2.9% *P*=0.0023 NNT=72	NR	NR	McMaster Overall Treatment Evaluation: met>pla (data NR)
Anonymous 2000 RESOLVD	Metoprolol succinate	3.7% vs. 8.1% NS	NR	0.5% vs. 1.4% NS	met CR=pla (data NR)	6-minute walk test change (meters) −1 vs. −3	met CR=pla (data NR)
Anonymous 1997 Australia/ New Zealand Heart Failure Research Collaborative Group	Carvedilol	9.6% vs. 12.6% NS	4.8% vs. 5.3% NS	6.7% vs. 7.2% NS	Improvement: 26% vs. 28% NS	Treadmill exercise duration/6-minute walk distance: carvedilol= pla (data NR)	NR
Edes 2005 ENECA	Nebivolol	NR	NR	NR	Improvement: (≥1 class) 26.1% vs. 29.3%; NS	NR	Mean decrease 9.13 vs. 11.01 NS points
Flather 2005 SENIORS	Nebivolol	15.8% vs. 18.1% (NS)	36% vs. 48% (*P*=NR)	NR	NR	NR	NR

Abbreviations: MLHFQ=Minnesota Living with Heart Failure Questionnaire; NNT, number needed to treat; NR, not reported; NS, not significant.
[a] Odds ratios (95% CI) adopted from previously published bayesian meta-analysis (Brophy, 2001).

Head-to-head trials

There are no direct comparator trials comparing 2 or more of the drugs proven to reduce mortality (bisoprolol, carvedilol, and sustained release metoprolol succinate). We are aware of 1 trial in process that compares the tolerance of bisoprolol and carvedilol in elderly patients (≥65 years) with systolic or diastolic chronic heart failure.[101]

Otherwise, we found 6 fair-quality, head-to-head trials comparing immediate-release metoprolol tartrate to carvedilol in patients with heart failure and 1 trial that compared nebivolol to carvedilol (see Evidence Tables 11 and 12 for characteristics and quality assessments and Evidence Table 13 for outcomes).[102-107] These trials recruited stable patients with Class II-IV (mainly II and III) heart failure, most of whom took ACE inhibitors and diuretics.

Only 1 trial (COMET) was adequately powered to evaluate mortality and cardiovascular events (N=3029). The target dose of carvedilol was 25 mg twice a day and the target for metoprolol tartrate was 50 mg twice a day. The patients were mostly (79.8%) men, with a mean age of 62 years and a mean ejection fraction of 26% on optimal treatment with ACE inhibitors and diuretics for New York Heart Association class II-IV heart failure.

When COMET was designed, extended-release metoprolol was not yet available, and immediate-release metoprolol was a logical comparator because in the MDC trial metoprolol tartrate was clearly effective, even though it did not change mortality. Specifically, metoprolol tartrate improved ejection fraction, left ventricular end diastolic pressure, and exercise time and prevented clinical deterioration, reducing the need for transplantation by almost 90% during the followup period.[94]

Mortality

In COMET, after a mean followup of 58 months (nearly 5 years), the intention-to-treat analysis showed an all-cause mortality reduction in favor of carvedilol (34% compared with 40%; number needed to treat, 18; $P<0.0017$). The annual mortality rate was 10% for metoprolol tartrate and 8.3% for carvedilol. For comparison, the rates were for metoprolol succinate in MERIT-HF (7.2%) and bisoprolol in CIBIS-II (8.8%). There was no difference between carvedilol and metoprolol in the combined endpoint of deaths plus all-cause admissions (74% compared with 76%).

COMET demonstrates unequivocally that carvedilol 25 mg twice a day was better than immediate-release metoprolol (metoprolol tartrate) twice a day. There is disagreement, however, about the relevance of the result, because immediate-release metoprolol had not been shown to reduce mortality in previous trials. Several years ago, after metoprolol tartrate failed to reduce mortality in the Metoprolol in Dilated Cardiomyopathy (MDC) trial, it was hypothesized that the patients who received it were subjected to daily variations in the degree of beta blockade. In COMET, the mean dose of metoprolol tartrate was less than that used in the MDC trial (85 mg daily compared with 108 mg daily), and the mean decrease in heart rate was also less (11.7 compared with 15 beats per minute). Subsequently, extended-release metoprolol (metoprolol succinate) was proven to reduce mortality in heart failure patients in the MERIT-HF trial. In MERIT-HF, the mean dose of metoprolol succinate was 159 mg daily and the mean reduction in heart rate was 14 beats per minute.

Other outcomes

Carvedilol compared with metoprolol. Evidence on numerous secondary outcomes from the COMET trial have been published.[108, 109, 110] Carvedilol was superior to immediate-release metoprolol in reducing rates of cardiovascular death, sudden death, stroke, cardiovascular events, and unstable angina, and similar to immediate-release metoprolol in reducing death due to circulatory failure and other cardiovascular deaths, as well as in reducing days lost due to impaired well being.[108, 109]

Greater reductions in rates of first hospitalization due to potential complication of heart failure treatment were more associated with immediate-release metoprolol than with carvedilol. Both interventions had similar effects on rates of overall hospitalization and cause-specific hospitalizations, with 1 exception.[108, 109] Rates of non-cardiovascular death, worsening heart failure, change in New York Heart Association classification, and medication withdrawal were similar for carvedilol and immediate release metoprolol.[108]

With regard to combined endpoints, carvedilol was superior in reducing rates of fatal or nonfatal myocardial infarction and the combination of cardiovascular death, heart transplantation, hospitalization for nonfatal acute myocardial infarction, or worsening heart failure and was similar to immediate-release metoprolol in reducing the combined rate of all-cause mortality and cardiovascular hospitalizations.[108] Another combined endpoint of days of life

lost due to death, hospitalization, impaired well-being, or need to increase diuretic use (deemed the 'patient journey') found carvedilol to be superior to metoprolol over 4 years when compared to baseline composite scores (P=0.0068).[109] It is important to note however, that this combined endpoint considered all factors to be equal; days lost due to death were considered equivalent to days lost due to hospitalization.

In the older trials, there was a nonsignificant trend favoring carvedilol over immediate-release metoprolol. Carvedilol and immediate release metoprolol (124+/–55 mg daily) had similar effects on quality of life, but metoprolol improved exercise capacity more. There were no differences between the carvedilol and metoprolol groups in quality of life.

Nebivolol compared with carvedilol. One trial of 70 patients with heart failure, a left ventricular ejection fraction of 40% or lower, and a New York Heart Association functional class of II or III, compared treatment with mean doses of carvedilol 44 mg and a lower than recommended target dose of nebivolol (4.4 mg) over 6 months. Compared with baseline, carvedilol and nebivolol demonstrated slight improvements in New York Heart Association functional class and the 6-minute walk test.[111]

Key Question 1f. For adult patients with atrial arrhythmia, do beta blockers differ in efficacy or effectiveness?

Several beta blockers have been used to reduce the heart rate in patients with atrial tachyarrhythmias and to prevent relapse into atrial fibrillation or flutter. A recent good-quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation.[112] Atenolol, nadolol, and pindolol were effective in controlling the ventricular rate, while labetalol was no more efficacious than placebo.

We found 1 head-to-head trial comparing bisoprolol 10 mg and carvedilol 50 mg in patients subjected to cardioversion of persistent atrial fibrillation (> 7 days).[113] This fair-quality, 12-month trial enrolled 90 patients (mean age, 65.5; 82% male) (Evidence Tables 14 and 15). Similar proportions of patients relapsed into atrial fibrillation during follow-up in the bisoprolol and carvedilol groups (53.4% compared with 43.6%; P=NS).

Two placebo-controlled trials evaluated beta blockers in patients with persistent atrial fibrillation.[114-116] One placebo-controlled trial found that metoprolol CR/XL 100 to 200 mg was effective in preventing relapse of atrial fibrillation/flutter after cardioversion (Evidence Table 14).[114, 115] This fair-quality trial was conducted in Germany and enrolled 433 patients after cardioversion of persistent atrial fibrillation that were 70% male, with a mean age of 60. Over 6 months, atrial fibrillation or flutter relapse rates were significantly lower in patients taking metoprolol CR/XL (48.7% compared with 59.9%; P=0.005). This trial was not powered to detect differences in rates of mortality as a primary endpoint. Death was reported as an adverse event and rates were not significantly different for the metoprolol CR/XL and placebo groups (3.1% compared with 0).

The other study examined the effects of carvedilol in managing patients with concomitant atrial fibrillation and heart failure.[116] This study was divided into 2 phases. The first phase involved a 4-month comparison of digoxin alone to the combination of digoxin and carvedilol and the second phase involved a 6-month comparison of digoxin alone to carvedilol alone. Forty-seven patients (mean age, 68.5; 61.7% male) with atrial fibrillation (mean duration, 131.5 weeks) and heart failure (predominantly New York Heart Association class II-III; mean left ventricular ejection fraction, 24.1%) were enrolled in this fair-quality study. When added to digoxin,

carvedilol significantly lowered the 24-hour ventricular rate (65.2 compared with 74.9 bpm; $P \leq 0.0001$) and improved mean left ventricular ejection fraction scores (30.6% compared with 26%; $P=0.048$) and severity of symptoms/functional capacity on a 33-point scale (6 compared with 8; $P=0.039$). There were no differences between monotherapies with either carvedilol or digoxin in the second phase, however.

Key Question 1g. For adult patients with migraine, do beta blockers differ in efficacy or effectiveness?

Summary

Six head-to-head trials show no difference in efficacy in reduction of attack frequency, severity, headache days or acute tablet consumption, or in improvement in any subjective or composite index in any of the comparisons made (atenolol or metoprolol durules or metoprolol or timolol compared with propranolol or nebivolol compared with metoprolol). Results from placebo-controlled trials on similar outcome measures generally supports those for atenolol, metoprolol durules, and propranolol seen in head-to-head trials. Placebo-controlled trial results also show that bisoprolol had a significant effect on attack frequency reduction and that pindolol had no appreciable effects.

Detailed Assessment

Head-to-head trials

We found 6 fair-quality[117-122] head-to-head trials of beta blockers for the treatment of migraine (Table 12). One study comparing bisoprolol and metoprolol appears to have been published twice.[123, 124] This trial was rated poor quality due to inadequate descriptions of methods of randomization and allocation concealment, lack of use of an intention to treat principle, and a high rate of attrition (37.6%).

The 6 included trials compared propranolol 160 mg to atenolol 100 mg,[120] slow release metoprolol (durules) 200 mg daily,[118] immediate release metoprolol 200 mg daily,[117] timolol 20 mg,[121, 122] propranolol 80 mg to metoprolol 100 mg daily,[119] and nebivolol 5 mg to metoprolol 142.5 mg.[125] All 6 trials were conducted outside of the United States, were relatively short-term in duration (12 to 20 weeks), and were small (30 to 96 patients). Most patients had common migraine per Ad Hoc Committee and World Federation of Neurology Research Group guidelines (83 to 93%) and migraine without aura per International Headache Society (92.8%). These patients have mean ages of 33.8 to 42.3, are 68.6% to 88.9% female, and have a history of migraine frequency of greater than 3 attacks per month. Use of concomitant analgesics and ergotamines was allowed for abortive migraine treatment. Headache frequency, intensity, severity, duration, and abortive treatment tablet usage efficacy parameters were analyzed using patient diary data.

The methods used to assess treatment effects differed across studies. Some of the common outcome results are summarized in Table 13 below. Analysis of variance was used to assess comparative efficacy of metoprolol 200 mg and propranolol 160 mg in 1 trial.[117]

Attack frequency

Metoprolol durules 200 mg, metoprolol tartrate 200 mg, and timolol 20 mg all were similar to propranolol 160 mg in decreasing 4-week attack frequency rates.[117-119, 121, 122] A recent, well-conducted systematic review comparing propanol to other beta blockers found that there was little difference between propanol and the comparators (metoprolol, nadolol, timolol) in reducing attack frequency (pooled standard mean difference, −0.01; 95% CI, −0.24 to +0.22) based on data from 4 crossover trials.[126] In a study comparing nebivolol to metoprolol there were no statistically significant differences in attack frequency, although nebivolol fared better with regards to tolerability.[125]

Migraine days

There were differences across trials in methods of assessment of this parameter. When the total number of headache days recorded over 42 days across all 28 patients analyzed was considered in the Stensrud trial, no difference between atenolol and propranolol treatment was found. Metoprolol durules and metoprolol tartrate reduced number of migraine days at rates similar to propranolol across 3 trials.[117-119] In a comparison of nebivolol to metoprolol over an 18-week period, no differences were found.[125]

Severity

Severity rating methods differed across trials. Metoprolol durules, metoprolol tartrate, and timolol all were similar to propranolol at comparable doses in decreasing attack severity.[118, 119, 121, 122] As measured using a 100-mm visual analog scale, headache severity at endpoint was similar for nebivolol and metoprolol (50 compared with 54 points).[125]

Tablet consumption

There were no differences in reduction of acute medication (analgesics, ergots) for metoprolol durules or metoprolol tartrate and propranolol.[118, 119, 121, 122] Moreover, the number of patients using pain medication at endpoint were similar between nebivolol and metoprolol.[125]

Subjective assessment

Patients in 2 trials[118, 119] were asked to make a subjective assessment of therapeutic improvement using descriptions of marked, moderate, slight, and unchanged or worse. There were no differences found between slow release metoprolol (durules) and propranolol (76% compared with 63%) or between low doses of immediate release metoprolol or propranolol (63% compared with 64%) in rates of decreased frequency of mean or median attacks per month.

Miscellaneous

Two trials[120-122] measured treatment efficacy using a composite score (attack frequency x severity x duration) and found no differences between atenolol or timolol and propranolol. The Gerber et al. trial included an analysis of duration of migraine in hours and didn't find any difference between metoprolol and propranolol in percent of patients qualifying as responder type A or B for decrease on this variable.

Table 12. Outcomes in head-to-head trials of migraine patients

Outcomes	Attack frequency/4 weeks (% decrease)	Headache days	Severity (% reduction)	Tablet consumption	Subjective (% patients regarding effect as "marked" or "moderate")	Miscellaneous
Stensrud 1980 Atenolol 100 mg vs. propranolol 160 mg N=28	NR	247 vs. 257	NR	NR	NR	Headache Index1 (mean): 410 vs. 437
Kangasniemi 1984 Metoprolol-d 200 mg vs. propranolol 160 mg N=35	43.4% vs. 43.4%	45.6% vs. 43.8%	21.8% vs. 29.8%	45.3% vs. 45.3%	76% vs. 63%	NR
Olsson 1984 Metoprolol 100 mg vs. propranolol 80 mg N=53	NR	25.4% vs. 32.8%	21.8% vs. 29.8%	Ergotamine: 47% vs. 43.1% Analgesic: 16.5% vs. 37.4%	63% vs. 64%	NR
Gerber 1991 Metoprolol 200 mg vs. propranolol 160 mg Metoprolol=22 Propranolol=19	No differences (ANOVA)	No differences (ANOVA)	No differences (ANOVA)	Ergotamine: No differences (ANOVA)	NR	Percent reduction in duration (hours): No differences (ANOVA)
Schellenberg 2008 Metoprolol 142.5 mg vs. nebivolol 5 mg N=30	61.7% vs. 51.5%	NR	54% vs. 50% Endpoint Means	77% vs. 67%	NR	NR

Abbreviation: NR, not reported.
Headache Index 1: attack frequency x severity x duration
Headache Index 2: attack frequency x severity

Placebo-controlled trials

We found 19 fair-quality, placebo-controlled trials (see Evidence Tables 16 and 17) of atenolol 100 mg,[127] bisoprolol 5 mg or 10 mg,[128] metoprolol slow release (durules) 200 mg,[129, 130 131] pindolol 7.5 mg to 15 mg,[132, 133] propranolol immediate release 80 mg to 240 mg,[134-142] and long-acting propranolol 160 mg.[143, 144] One trial[145] did not report propranolol dosage and will be discussed separately.

All but 2[136, 145] of these trials were conducted outside of the United States A crossover design was used in 12 trials, while the other 6 compared parallel groups. All but 2 trials reported allowing the use of various concomitant medications to abort migraine pain including common analgesics, ergotamines, and narcotics. These trials ranged in duration from 8 to 52 weeks, generally enrolling patients with a 1 to 2 year history of common or classic migraine (Ad Hoc Committee), generally occurring at an average frequency of 3 per week. One trial included only

patients with classic migraine.[130] Patient characteristics reflected the target migraine population, with mean ages in the range of 37 to 39 and gender predominantly female (>75%). Sample sizes ranged from 24 to 259 patients enrolled. Assessment of attack frequency, duration, severity, and use of acute medication variables was made using patient diary card data.

Placebo-controlled trial data was consistent with head-to-head trial data for atenolol 100 mg and slow-release metoprolol (durules) 200 mg, but added no additional evidence that is not reported in the head-to-head trials. Propranolol 80 mg and 160 mg, as discussed above, added information regarding efficacy of bisoprolol and pindolol. An exception was found in 1 of the 10 fair-quality trials of propranolol[137] where a dosage of 120 mg was not significantly superior to placebo in increasing the proportion of patients that had at least a 50% reduction of migraine attacks in the last 4 weeks of treatment (42.3% compared with 30.9%) or in reducing the mean duration of migraine in hours per month (34.4% compared with 13.7%).

Bisoprolol

The results of 1 placebo-controlled trial of 12 week's duration and involving 226 patients[128] indicated that both bisoprolol 5 and 10 mg daily had a significant ($P<0.05$) effect in reducing attack frequency (39% for both bisoprolol doses compared with 22% for placebo). Neither dose of bisoprolol showed any obvious influence on reducing attack duration or severity.

Pindolol

The results of 2 placebo-controlled trials of pindolol 7.5 to 15 mg daily[132, 133] in a total of 58 patients with predominantly common migraine showed no obvious advantage of this nonselective beta blocker in reducing averages per 4 weeks in headache frequency, headache index, or duration of attacks.

Twelve other placebo-controlled trials of beta blockers were found.[121, 122, 146-155] These were rated poor quality due to insufficient detail in reporting randomization and allocation concealment methods, failure to perform efficacy analyses using an intention to treat principle, and rates of attrition ranging from 24% to 48.1%, which were not discussed here.

We found 1 meta-analysis[156] that evaluated the effects of propranolol in 2403 migraine patients across a combination of 53 head-to-head, active- and placebo-controlled trials published through 1991. This review was rated poor quality due to failure to report critical assessment of internal validity and will not be discussed here. We independently assessed and included 3 head-to-head and 12 placebo-controlled trials from this meta-analysis in our report.

Key Question 1h. For adult patients with bleeding esophageal varices, do beta blockers differ in efficacy or effectiveness?

Summary

One small head-to-head trial showed no difference between atenolol and propranolol in rates of non-fatal/fatal rebleeding and all-cause mortality. Results of 1 trial of nadolol and 8 small placebo-controlled trials of immediate release and 2 formulations of extended release propranolol do not provide any additional indirect evidence of the comparative efficacy across beta blockers in these clinical outcomes. The somewhat mixed results across the placebo-controlled trials of propranolol suggest that treatment initiation interval may have an effect on rebleeding rates.

Detailed Assessment

Head-to-head trials

We found 1 head-to-head trial of beta blockers for the treatment of bleeding esophageal varices.[157] This trial compared the efficacy of propranolol 40 to 160 mg daily, a nonselective beta blocker, atenolol 100 mg daily, a selective beta blocker, and placebo in cirrhotic patients. The results of this trial are summarized in Evidence Tables 18 and 19. This trial was rated fair quality. This trial, conducted in Italy, was designed to measure rebleeding and death and had a mean follow-up of 357 days. The patient population enrolled was typical for esophageal variceal bleeding, with a mean age of 53, 80.8% male and 81.9% alcoholic patients. This study also enrolled a small proportion of patients in which the prior hemorrhage was of a gastric erosion (12.8%) or unknown (inconclusive endoscopy) (6.4%) origin. Concomitant use of ranitidine, oral antacids, spironolactone, saluretics, lactulose, and nonabsorbable antibiotics was allowed.

No significant differences were found between propranolol and atenolol at 1 year for percentage of patients with fatal/nonfatal rebleeding episodes (2.4% compared with 3.1%) or total deaths (12% compared with 10%) or deaths due to rebleeding (3.1% compared with 3.1%), liver failure (6.2% compared with 3.1%) or other unrelated causes (3.1% compared with 3.1). Results of a multivariate analysis of parameters hypothesized to have had an influence on rebleeding were also reported. Drinking habits after enrollment was found to have significant effect on rebleeding, in that patients continuing to drink had higher incidences of rebleeding in both the propranolol (drinkers 50% compared with abstainers 0%) and atenolol (drinkers 43% compared with abstainers 27%) groups. Results of the analyses of the other parameters (severity of prior bleed, randomization time, number of bleeds prior to enrollment, treatment center, interval between index bleed, and endoscopy) were insignificant.

Other-controlled trials

We found numerous fair-quality, placebo-controlled trials of nadolol[158] and propranolol[159-166] for the secondary prevention of bleeding esophageal varices secondary to cirrhosis and schistosomiasis.[167] Results are summarized in Evidence Tables 18 and 19. These trials were all conducted outside of the United States, enrolled samples of 12 to 84 patients, and ranged from 3 months to 2 years in duration. Mean ages ranged from 43 to 60 for the cirrhotic and 35.8 for non-cirrhotic patients. Populations were predominantly male with alcoholism as the most common etiology for cirrhosis. Treatment was initiated earlier, within 72 hours of the index bleeding episode, in only 3 of the trials.[159, 162, 166]

Variceal rebleeding rates

As shown in Table 13 below, compared to placebo, no differences in effect on variceal rebleeding rates were shown for immediate release propranolol in 2 early treatment trials. [159, 166] A significant difference between the effects of slow release propranolol and placebo was found in a third early treatment trial (20% compared with 75%; $P<0.05$).[162] For trials of later (≥14 days)[161, 163, 164, 168] and unspecified[160, 169] treatment initiation, atenolol was equivalent to placebo (31% compared with 24%), nadolol was superior (25% compared with 71%; $P<0.05$), results of immediate release propranolol trials were mixed, and long-acting propranolol was superior (2% compared with 20%; $P<0.02$).

Table 13. Variceal rebleeding rates

Trial	Interventions	Sample size	Treatment initiation interval	Rebleeding rates
Early intervention				
Burroughs 1983	Propranolol vs. placebo	N=48	48 hours	46.1% vs. 50%
Villeneuve, 1986	Propranolol vs. placebo	N=79	6-72 hours	76.2% vs. 81.2%
Jensen 1989	Propranolol SR vs. placebo	N=31	24 hours	20% vs. 75%; *P*<0.05
Late intervention				
Colombo 1989	Atenolol vs. placebo	N=94	≥ 15 days	31% vs. 51%
Gatta 1987	Nadolol vs. placebo	N=24	15-40 days	25% vs. 71%; *P*<0.05
Colombo 1989	Propranolol vs. placebo	N=94	≥ 15 days	24% vs. 51%; *P*<0.01
Lebrec 1981a	Propranolol vs. placebo	N=24	10-15 days	0 vs. 41.7%; *P*=0.037
Lebrec 1981b	Propranolol vs. placebo	N=74	2 weeks	15.8% vs. 63.9%; *P*<0.0001
Lo 1993	Propranolol vs. placebo	N=59	Unspecified	19.2% vs. 11.1%
Sheen 1989	Propranolol vs. placebo	N=18	10-14 days	27.8% vs. 55.5%
El Tourabi 1994	Propranolol long-acting vs. placebo	N=82	Unspecified	2% vs. 20%; *P*<0.02

P value based on log-rank test

Deaths due to variceal rebleeding were reported by 7 comparisons to placebo across 6 trials.[159-161, 163, 166, 168] Results are summarized in Table 14 below and in Evidence Tables 18 and 19. In 1 trial of atenolol and 5 trials of propranolol, no differences from placebo in effect on death due to variceal rebleeding were established regardless of treatment initiation interval. In 1 trial of patients with portal hypertension secondary to schistosomiasis,[169] however, significantly more patients (17%) experienced death due to variceal rebleeding on placebo than after late intervention (2 weeks) with propranolol (0%).

Table 14. Death due to variceal rebleeding

Trial	Interventions	Sample size	Treatment initiation Interval	Rates of death due to rebleeding
Early intervention				
Burroughs 1983	Propranolol vs. placebo	N=48	48 hours	15% vs. 9%
Villeneuve 1986	Propranolol vs. placebo	N=79	6-72 hours	12% vs. 19%
Late intervention				
Colombo 1989	Atenolol vs. placebo	N=94	≥ 15 days	3% vs. 10%
Colombo 1989	Propranolol vs. placebo	N=94	≥ 15 days	3% vs. 10%
Lebrec 1981b	Propranolol vs. placebo	N=74	2 weeks	0% vs. 17%; *P*<0.05
Lo 1993	Propranolol vs. placebo	N=59	Unspecified	12% vs. 7%
Sheen 1989	Propranolol vs. placebo	N=18	10-14 days	0% vs. 11%

All-cause mortality

No trial of patients with bleeding esophageal varices involved large enough sample sizes to measure all-cause mortality with sufficient power. Although crude trends suggest numerically smaller numbers of patients taking atenolol, nadolol and propranolol experienced deaths due to any cause in all but 1 trial of propranolol,[159] no significant differences between beta blockers and placebo were found (Table 15).

Table 15. All-cause mortality in patients with bleeding esophageal varices

Trial	Interventions	Sample size	Treatment initiation Interval	All-cause mortality
Early intervention				
Burroughs 1983	Propranolol vs. placebo	N=48	48 hours	15% vs. 23%
Villeneuve 1986	Propranolol vs. placebo	N=79	6-72 hours	45% vs. 38%
Late intervention				
Colombo 1989	Atenolol vs. placebo	N=94	≥ 15 days	9% vs. 23%
Gatta 1987	Nadolol vs. pla	N=24	15-40 days	8% vs. 27%
Colombo 1989	Propranolol vs. placebo	N=94	≥ 15 days	13% vs. 23%
Lo 1993	Propranolol vs. placebo	N=59	Unspecified	31% vs. 33%
El Tourabi 1994	Propranolol long-acting vs. placebo	N=82	Unspecified	7% vs. 18%

Key Question 2. Do beta blocker drugs differ in safety or adverse effects?

Summary

Side effects are common among patients taking beta blockers. In longer-term trials (12 to 58 months) directly comparing beta blockers in patients with hypertension (atenolol compared with bisoprolol compared with propranolol), heart failure (carvedilol compared with metoprolol), bleeding esophageal varices (atenolol compared with propranolol), or atrial fibrillation (bisoprolol compared with carvedilol), a few differences in specific adverse events were noted. But, overall, no particular beta blocker stood out from the others as being consistently associated with a significantly less favorable adverse effect profile.

In everyday practice, weight gain, fatigue, dizziness, and dyspnea are the most common side effects in patients with heart failure. About 1 in 5 patients require discontinuation of the initial beta blocker choice. In a retrospective review of 1 series of 268 patients seen in a United States heart failure clinic, 54% were started on carvedilol and 46% on metoprolol succinate or metoprolol tartrate.[170] Overall, about 1 in 5 patients (51 total) could not tolerate the initial choice of treatment. Forty of the 51 patients who could not tolerate the initial choice were switched to another beta blocker. Twenty-two of these 40 patients tolerated the second choice, with equal proportions tolerating a switch to carvedilol from metoprolol and to metoprolol from carvedilol.

A higher rate of beta blocker intolerance was reported in another trial that enrolled 90 consecutive patients in a heart failure clinic in Denmark.[171] This trial compared bisoprolol and carvedilol and was designed to measure treatment failure rates under conditions that mimic daily

clinical practice. The eligibility criteria were lax and the dosing regimen was flexible. Overall, 40% of patients (35 of 87) did not tolerate beta blocker therapy. Intolerance rates were similar in the bisoprolol and carvedilol groups (39% compared with 40%). This trial had some important methodological flaws, however. The trial used an inadequate method of randomization. Between-group differences at baseline confirm the inadequacy of the randomization method. The bisoprolol group was comprised of a significantly higher proportion of females (31% compared with 17%) and a numerically lower proportion of patients with a left ventricular ejection fraction < 25% (27% compared with 43%). Further, the team that treated and assessed the patients was not blinded to beta blocker assignment and the analysis excluded 3 patients that died prior to completing 2 months of follow-up. Group assignment of the 3 excluded patients was not reported. For these reasons, we rated this trial as poor quality and recommend a cautious interpretation of these potentially unreliable results.

Detailed Assessment

Adverse events of beta blockers most commonly reported in randomized controlled trials include cardiovascular symptoms of bradycardia and hypotension and central nervous system symptoms of dizziness. Relatively low rates of withdrawal due to these adverse events suggest that they were mild to moderate in severity. Other adverse events associated with beta blockers that were less commonly reported include sexual dysfunction and various dermatologic and gastrointestinal symptoms.

Head-to-head safety analyses were provided by 9 trials of patients with hypertension (Evidence Table 1),[5, 8-11, 21, 22 19, 23] 4 trials of patients with angina (Evidence Table 3),[37-39, 172] 5 trials of patients with heart failure (Evidence Table 11),[95, 103, 106, 173, 111] 7 trials of migraine patients (Evidence Table 16),[117-120, 122, 174, 125] 1 trial of patients with bleeding esophageal varices (Evidence Table 18),[157] 3 trials of patients post-myocardial infarction (Evidence Table 7),[53, 55, 56] and 1 trial of patients with atrial fibrillation (Evidence Table 14).[113] Trial characteristics have been described in detail previously and can also be found in the cited evidence tables. In general trials ranged in duration from 4 weeks to 58 months. Sample sizes ranged from 28 to 3029 patients. All but 2[117, 125] of the head-to-head trials in patients with migraine used crossover designs, only reporting results of the combined intervention periods. Furthermore, in a hypertension study examining nebivolol and metoprolol,[23] authors reported "no critical" adverse events were found, but did not supply data nor did they define "critical" adverse events.

Only 1 trial[9] of atenolol 100 mg and pindolol SR 20 mg in 107 essential hypertensive patients was designed specifically for adverse event assessment and was rated good quality. Safety assessment in the remaining 21 head-to-head trials was fair to poor quality due to a lack of descriptive information regarding evaluation techniques. Events analyzed were generally not specified or defined. There was much heterogeneity across the trials in specific adverse events reported. All safety data reported can be found in the evidence tables cited above. The safety data that was most consistently reported (overall adverse event rate, incidence of bradycardia, dizziness, and hypotension, and withdrawals due to adverse events) across a more limited number of trials are summarized in Evidence Table 11.

Overall adverse events

Overall adverse event incidence was reported in 17 head-to-head trials.[5, 8, 10, 21, 22, 38, 39, 106, 118, 119, 122, 123, 172 19, 37, 111, 125] Rates varied across the trials. For example, rates for carvedilol and

metoprolol in a 3-month trial of 368 angina patients were 30% and 25%, respectively, as compared to 96% and 94% in a 58 month trial of 3029 patients with heart failure. No significant differences between the beta blocker comparisons were found, with 1 exception. In one 8-week trial of 40 angina patients,[38] adverse events were more frequent in the propranolol group (94.4%) than in the pindolol group (17.4%; $P<0.0001$). Specific adverse events seen more frequently in the propranolol group include fatigue (44.4% compared with 0; $P<0.0005$) and mild hypotension (27.8% compared with 0; $P=0.0114$). The difference in safety favoring pindolol should be interpreted with caution due to variation between groups in illness severity at baseline. The mean 2-week angina attack rate was higher in the propranolol group during run-in [28.5 (95% CI, 26.4 to 30.6) compared with 18.4 (95% CI, 17.4 to19.4)]. This suggests problems with the randomization methods.

Withdrawals due to adverse events were reported by 13 head-to-head trials.[5, 8, 11, 21, 22, 95, 113, 122, 123, 157 37, 111, 125] No significant differences were found in any of the comparisons.

Specific adverse events

Bradycardia

Rates of bradycardia were reported in short-term hypertension trials, in longer-term heart failure trials, a 2-month angina trial,[3, 6, 17, 18, 937, 106, 111] and in a long-term trial for treatment of migraine.[125] Overall, no significant differences between beta blockers were reported, with the exception of the 1 trial, which found a difference of bradycardia/electrocardiogram pauses >2.5 seconds for carvedilol 3 (9%) and 1 (3%) for nebivolol.[111]

Dizziness

Eight head-to-head trials reported dizziness incidence.[21, 56, 103, 111, 120, 122, 123, 172] All but 1 reported no significant differences between beta blockers.[103] Carvedilol was associated with higher rates of dizziness than metoprolol in a 44-month trial of 122 patients with heart failure (14.7% compared with 1.3%; $P=0.0046$).[103] This significant difference was not seen in another shorter trial [3 months in 368 patients with angina (4.8% compared with 5.0%)],[172] nor was there a significant difference in rates of dizziness in a head-to-head trial of carvedilol compared with atenolol in patients with recent myocardial infarction (36.4% compared with 27.2%; $P=0.131$).[56] Reasons for this inconsistency may include differences in definition of dizziness and evaluation techniques between the 2 trials. This assumption cannot be verified, however, as the methods were not provided. Indirect comparison of the inconsistent head-to-head trial results to available fair- to good-quality placebo-controlled trials safety data did not offer any additional information as dizziness rates in metoprolol trials were not reported.

Hypotension

Rates of hypotension were similar for carvedilol and metoprolol across 2 longer-term trials of patients with heart failure.[103, 106] Only 2.7% of patients from either treatment group experienced hypotension in the smaller (N=122), 44-month trial. After 58 months in the COMET trial (N=3029), 14% of patients taking carvedilol and 11% of patients taking metoprolol had hypotensive events. A study of left ventricular dysfunction after acute myocardial infarction (carvedilol compared with metoprolol), reported incidence of hypotension leading to withdrawal, but did not report the incidence for each study arm.[55] In a 6-month heart failure study, no differences were found between nebivolol and carvedilol.[111] A 30-week trial of treatment for migraine found similar rates between metoprolol compared with nebivolol.[125]

New-onset diabetes. Direct comparisons between beta blockers on risk of new-onset diabetes were only available from 1 retrospective analysis of data from the COMET trial, which compared metoprolol tartrate and carvedilol in adults with heart failure.[173] New-onset diabetes was identified post-hoc among a cohort of 2298 patients without diabetes at baseline. The endpoint of new-onset diabetes was based on patient reporting and notes in hospital files and was considered present when there was documentation of a diagnosis of diabetes mellitus or diabetic coma, patients started antidiabetic treatment during the trial, or if patients had 2 or more random blood glucose readings above 11.1 mmol/l. The main finding of this analysis was that more patients receiving metoprolol tartrate developed new-onset diabetes than those receiving carvedilol (10.1% compared with 8.7%; hazard ratio, 0.78; 95% CI, 0.61 to 0.997). Although noteworthy, this finding should be interpreted with caution, keeping in mind that it is based on a post-hoc analysis and relies on a clinical, rather than guideline-based definition of diabetes.

Otherwise the only evidence we found came from a meta-analysis that pooled data from 12 trials (94 492 patients) of beta blockers compared with placebo, diuretics, ACE inhibitors, and calcium channel blockers which generated combined estimates of risk of new-onset of diabetes for each beta blocker.[175] Pooled estimates based on a random effects model found that when compared to other comparators (placebo, diuretics, ACE inhibitors, calcium channel blockers) there is an increased the risk of new-onset DM for atenolol (pooled RR, 1.30; 95% CI, 1.11 to 1.52) and metoprolol (pooled RR, 1.34; 95% CI, 1.04 to 1.73), but not for propranolol (pooled RR, 0.77; 95% CI, 0.37 to 1.60).[175] It should be noted that had a fixed effects model been used, only atenolol would have resulted in a statistically significant finding. The results of this meta-analysis should be interpreted with caution, as it did not evaluate the potential effects of variation among trials in internal validity factors.

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one beta blocker is more effective or associated with fewer adverse effects?

Summary

There is no data that suggests that any beta blocker is superior in any subgroup of patients based on demographics, other medications, or comorbidities.

Detailed Assessment

Head-to-head trials

None of the 14 fair-quality head-to-head trials included in our efficacy analyses across all indications provided any subgroup analyses that differentiated one beta blocker from another based on demographics, concomitant medications, or comorbidities.

Placebo-controlled trials

We are aware of 1 placebo-controlled trial that examined the efficacy and tolerability of nebivolol in hypertensive African American patients.[176] This study, however, did not meet our inclusion criteria as its focus was on blood pressure lowering and it did not report long-term health outcomes.

Meta-analyses

A recent systematic review conducted by the Cochrane Collaboration compared beta blockers to placebo in reducing the risk of severe hypertension and need for additional antihypertensives during pregnancy.[177] Studies of acebutolol, atenolol, metoprolol, pindolol, and propranolol were included in this review, but no evidence of comparative effectiveness is provided. Rather, the focus of the review is on comparing beta blockers as a class to placebo. The review found that there was insufficient evidence to draw conclusions about the effects of beta blockers on perinatal mortality or preterm birth.

The Beta Blocker Pooling Project[178] analyzed mortality in post-infarction patients relative to subgroup risk factors from trials of propranolol,[50, 67, 179] pindolol,[67] and other beta blockers not available in the United States. This analysis found that none of the age, gender, heart failure, or prior diabetes mellitus baseline characteristics interacted significantly with the effect on mortality. This analysis also does not offer any meaningful information about the comparative efficacy of beta blockers in these subgroups.

A 2003 meta-analysis[180] analyzed the effects of bisoprolol (CIBIS-II), carvedilol (US Carvedilol, COPERNICUS), and controlled release metoprolol (MERIT-HF) on mortality in heart failure patients stratified by gender, race, and diabetics. Results are summarized in Table 16 below and suggest that beta blockers are equally effective in reducing mortality in subpopulations stratified by gender and race.

Observational analyses

A 12-month observational study comparing the tolerability of carvedilol (target dose 25 mg daily) in patients (ages ≥70) with and without diabetes mellitus found the rates of withdrawal due to adverse events (bradycardia, bronchospasm) were low in both the diabetes and nondiabetes subgroups (6% compared with 3%).[181]

Table 16. Results of Shekelle (2003) meta-analysis by gender, race, and diabetics

Group of interest	Number of studies (patients in group of interest)	RR for mortality for group of interest (95% CI)	RR for mortality for other subjects (95% CI)
Women	4 (2134)	0.63 (0.44−0.91)	0.66 (0.59−0.75)
Blacks	3 (545)	0.67 (0.39−1.16)	0.63 (0.52−0.77)
Diabetics	3 (1883)	0.77 (0.61−0.96)	0.65 (0.57−0.74)

Subgroup analyses and prescribing information

Atenolol

The SHEP trial assessed the use of chlorthalidone compared with placebo in controlling hypertension. Once desired blood pressure was reached, participants were further randomized to receive atenolol or reserpine. A subgroup analysis of long-term data (median 14.3 years) found that adding atenolol to chlorthalidone did not significantly affect mortality relative to placebo in diabetic patients, including both patients who were diabetic at baseline and those who developed diabetes during time on trial.[182]

Carvedilol

Prescribing information for carvedilol (http://us.gsk.com/products/assets/us_coreg.pdf) reports that effects on efficacy and adverse events were equivalent regardless of age (48% were ≥ 65 years; 11% were ≥75 years) in patients with left ventricular dysfunction following myocardial infarction in the CAPRICORN trial.[61] We found no other source of publication of results from this subgroup analysis.

A number of additional meta-analyses have been published that evaluate the effects of carvedilol in subgroups of patients based on demographics and/or comorbidities. The United States Carvedilol Heart Failure Study Group published an analysis[183] of the pooled results from a stratified set of 3 fair-quality and 1 poor-quality concurrently conducted protocols,[84-87] discussed in detail above, that showed no significant interaction between race and carvedilol treatment in patients with mild to moderate heart failure. More recent analyses from the COPERNICUS trial[89] show that carvedilol had similar effects regardless of age and gender in patients with *severe* heart failure.

The most recent and largest manufacturer-funded meta-analysis (N=5757) of published and unpublished data from 7 clinical trials focused on evaluating the effects of carvedilol in patients with heart failure, with and without comorbid diabetes.[184] Consistent with previous analyses, the main findings confirmed that similar reductions in risk of all-cause mortality were seen in heart failure patients, regardless of diabetes status. The relative risk reduction in the subgroup of patients with diabetes was 28% (95% CI, 3 to 46) and was 37% (95% CI, 22 to 48) in the non-diabetic patients.

Labetolol

Product information for labetalol (http://www.prometheuslabs.com/pi/TrandateTab.pdf) suggests that required maintenance doses may be lower in geriatric patients due to a reduced rate of elimination. However, we did not find any evidence of differential efficacy of labetalol relative to age.

Metoprolol

A fair-quality review[185] that pooled results from 5 placebo-controlled trials of metoprolol (Amsterdam, Belfast, Goteborg, Stockholm, Lopressor Intervention Trial) found that neither age nor gender had a significant influence on mortality. When considered individually, results from the Goteborg Metoprolol Trial[186] show a nonsignificant trend that patients aged 65 to 74 years had a more marked reduction in mortality at 3 months post-myocardial infarction (45%) than did all patients aged 40 to 74 (36%). Results from the MERIT-HF trial also reported that neither age nor gender had any influence on the effects of metoprolol CR in patients with mild to moderate heart failure.

A subgroup analysis of the MERIT-HF trial evaluated the influence of comorbid diabetes on the effects of metoprolol CR.[187] This analysis found higher rates of all-cause mortality in the placebo group when compared to metoprolol (12.7% compared with 10.1% per patient year; risk reduction, 18%; 95% CI, +44 to −19). Metoprolol CR also significantly reduced risks of hospitalizations for worsening heart failure (including those patients identified as having severe heart failure) regardless of diabetic status.

Propranolol

The fair-quality, placebo-controlled Beta Blocker Heart Attack Trial[67] comprised of 3837 patients found that the protective of propranolol on mortality 25 months (average follow-up) following myocardial infarction was equivalent regardless of age or gender.

Nebivolol

Subgroup analysis of the SENIORS trial found no significant differences in the effect of nebivolol on subpopulations of gender, ejection fraction, age, diabetes, and prior myocardial infarction.[72]

SUMMARY

Results of this review are summarized below in Table 17 by key question and in Table 18 by beta blocker.

Table 17. Strength of the evidence

	Strength of evidence[a]	Conclusion
Key Question 1. Comparative efficacy		
a. Hypertension	Overall grade: Poor	No head-to-head trials of long-term (≥6 months) health or quality-of-life outcomes. Reliable indirect comparisons cannot be made by evidence from 3 long-term placebo-controlled trials of propranolol and atenolol.
b. Angina	Overall grade: Fair	No significant differences in 6 head-to-head trials of carvedilol compared with metoprolol, pindolol compared with propranolol, betaxolol, and propranolol, and betaxolol compared with metoprolol in patients with stable angina. Atenolol equivalent to bisoprolol in patients with chronic stable angina and chronic obstructive pulmonary disease. Atenolol equivalent to labetalol when added to chlorthalidone in patients with chronic stable angina. One short-term, placebo-controlled trial of propranolol did not add any meaningful evidence of comparative efficacy in the above parameters.
c. Status-post coronary artery bypass graft	Overall grade: Poor	Metoprolol did not benefit mortality or ischemic events in a longer-term (>7 days) placebo-controlled trial (MACB).
d. Recent myocardial infarction	Overall grade: Fair-good	One fair-quality head-to-head trial found no differences in mortality after 1 year between atenolol and propranolol, but this was a relatively small trial; 1 fair-quality head-to-head trial found no differences in time to serious cardiovascular events between carvedilol and atenolol. One fair-quality trial of carvedilol and metoprolol tartrate found no differences in time to first cardiac adverse event or all-cause mortality. Similar mortality reductions reported for acebutolol,

	Strength of evidence[a]	Conclusion
		metoprolol tartrate, propranolol, and timolol in placebo-controlled trials of patients following myocardial infarction without other complications. Similar reductions in sudden death and reinfarction were reported for metoprolol tartrate and timolol and in sudden death for propranolol. No studies of carvedilol phosphate (extended-release carvedilol) in patients with recent myocardial infarction were identified. Carvedilol reduced mortality and reinfarction in 1 placebo-controlled trial of patients with a mean left ventricular ejection fraction of <32.7% (CAPRICORN). Four systematic reviews were not designed to assess comparative efficacy.
e. Heart failure	Health outcomes in head-to-head trials: Fair	Carvedilol more effective than metoprolol tartrate in reducing total mortality in COMET in patients with mild to moderate heart failure.
	Symptoms in head-to-head trials: Good	Carvedilol equivalent to metoprolol tartrate in improving symptoms (quality of life; NYHA) and exercise capacity in 4 head-to-head trials. Improvements in NYHA function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol.
	Placebo-controlled trials in mild-moderate heart failure: Good	Metoprolol succinate reduced total mortality, sudden death, and death due to progressive heart failure and improved quality of life (MERIT-HF). Carvedilol reduced total mortality, sudden death, and death due to pump failure (MOCHA). Nebivolol significantly reduced the composite outcome of all-cause mortality or cardiovascular hospital admission, but had nonsignificant effects each component as individual secondary outcomes. Bisoprolol reduced total mortality and sudden death. No studies of carvedilol phosphate (extended-release carvedilol) in patients with mild to moderate heart failure were identified.
	Placebo-controlled trials in severe heart failure: Fair for carvedilol and Fair for metoprolol succinate	Carvedilol reduced mortality and the combined endpoint of mortality and hospitalizations in a prospective trial. A post-hoc subgroup analysis of MERIT-HF suggests that metoprolol succinate is similarly effective in comparable patients. No studies of carvedilol phosphate (extended-release carvedilol) in patients with severe heart failure were identified.
f. Atrial arrhythmia	Overall grade: Fair	Bisoprolol equivalent to carvedilol in preventing relapse of atrial fibrillation in a head-to-head trial. Metoprolol succinate reduced incidence of atrial arrhythmia/fibrillation in a placebo-controlled trial. Carvedilol reduced 24-hour ventricular rate in patients with atrial fibrillation and heart failure in 1 placebo-controlled trial. These placebo-controlled trials did not offer

	Strength of evidence[a]	Conclusion
		comparative data.
g. Migraine	Overall grade: Fair	Atenolol, slow release metoprolol, immediate release metoprolol, and timolol were all similar to propranolol in their effects on pain outcomes and acute medication use in 5 head-to-head trials. No significant differences were found between nebivolol and metoprolol on frequency of migraine attacks and severity.
h. Bleeding esophageal varices	Overall grade: Poor	Results of 1 head-to-head trial of atenolol and propranolol, 1 placebo-controlled trial of nadolol, and 6 placebo-controlled trials of immediate release and 2 formulations of extended release propranolol, all fair quality, didn't clearly differentiate one beta blocker from another.
Key Question 2. Adverse effects		
Hypertension, stable angina, heart failure, atrial arrhythmia, migraine, bleeding esophageal varices, previous myocardial infarction	Overall grade: Fair	A few differences in specific adverse event rates were noted across longer-term trials directly comparing one beta blocker to another. Overall, no particular beta blocker stood out from the others as being consistently associated with a less favorable adverse effect profile.
Key Question 3. Subgroups		
a. Demographics (age, gender, race)	Overall grade: Fair	Evidence showed that age, gender, and race did not impact the effectiveness of carvedilol, immediate and controlled release metoprolol, and propranolol. There was insufficient evidence on the effect of beta blockers on perinatal mortality or preterm birth based on 1 systematic review.
b. High risk populations	Overall grade: Fair	*Heart failure.* Subgroup analyses of placebo-controlled trials showed that a history of myocardial infarction may reduce the protective effect of bisoprolol on mortality (CIBIS). No risk factor was found to confound the protective effect of carvedilol (COPERNICUS) or controlled release metoprolol (MERIT-HF) on mortality. *Post-myocardial infarction.* The MIAMI trial found that metoprolol had the greatest protective effect on mortality in patients with numerous risk factors. The BHAT trial found no variation in propranolol's protective effect on total mortality based on history of heart failure. *Diabetes.* Subgroup analysis of the SHEP trial found that the addition of atenolol to chlorthalidone did not significantly affect mortality relative to placebo. Metoprolol use reduced all-cause mortality and hospitalizations relative to placebo in a subgroup analysis of the MERIT-HF trial.

Abbreviations: NYHA, New York Heart Association classification.
[a] Quality of evidence ratings based on criteria developed by the Third United States Preventive Services Task Force.

Table 18. Summary of comparative efficacy

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
Acebutolol								Effective in reducing all-cause mortality
Atenolol		Equivalent to bisoprolol in patients with comorbid chronic obstructive pulmonary disease in reducing attack frequency; Equivalent to labetalol in reducing nitrate use when both combined with chlorthalidone				Equivalent to propranolol in decreasing migraine days	Equivalent to propranolol for reducing all-cause mortality and deaths due to rebleeding	Equivalent to carvedilol in time to serious cardiovascular event post-myocardial infarction
Betaxolol		Equivalent to propranolol; Equivalent to metoprolol tartrate in chest pain episodes; Equivalent to metoprolol tartrate in 5 of 6 quality-of-life dimensions						
Bisoprolol		Equivalent to atenolol in patients with comorbid chronic obstructive pulmonary disease		More effective than placebo in all-cause mortality and sudden death	Equivalent to carvedilol in preventing relapse of atrial fibrillation			
Carteolol								

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
Carvedilol		Equivalent to metoprolol in increasing exercise tolerance		More effective than metoprolol tartrate in all-cause mortality, cardiovascular events, unstable angina in mild-moderate HF (COMET); Equivalent to metoprolol tartrate in improving symptoms and exercise parameters; Improvements in NYHA function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol; More effective than placebo in total mortality, sudden death, death due to pump failure (MOCHA); More effective than placebo in all-cause mortality in patients with *severe* heart failure (COPERNICUS)	Equivalent to bisoprolol in preventing relapse of atrial fibrillation; More effective than placebo in reducing 24-hour ventricular rate in patients with atrial fibrillation and heart failure			Effective in reducing all-cause mortality in patients with left ventricular dysfunction post-myocardial infarction; Equivalent to atenolol in time to serious cardiovascular event post-myocardial infarction; Equivalent to metoprolol tartrate in all-cause mortality, cardiovascular death, nonfatal reinfarction
Carvedilol phosphate								
Labetalol		Equivalent to atenolol in reducing nitrate use when both combined with chlorthalidone						
Metoprolol tartrate		Equivalent to carvedilol in increasing exercise tolerance; Equivalent to betaxolol in chest pain episodes; Equivalent to betaxolol in 5 of 6 quality-of-life	Equivalent to placebo for mortality	Less effective than carvedilol in reducing total mortality, cardiovascular events, unstable angina (COMET); Equivalent to carvedilol in improving symptoms/ exercise parameters		Equivalent to propranolol in all parameters measured; Equivalent to nebivolol in		Effective in reducing total mortality, sudden death, and reinfarction; Equivalent to carvedilol in all-

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
		dimensions				all parameters measured		cause mortality, cardiovascular death, nonfatal reinfarction
Metoprolol succinate	Less effective than nebivolol in quality of sleep; Less effective than nebivolol in erectile function			More effective than placebo in reducing total mortality, sudden death, death due to progressive heart failure and improved quality of life in mild-moderate heart failure (MERIT-HF); More effective than placebo in reducing mortality in severe heart failure (post-hoc, subgroup analysis of MERIT-HF)	CR/XL formulation more effective than placebo in lowering atrial fibrillation/flutter relapse rates			
Nadolol							More effective than placebo in effect on rebleeding rates	
Penbutolol								
Pindolol		Equivalent to propranolol in increasing exercise tolerance, decreasing attack frequency						Equivalent to placebo in all-cause mortality
Propranolol	Equivalent to placebo in mortality, cardiovascular events, quality of life	Equivalent to betaxolol and pindolol				Equivalent to atenolol, metoprolol tartrate, metoprolol succinate, and timolol	Equivalent to atenolol for reducing all-cause mortality and deaths due to rebleeding	Effective in reducing total mortality and sudden death

Drug	Hypertension	Angina	After coronary artery bypass graft	Heart failure	Atrial arrhythmias	Migraine	Bleeding esophageal varices	Myocardial infarction
Timolol						Equivalent to propranolol		Effective in reducing total mortality, sudden death, and reinfarction
Nebivolol	More effective than metoprolol succinate in quality of sleep More effective than metoprolol succinate in erectile function			Equivalent to placebo in all-cause mortality and cardiovascular hospital admission as individual secondary outcomes; More effective than placebo as composite outcome; Equivalent to placebo in NYHA, time to first hospitalization, quality of life, survival rate; Equivalent to placebo in exercise test; Improvements in NYHA function class and on walking distance (6-minute walk test) were similarly slight for both carvedilol and nebivolol		Equivalent to metoprolol in all parameters measured		

Abbreviations: NYHA, New York Heart Association classification.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategies for Update 4

First searches: November 2008

Database: Ovid MEDLINE(R) <1996 to October Week 5 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (140)
2 atenolol.mp. or exp Atenolol/ (2416)
3 betaxolol.mp. or exp Betaxolol/ (384)
4 bisoprolol.mp. or exp Bisoprolol/ (567)
5 carteolol.mp. or exp Carteolol/ (143)
6 carvedilol.mp. (1594)
7 labetolol.mp. or exp Labetalol/ (224)
8 metoprolol.mp. or exp Metoprolol/ (2138)
9 nadolol.mp. or exp Nadolol/ (329)
10 exp Penbutolol/ or penbutolol.mp. (36)
11 pindolol.mp. or exp Pindolol/ (828)
12 propranolol.mp. or exp Propranolol/ (6273)
13 timolol.mp. or exp Timolol/ (1317)
14 nebivolol.mp. (332)
15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (14046)
16 limit 15 to (english language and humans and yr="2007 - 2008") (934)
17 limit 16 to (clinical trial, all or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial) (369)
18 observational stud$.mp. (16111)
19 exp Cohort Studies/ or cohort$.mp. (461575)
20 exp Retrospective Studies/ or retrospective$.mp. (248093)
21 18 or 19 or 20 (650615)
22 21 and 16 (192)
23 22 or 17 (436)
24 from 23 keep 1-436 (436)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (14)
2 atenolol.mp. or exp Atenolol/ (46)
3 betaxolol.mp. or exp Betaxolol/ (6)
4 bisoprolol.mp. or exp Bisoprolol/ (23)
5 carteolol.mp. or exp Carteolol/ (0)
6 carvedilol.mp. (24)
7 labetalol.mp. or exp Labetalol/ (12)
8 metoprolol.mp. or exp Metoprolol/ (45)
9 nadolol.mp. or exp Nadolol/ (6)

10 penbutolol.mp. or exp Penbutolol/ (2)
11 nebivolol.mp. (9)
12 propranolol.mp. or exp propranolol/ (40)
13 pindolol.mp. or exp Pindolol/ (21)
14 timolol.mp. or exp timolol/ (15)
15 6 or 11 or 3 or 7 or 9 or 12 or 2 or 14 or 8 or 1 or 4 or 13 or 10 or 5 (106)
16 hypertension.mp. [mp=title, full text, keywords] (374)
17 angina.mp. [mp=title, full text, keywords] (146)
18 coronary artery bypass graft.mp. [mp=title, full text, keywords] (68)
19 myocardial infarction.mp. [mp=title, full text, keywords] (404)
20 heart failure.mp. [mp=title, full text, keywords] (212)
21 atrial arrhythmia.mp. [mp=title, full text, keywords] (0)
22 bleeding esophageal varices.mp. [mp=title, full text, keywords] (2)
23 varices.mp. [mp=title, full text, keywords] (23)
24 migraine.mp. (57)
25 21 or 17 or 20 or 22 or 18 or 24 or 16 or 19 or 23 (902)
26 25 and 15 (82)
27 (2007$ or 2008$).do. (633)
28 27 and 26 (2)
29 from 28 keep 1-2 (2)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (15)
2 atenolol.mp. or exp Atenolol/ (34)
3 betaxolol.mp. or exp Betaxolol/ (13)
4 bisoprolol.mp. or exp Bisoprolol/ (16)
5 carteolol.mp. or exp Carteolol/ (9)
6 carvedilol.mp. (12)
7 labetalol.mp. or exp Labetalol/ (20)
8 metoprolol.mp. or exp Metoprolol/ (34)
9 nadolol.mp. or exp Nadolol/ (20)
10 penbutolol.mp. or exp Penbutolol/ (7)
11 nebivolol.mp. (4)
12 propranolol.mp. or exp propranolol/ (58)
13 pindolol.mp. or exp Pindolol/ (22)
14 timolol.mp. or exp timolol/ (22)
15 6 or 11 or 3 or 7 or 9 or 12 or 2 or 14 or 8 or 1 or 4 or 13 or 10 or 5 (87)
16 hypertension.mp. [mp=title, abstract, full text, keywords, caption text] (728)
17 angina.mp. [mp=title, abstract, full text, keywords, caption text] (182)
18 coronary artery bypass graft.mp. [mp=title, abstract, full text, keywords, caption text] (29)
19 myocardial infarction.mp. [mp=title, abstract, full text, keywords, caption text] (393)
20 heart failure.mp. [mp=title, abstract, full text, keywords, caption text] (283)
21 atrial arrhythmia.mp. [mp=title, abstract, full text, keywords, caption text] (2)

22 bleeding esophageal varices.mp. [mp=title, abstract, full text, keywords, caption text] (3)
23 varices.mp. [mp=title, abstract, full text, keywords, caption text] (35)
24 migraine.mp. (74)
25 21 or 17 or 20 or 22 or 18 or 24 or 16 or 19 or 23 (1125)
26 25 and 15 (59)
27 from 26 keep 1-59 (59)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (337)
2 atenolol.mp. or exp Atenolol/ (2468)
3 betaxolol.mp. or exp Betaxolol/ (310)
4 bisoprolol.mp. or exp Bisoprolol/ (368)
5 carteolol.mp. or exp Carteolol/ (136)
6 carvedilol.mp. (502)
7 labetalol.mp. or exp Labetalol/ (503)
8 metoprolol.mp. or exp Metoprolol/ (2060)
9 nadolol.mp. or exp Nadolol/ (288)
10 penbutolol.mp. or exp Penbutolol/ (107)
11 nebivolol.mp. (113)
12 propranolol.mp. or exp propranolol/ (3942)
13 pindolol.mp. or exp Pindolol/ (785)
14 timolol.mp. or exp timolol/ (1240)
15 6 or 11 or 3 or 7 or 9 or 12 or 2 or 14 or 8 or 1 or 4 or 13 or 10 or 5 (10652)
16 hypertension.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (20388)
17 angina.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6532)
18 coronary artery bypass graft.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1101)
19 myocardial infarction.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (10149)
20 heart failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6445)
21 atrial arrhythmia.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (42)
22 bleeding esophageal varices.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (170)
23 varices.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1166)
24 migraine.mp. (2099)
25 21 or 17 or 20 or 22 or 18 or 24 or 16 or 19 or 23 (42595)
26 25 and 15 (6356)
27 limit 26 to yr="2007 - 2008" (153)

28 from 27 keep 1-153 (153)

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Second searches: March 2009

Database: Ovid MEDLINE(R) <1996 to February Week 1 2009>
Search Strategy:
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1 acebutolol.mp. or exp Acebutolol/ (142)
2 atenolol.mp. or exp Atenolol/ (2451)
3 betaxolol.mp. or exp Betaxolol/ (386)
4 bisoprolol.mp. or exp Bisoprolol/ (581)
5 carvedilol.mp. (1635)
6 labetolol.mp. or exp Labetalol/ (229)
7 metoprolol.mp. or exp Metoprolol/ (2186)
8 nadolol.mp. or exp Nadolol/ (337)
9 exp Penbutolol/ or penbutolol.mp. (36)
10 pindolol.mp. or exp Pindolol/ (831)
11 propranolol.mp. or exp Propranolol/ (6355)
12 timolol.mp. or exp Timolol/ (1347)
13 nebivolol.mp. (347)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (14221)
15 limit 14 to (english language and humans) (7080)
16 (20081$ or 2009$).ed. (229157)
17 16 and 15 (178)
18 limit 17 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or randomized controlled trial) (63)
19 observational stud$.mp. (16813)
20 exp Cohort Studies/ or cohort.mp. (469080)
21 exp Retrospective Studies/ or retrospective$.mp. (256019)
22 21 or 19 or 20 (664341)
23 22 and 17 (38)
24 18 or 23 (79)
25 from 24 keep 1-79 (79)

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Appendix C. Quality assessment for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination criteria. This appendix lists questions that are posed for each included study in order to assess study quality. These quality-assessment questions differ for systematic reviews, controlled trials, and nonrandomized trials.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good," "fair," or "poor." Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria that may indicate the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies?
   A good-quality review should focus on a well-defined question or set of questions. These questions ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 components of study design: indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?
   If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, dates, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only Medline was searched for a review looking at proton pump inhibitors then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?
   A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, how randomization was done, whether outcome

assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use a published checklist or scale or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?
   The review should demonstrate that the studies included are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample sizes, patient characteristics, interventions, settings, outcome measures, follow-up periods, drop-out rates (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?
   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis). For reviews that provide a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual studies should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of internal validity

1. Was the assignment to treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random-numbers table

   Inferior approaches to sequence generation:
   - Use of alternation, case record number, birth date, or day of week

   Not reported

2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization:
   - Centralized or pharmacy-controlled randomization
   - Serially numbered identical containers
   - On-site computer-based system with a randomization sequence that is not readable until allocation

   Inferior approaches to concealment of randomization:
   - Use of alternation, case record number, birth date, or day of week

Open random-numbers list
Serially numbered envelopes (Even sealed opaque envelopes can be subject to manipulation.)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup (giving numbers for each group)?

Assessment of external validity (applicability)

1. How similar is the population to the population to which the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.

Nonrandomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion unbiased? In other words, was any group of patients systematically excluded?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate with reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of external validity

1. Was the description of the population adequate?

2. How similar is the population to the population to which the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

References:

Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews.* CRD Report Number 4. 2nd ed. University of York, UK; 2001.

Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* Apr 2001;20(3 Suppl):21-35.

Appendix D. Excluded studies

The following full-text publications were considered for inclusion but failed to meet the criteria for this report.

Part I. Excluded for Update 4

Publication	Reason for Exclusion
Abalos, Duley, Steyn, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2008;3:3.	Wrong study design
Abraham WT, Massie BM, Lukas MA, et al. Tolerability, safety, and efficacy of beta-blockade in black patients with heart failure in the community setting: insights from a large prospective beta-blocker registry. *Congestive Heart Failure.* Jan-Feb 2007;13(1):16-21.	Wrong outcome
Ahrens W, Hagemeier C, Muhlbauer B, et al. Hospitalization rates of generic metoprolol compared with the original beta-blocker in an epidemiological database study. *Pharmacoepidemiology & Drug Safety.* Dec 2007;16(12):1298-307.	Wrong outcome
Aneja P, Srinivas A and Biswas AD. Comparative clinical study of the efficacy and safety of a S-metoprolol ER tablet versus a racemate metoprolol ER tablet in patients with chronic stable angina. *International Journal of Clinical Pharmacology & Therapeutics.* May 2007;45(5):253-8.	Wrong study design
Aursnes I, Osnes J-B, Tvete IF, et al. Does atenolol differ from other beta-adrenergic blockers? *BMC Clinical Pharmacology.* 2007;7:4.	Wrong publication type
Brehm BR, Wolf SC, Gorner S, et al. Effect of nebivolol on left ventricular function in patients with chronic heart failure: a pilot study. *European Journal of Heart Failure.* Dec 2002;4(6):757-63.	Wrong study design
Capucci A, Botto G, Molon G, et al. The Drug And Pace Health cliNical Evaluation (DAPHNE) study: a randomized trial comparing sotalol versus beta-blockers to treat symptomatic atrial fibrillation in patients with brady-tachycardia syndrome implanted with an antitachycardia pacemaker. *American Heart Journal.* Aug 2008;156(2):373.e1-8.	Wrong study design
Coca A, Messerli FH, Benetos A, et al. Predicting stroke risk in hypertensive patients with coronary artery disease: a report from the INVEST. *Stroke.* Feb 2008;39(2):343-8.	Wrong drug
Dahlof B, Devereux RB, Kjeldsen SE, et al. Atenolol as a comparator in outcome trials in hypertension: a correct choice in the past, but not for the future? *Blood Pressure.* 2007;16(1):6-12.	Wrong publication type
Dart AM, Cameron JD, Gatzka CD, et al. Similar effects of treatment on central and brachial blood pressures in older hypertensive subjects in the Second Australian National Blood Pressure Trial. *Hypertension.* Jun 2007;49(6):1242-7.	Wrong drug
DasGupta P, Jain D, Lahiri A, et al. Long term efficacy and safety of carvedilol, a new beta-blocking agent with vasodilating properties, in patients with chronic ischaemic heart disease. *Drug Invest.* 1992;4(3):263-272.	Wrong study design

Publication	Reason for Exclusion
Delea TE, Taneja C, Moynahan A, et al. Valsartan versus lisinopril or extended-release metoprolol in preventing cardiovascular and renal events in patients with hypertension. *American Journal of Health-System Pharmacy.* Jun 1 2007;64(11):1187-96.	Wrong outcome
Dobre D, Haaijer-Ruskamp FM, Voors AA, et al. beta-Adrenoceptor antagonists in elderly patients with heart failure: a critical review of their efficacy and tolerability. *Drugs & Aging.* 2007;24(12):1031-44.	Wrong publication type
Dungen H-D, Apostolovic S, Inkrot S, et al. Bisoprolol vs. carvedilol in elderly patients with heart failure: rationale and design of the CIBIS-ELD trial. *Clinical Research in Cardiology.* Sep 2008;97(9):578-86.	Wrong publication type
Earl GL, Verbos-Kazanas MA, Fitzpatrick JM, et al. Tolerability of beta-blockers in outpatients with refractory heart failure who were receiving continuous milrinone. *Pharmacotherapy.* May 2007;27(5):697-706.	Wrong outcome
Garcia-Monco JC, Foncea N, Bilbao A, et al. Impact of preventive therapy with nadolol and topiramate on the quality of life of migraine patients. *Cephalalgia.* Aug 2007;27(8):920-8.	Wrong study design
Go AS, Yang J, Gurwitz JH, et al. Comparative effectiveness of beta-adrenergic antagonists (atenolol, metoprolol tartrate, carvedilol) on the risk of rehospitalization in adults with heart failure. *American Journal of Cardiology.* Aug 15 2007;100(4):690-6.	Wrong study design
Kataoka M, Satoh T, Yoshikawa T, et al. Comparison of the effects of carvedilol and metoprolol on exercise ventilatory efficiency in patients with congestive heart failure. *Circulation Journal.* Mar 2008;72(3):358-63.	Wrong outcome
Krum H, Sackner-Bernstein J and al. e. Double-blind, palcebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation.* 1995;92(6):1499-1506.	Wrong study design
Rector TS, Anand IS, Nelson DB, et al. Carvedilol versus controlled-release metoprolol for elderly veterans with heart failure. *Journal of the American Geriatrics Society.* Jun 2008;56(6):1021-7.	Wrong outcome
Rinfret S, Abrahamowicz M, Tu J, et al. A population-based analysis of the class effect of beta-blockers after myocardial infarction. *American Heart Journal.* Feb 2007;153(2):224-30.	Wrong outcome
Taylor FR. Weight change associated with the use of migraine-preventive medications. *Clinical Therapeutics.* Jun 2008;30(6):1069-80.	Wrong publication type
Uhlir O, Dvorak I, Gregor P, et al. Nebivolol in the treatment of cardiac failure: a double-blind controlled clinical trial. *Journal of Cardiac Failure.* Dec 1997;3(4):271-6.	Wrong study design
Van Bortel LM, Fici F and Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. *American Journal of Cardiovascular Drugs.* 2008;8(1):35-44.	Wrong publication type

Part II. Previously excluded

1. Agrawal RL. Double-blind comparison of Inderal LA (160 mg), Half-Inderal LA (80 mg), and Half-Inderal LA plus bendrofluazide (2. *Br. J. Clin. Pract.* 1987;41(9):916-920.
2. Agrawal RL, Alliott RJ, George M, et al. The treatment of hypertension with propranolol and bendrofluazide. *Journal of the Royal College of General Practitioners.* 1979;29(207):602-606.
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4. Ajayi AA, Sofowora GG, Adigun AQ, Asiyanbola B. Adjunctive sympathoplegic therapy to ACE inhibition in Blacks with congestive heart failure: a comparison of alpha-1 with beta-1 blockade on exercise tolerance and cardiac sympathovagal reflex activity. *Ethnicity & Disease.* 2003;13(1):71-79.
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17. Anonymous. Comparison of the effects of amiodarone versus metoprolol on the frequency of ventricular arrythmias and on mortality after acute myocardial infarction. *Am. J. Cardiol.* 1993;72:1234-1238.

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19. Anonymous. New beta blocker reduces heart failure mortality by two-thirds. *Geriatrics.* 1996;51(1):16-19.
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Postoperative Atrial Fibrillation (SPPAF), a randomized, placebo-controlled trial. *Am. Heart J.* 2004;147(4):636-643.
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Drug Class Review

Beta Adrenergic Blockers

Final Report Update 4
Evidence Tables

July 2009

Update 3: September 2007
Update 2: May 2005
Update 1: September 2004
Original Report: September 2003

The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Mark Helfand, MD, MPH
Kim Peterson, MS
Vivian Christensen, PhD
Tracy Dana, MLS
Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Head-to-head controlled trials			
Walle 1994 Fair	Head-to-head Crossover Double blind	Patients of either sex, more than 21 years of age, with mild to moderate hypertension (diastolic blood pressure in the range of 95 to 110 mmHg) were eligible for the study. The study subjects were either to have received no previous antihypertensive treatment or to have been previously treated	Cardiiovascular diseases, such as angina pectoris, secondary hypertension, grade II or III AV block, heart failure, or a history of myocardial infarction (within 12 months); cerebrovascular ischemia: asthma/ chronic bronchitis; insulin-dependent diabetes; and malignancy or chronic disease requiring treatment
Sundar 1991	Head-to-head Crossover	Patients, who were between the age 35 and 60 years, either never received antihypertensive treatment or had discontinued the drugs for at least 2 weeks prior to entry into trial	Patients with accociated conditions like moderate to severtr congestive infarction within 6 months, accelerated hypertension and those with severe gastrointestinal, renal or hepatie dysfunction were excluded

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Head-to-head controlled trials				
Walle 1994 Fair	Run-in: 4-wk, SB, placebo Treatment periods: Metoprolol CR 100 mg vs. Atenolol 100 mg x 6 weeks Washout: NR	No	Psychologic General Well-Being (PGWB) index Minor Symptom Evaluation (MSE) profile	Mean age: 58 y/o, 43.3% male. Ethinicity: NR
Sundar 1991	Wash-out period: 2 weeks between the interventions atenolol (ate): 100mg per day propranolol (pro): 80mg per day duration of treatment: 4 weeks	NR	Quality of life questionnaire (5-point scale) -the sense of well being and satisfaction with life -the physical state -the enotional state -intellectual functions -ability to perform in social roles -sexual life	Age, Ethnicity: NR Gender: 100% male

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head-to-head controlled trials				
Walle 1994 Fair	mean weight: 76kg mean height: 171cm mean duration of hypertention: 9 yrs mean BP: 102/178	NR/NR/60	2/0/58	Metoprolol CR vs. atenolol PGWB Index (total mean scores): 102.7 vs. 102.0; *P*=NS MSE profile - morning (mean values); all *P*=NS Contentment: 33.1 vs. 32.4 Vitality: 35.2 vs. 35.4 Sleep: 31.8 vs. 30.0 MSE profile - morning (single items rated using VAS) Sexual interest: favored atenolol (*P*<0.05) (data NR) Muscular tension, numbness, self-consciousness, sociability, appetite, sweating, physical competance, dreams: *P*=NS, data NR
Sundar 1991	NR	NR/NR/44	18/0/26	ate vs. pro: -the sense of well being and satisfaction with life -the physical state -the enotional state -intellectual functions -ability to perform in social roles -sexual life *all NS

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-head controlled trials			
Walle 1994 Fair	Clinical observation, active questionning	Overall AEs: no differences (data NR) Serious AEs: 0 vs. 2 (bradycardia and syncope; both leading to withdrawal)	meto vs. ate = 0 vs. 2 (3.3%)
Sundar 1991	Reported by patients	ate vs. pro (%) headache: 0 vs. 0 weakness: 10.5 vs. 10.7 warmth: 2.6 vs. 0 oedema: 0 vs. 0 dyspnoea: 5.3 vs. 0 constipation: 0 vs. 0	NR

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Head-to-head controlled trials			
Steiner 1990	Head-to-head Parallel	The patients were required to have been diagnosed with mild-to-moderate essential hypertension for at least 1 yea, be at least 21 years of age, emloyed or retired, eucated at high-school level or equivalent, and married or libing with an significant other.	Patients could not have major concomitant medical or mental problems or significant changes in living conditions (e.g., recent death of spouse), or require concomitant therapy that could confound the study results

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Head-to-head controlled trials				
Steiner 1990	placebo run-in for 3-5 weeks titration for 1-4 weeks (lowering of DBP by at least 10 mmHg or to 90mmHg or less) maintenance for 4 weeks Propranolol 80-240mg per day (mean=133.4mg per day) Atenolol 50-100mg per day (mean=56.4mg per day)	No	Four-point scale in the Symptom Check List-90-R (SCL) (by patients) Psychological General Well-Being (PGWB) Index (by patients and spouses or significant others) Insomnia Symptom Questionnaire Sexual Function Questionnaire for male patients (modified) Life satisfaction Index	Age, Ethnicity: NR Gender: 100% male

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head-to-head controlled trials				
Steiner 1990	NR	489/360/344 (179 for pro and ate)	27/1/151 pro: 73 ate: 78	Propranolol vs. Atenolol PGWB Index (patients) -Global, anxiety, depressed mood, positive well-being, general health vitality: NS -Self-control: -0.17 vs. 0.32, *P*<0.05 PGWB Index (significant other) -Global, anxiety, depressed mood, self-control, general health vitality: NS -Positive well-being: -0.65 vs. 0.33, *P*<0.05 Symptom Checklist -Global: -0.02 vs. -3.46, *P*<0.05 -Anxiety: -0.35 vs. -1.49, *P*<0.05 -Obsession: 0.03 vs. -1.34, *P*<0.05 -Hostility: 0.38 vs. -0.65, *P*<0.05 Life Satisfaction Index -Global: -1.13 vs. 1.19, *P*<0.05 -Social satisfaction: -0.24 vs. 0.71, *P*<0.05 -Life satisfaction, work satisfaction: NS Sleep function, Sexual function: all NS

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-head controlled trials			
Steiner 1990	Reported by patients	pro(%) vs. ate(%), all NS Bradycardia: 4(4.5) vs. 9(10) Gastrointestinal distress: 9(10.1) vs. 7(7.8) Dry mouth: 5(5.6) vs. 4(4.4) Anxiety: 7(7.9) vs. 2(2.2) Sleep disturbance: 4(4.5) vs. 6(6.7) Libido decreased/impotence: 8(9): 5(5.6) Weakness/fatigue: 15(16.9) vs. 8(8.9) Headache: 12(13.5) vs. 9(10) Total: 57(64) vs. 50(55.6)	pro: 5(6.85) ate: 0(0)

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Head-to-head controlled trials			
Dahlof 1988	Head-to-head Crossover	Patients with either sex with mild to moderate primary hypertension, either newly diagnosed or previously treated with monoterapy	1. The patient had not followed the instructions to fill in and return the questionnaire on 3 occasions during the run-in period 2. The diastolic blood pressure <90mmHg or >105mmHg 3. Previous treatment with metoprolol or atenolol 4. AV-block 2 or 3 5. Non-compensated congestive heart failure 6. Insulin-treated diabetes 7. Bradycardia (heart rate <50 beats/min) 8. Bronchial asthma 9. Any serious concomitant illness or drug abuse which can interfere with the treatment 10. Unwillingness to participate in the study
Blumenthal 1988	Head-to-head exposure design unclear	Participants were eligible for the study if they had resting diastolic blood pressures that were within 90 to 110 mmHg on four separate occassions, using a random zero device, during a 2-week screening interval before testing. Subjects did not take any antihypertensive medication for at least 6 weeks before the screening and were free of any significant disease other than hypertension.	NR

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Head-to-head controlled trials				
Dahlof 1988	placebo run-in: 2 weeks atenolol (ate) 50 mg od metoprolol CR (meto) 100 mg od Duration: 6 weeks	NR	MSE-profile Jern's quality of life questionnaires Beta-blocker questionnaires (subjective symptoms reported) Timing: before, during and after the intervention	mean age: 54.4 ±8.8, 51(66%) male Ethnicity: NR
Blumenthal 1988	Week 1 (b.i.d): Atenolol (ate): 50mg+placebo Propranolol (pro): 40mg+40mg Placebo (pla): placebo+placebo Week 2 (b.I.d): If BP was not reduced by 10mmHg and remained below 90mmHg, increase dosage to: ate 100mg; pro 80mg. Duration: 2 weeks	NR	Psychmetric testing: -The profile of mood states (POMS) -SCL-90 -A side effects measure Timing: before and after drug administration	mean age=42.5, 100% male (22 whites and 4 blacks)

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head-to-head controlled trials				
Dahlof 1988	Duration of hypertension: 3.5±5 years WHO I: 75 WHO II: 2 Supine BP: SBP 159±14.9, DBP 97.8±4.8 Heart rate: 74±10.4	NR/NR/77	3/0/74	meto vs. ate MSE-profile, contentment, hedonic tone, vitality, activity, sleep, relaxation: NS Subjective symptoms- leg fatigue, constipation, diarrhoea, bradycardia, cold hands and feet, heavy breathing: NS Palpitation: meto> ate, *P*<0.05 Preference (n): 31 vs. 23, NS
Blumenthal 1988	15 (62%) had not taken any antihypertensive medication at any time before participation in the study. 0 (0%) took any sedative medication 23 (80%) had at least some college education 25 (98%) were employed on a full-time basis.	NR/ NR/ 26	0/0/26	POMS (before vs. after): ate: tension- 11.87 vs. 6.12, *P*<0.002 depression- NS anger- 7.12 vs. 2.00, *P*<0.03 pro: all NS; pla: all NS SCL-90 (before vs. after): ate: anxiety- NS hostility- 55.00 vs. 48.37, *P*<0.04 phobic anxiety- NS; depression- NS pro: all NS; pla: all NS

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-head controlled trials			
Dahlof 1988	Beta-blocker questionnaires (subjective symptoms reported)	Subjective symptoms- leg fatigue, constipation, diarrhoea, bradycardia, cold hands and feet, heavy breathing: NS Palpitation: meto> ate, *P*<0.05	2(2.6%)
Blumenthal 1988	Questionnaire. Reported by patients	sleep items: NS sexual functioning: NS energy: 4 (ate) and 4 (pro) reported being more tired in the morning, while 6 (pla) reported less fatigue.	0

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Head-to-head controlled trials			
Buhler 1986	Head-to-head Crossover Double blind	Patients with a diastolic blood pressure (DBP) of 100-120 mmHg (Korotkoff V) om the seated position	Patients were on other antihypertensive drugs, had contraindications for beta-blocker therapy, severe disease, or who were known for their poor compliance. Patients with impaired renal function, i.e., serum creatinine>150 umol/l, were also excluded.
Placebo-controlled trials			
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	Placebo-controlled	21-65 years old; between 110 and 160% ideal weight (Metropolitan Life Insurance Height-Weight Tables); diastolic BP at baseline of 90-100 mm Hg	History of myocardial infarction, stroke, or asthma, or a serum creatinine level of 177 mmol/d or greater, insulin-dependent diabetes, allergy to thiazides or beta-blockers, pregnancy, or likelihood of difficulty in complying with the interventions

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Head-to-head controlled trials				
Buhler 1986	Wash-out period: 2 weeks Bisoprolol (bis) 10mg or Atenolol (ate) 50 mg for 2 weeks. Then, if DBP> 95mmHg, increase to: bis 20mg or ate 100mg. Total duraion: 8 weeks Wash-out period: 2 weeks. Then crossover.	NR	self-assessment questionnaire	86 (82.7%) male male: mean age=53.8 female: mean age=50.8 Ethinicity: NR
Placebo-controlled trials				
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	Atenolol (ate) 50 mg Chlorthalidone (chl) 25 mg Placebo (pla)	*Dietary interventions* 1) Usual Diet 2) Low sodium (goal of 52 mmol/d for participants weighing 50 kg or less to 100 mmol/d for those weighing 92 kg) + high potassium (goal: 62 mmol/d to 115 mmol/d) 3) Weight loss group (goal: 4.5 kg or 10% of baseline weight, whichever was greater)	Life Satisfaction Scale Physical Complaints Inventory Symptoms Checklist	*Per protocol analysis (n=697)* Mean age=49 56% male 68% white

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head-to-head controlled trials				
Buhler 1986	10 were not available for the crossover comparison because of: intercurrent disease (n=1), BP response deemed unsatisfactory by the investigator (n=3), and unwanted effects (n=6).	138/134/116	12/0/104	Baseline:bis/ baseline:ate (all NS) headache- 20:7/ 19:9 tiredness- 17:20/ 17:13 Nervousness- 17:10/ 10:8 Sleep problems- 18:11/ 15:10 Cold extremities- 14:13/ 16:12 Sweating- 12:9/ 11:11 Tingling sensations- 12:6/ 9:5 Feeling of weakness- 11:6/ 5:7 Dizziness- 11:3/ 8:7 Joint pain- 9:9/ 6:8 Depressed mood- 12:11/ 9:5 Sex problems- 5:7/ 6:4
Placebo-controlled trials				
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	Previous dug treatment = 66.2% Smokers = 14% Alcohol use (at least once a week) = 39.7%	10, 148 screened/878 eligible/878 randomized	181(20.6%) withdrawn/0 lost to fu/697 analyzed	*Per protocol analysis (pla n=232; ate n=238)* *(*negative score indicates improvement)* *Total physical problems: pla=(-0.15); ate=(-0.14) *Overall psychological functioning: pla=(-0.14); ate=(-0.14) Overall life satisfaction: pla=(-0.04); ate=0.02 *Sexual physical problems: pla=(-0.12); ate=(-0.09) *Depression: pla=(-0.15); ate=(-0.14) *Anxiety: pla=(-0.14); ate=(-0.15) *Sleep disturbances: (-0.29); ate=(-0.26) *Fatigue: (-0.20); ate=(-0.15) Satisfaction with physical health: pla=0.21; ate=0.19 Sexual satisfaction: pla=(-0.14); ate=0.04

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-head controlled trials			
Buhler 1986	self-assessment questionnaire	Baseline:bis / baseline:ate (number), all NS headache- 20:7/ 19:9 tiredness- 17:20/ 17:13 Nervousness- 17:10/ 10:8 Sleep problems- 18:11/ 15:10 Cold extremities- 14:13/ 16:12 Sweating- 12:9/ 11:11 Tingling sensations- 12:6/ 9:5 Feeling of weakness- 11:6/ 5:7 Dizziness- 11:3/ 8:7 Joint pain- 9:9/ 6:8 Depressed mood- 12:11/ 9:5 Sex problems- 5:7/ 6:4	bis (1): dizziness ate (5): diarrhea, skin rash, asthmatic bronchitis, vertigo, headache
Placebo-controlled trials			
Oberman, 1990 Wassertheil-Smoller, 1991 Wassertheil-Smoller, 1992 United States *Trial of Antihypertensive Interventions and Management (TAIM)* Fair quality	NR	NR	NR

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Placebo-controlled trials			
Perez-Stable, 2000 Fair quality	Placebo-controlled	Patients with mild hypertension, defined as an average diastolic blood pressure between 90 and 104 mm Hg on three readings taken during each of two screening visits 2 weeks apart; aged 18-59	Concomitant use of insulin, bronchodilators, antidepressants or antihypertensive medications within 1 month of screening; coronary artery disease, vascular heart disease, renal insufficiency, cerebrovascular disease, and secondary causes of hypertension

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Placebo-controlled trials				
Perez-Stable, 2000 Fair quality	Propranolol (pro) 80-400 mg daily *(n=156)* Placebo (pla) *(n=156)*	NR	*Cognitive Function Test Battery* Stimulus Evaluation/Response Selection Continuous Performance Task(CPT) Digit Symbol Substitution Task(DSST) California Veral Learning Test(CVLT) *Psychological Measures* Center for Epidemiological Studies Depression Scale(CES-D) Beck Depression Inventory(BDI)	Age: Pro=4; Pla=45 % male: Pro=67; Pla=66 % White: Pro=76; Pla=71

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Placebo-controlled trials				
Perez-Stable, 2000 Fair quality	Current smokers: Pro=10%; Pla=11% Current daily drinkers of alcohol: Pro=11%; Pla=12% Mean DBP: Pro=96; Pla=96 Mean SBP: Pro=140=Pla=141	nr/nr/312	NR/NR/203	**Mean changes in:** Selection reaction time(ms): pro=(-3); pla=(-10) ***CPT*** Reaction time(ms): pro=12; pla=6 Correct responses: pro=0; pla=0 Commission errors: pro=(-1); pla=(-1) Omission errors: pro=0.1; pla=0.1 **DSST** correct responses: pro=3; pla=5 ***CVLT*** Monday total: pro=3; pla=1 Tuesday list: pro=2; pla=0 Short-delay free recall: pro=3; pla=2 Short-delay cued recall: pro=4; pla=3 Long-delay free recall: pro=5; pla=4 Long-delay cued recall: pro=5; pla=2 Recognition: pro=3; pla=3 **CES-D:** pro=0; pla=0 **BDI:** pro=(-1); pla=baseline value nr

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo-controlled trials			
Perez-Stable, 2000	NR	NR	NR
Fair quality			

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Placebo-controlled trials			
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	Placebo-controlled Single blind	***Mild hypertension*** Men and women; aged 35-64; with mild hypertension (diastolic BP 90-109 mm Hg, together with systolic pressure below 200 mm Hg)	Secondary hypertension; already on antihypertensive treatment; cardiac failure; MI or stroke within previous 3 months, angina; intermittent claudication; diabetes; gout; asthma; other serious disease; pregnancy
Head-to-head controlled trials			
Brixius 2007	Head-to-head	Male out-patients aged (40-55) w/ newly diagnosed or existing mild (stage I; SBP 140-159 mmHg and DBP 90-99 mmHg) essential hypertension or taking antihypertensive medication. Also in a stable, monogamous heterosexual partnership for at least 6 months and to have no symptoms of sexual disfunction, even if taking beta-blockers or diuretics.	Patients with history of DM, alcohol and/or drug abuse, major cardiovasuclar and non-cardiovascular diseases, or those receiving concomitant treatment related ot hypertension and/or ED.

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Placebo-controlled trials				
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	Propranolol (pro) up to 320 mg daily *(n=4403)* Bendrofluazide (ben) 10 mg daily *(n=4297)* Placebo (pla) *(n=8654)* with goal of maintaining DBP below 90 mm Hg x 5 years	Methydopa	Data for terminating events (e.g., strokes, coronary events, all cardiovascular events, and all cause mortality) were analyzed every six months	Mean age: pro=52; ben=52; pla=52 %male: pro=51.9; ben=52.1; pla=52.3 Race nr
Head-to-head controlled trials				
Brixius 2007	Group A: nebivolol (neb) 5 mg once daily X 12 weeks; placebo x 2 weeks, metropolol succinate 95 mg daily x 12 weeks. Group B: metropolol succinate 95 mg daily x 12 weeks, once daily placebo x 2 weeks, nebivolol (neb) 5 mg daily X 12 weeks	NR	AE: NR Timing: screening visit, baseline, every 4 weeks.	mean age: group A 48.4; group B 47.2 Male: 100% Ethnicity: NR

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Placebo-controlled trials				
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	*(Mean values for men/women)* Body weight(kg): pro=81/70; pla=81/70 SBP(mm Hg): pro=158/165; pla=158/165 DBP(mm Hg): pro=98/98; pla=98/98 % cigarette smokers: pro=30/25; pla=32/27 % with LV hypertrophy on ECG: pro=0.3/0.2; pla=0.4/0.4 % with Q-wave abnormalities: pro=1.2/1.7; pla=1.5/1.4 % with history of stroke: pro=0.7/0.7; pla=0.7/0.7	515,000 screened/46,350 eligible/17,354 enrolled	nr/nr/17,354 analyzed	*# events/rate per 1000 patient years* Strokes: pro=42/1.9; pla=109/2.6 Coronary events: pro=103/4.8; pla=234/5.5 All cardiovascular events: pro=146/6.7; pla=352/8.2 Non-cardiovascular deaths: pro=55/2.5; pla=114/2.7 All deaths: pro=120/5.5; pla=253/5.9
Head-to-head controlled trials				
Brixius 2007	BMI: group A 28.1; group B 27.2 SBP (mmHg): group A 149.4; group B 148.2 DBP (mmHg): group A 92.9; group B 93 % smokers: group A 11 (44%); group B 11 (48%)	Screened: 50 Eligible: 48 Enrolled: 48	2 (prior to randomization)/nr/48	AE outcomes: nr

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo-controlled trials			
Anonymous, 1977 Greenberg, 1984 Anonymous, 1985 Miall, 1987 Anonymous, 1988a Anonymous, 1988b Anonymous, 1992 Lever, 1993 UK *Medical Research Council (MRC)* *Fair quality*	NR	NR	# patients/% Impaired glucose tolerance: pro=43/0.98%; pla=82/0.95% Gout: pro=12/0.27%; pla=14/0.16% Impotence: pro=50/1.14%; pla=20/0.23% Raynaud's phenomenon: pro=75/1.70%; pla=7/0.08% Skin disorder: pro=21/0.48%; pla=7/0.08% Dyspnoea: pro=110/2.5%; pla=10/0.12% Lethargy: pro=104/2.36%; 13/0.15% Nausea/dizziness/headache: pro=103/2.34%; pla=49/0.57% Overall: pro=518/11.76%; pla=202/2.33%
Head-to-head controlled trials			
Brixius 2007	nr	"No critical findings regarding safety issues occurred during the study."	0 (0/48)

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Yilmaz 2008 Turkey	Head-to-head	Male out-patients > 18 years, who were newly diagnosed systolic or diastolic sage 1 hypertension (SBP > 140 mmHg but < 160 mmHg, or a mean seated DBP of > 90 mmHg but < 100 mmHg, prescription of first-time drug therapy, ability to describe their sleep quality.	Previous use of any antihypertensive medication, hypertension beyond sage 1, cardiovascular disease, chronic obstructive pulmonary disease, symptomatic cerebrovascular disease, significant systemic disease, history of psychiatric illness (including primary insomnia, hepatic failure), serum creatinine levels of >1.4 mg/dL, DM, fasting blood glucose of >125 mg/dL, current pregnancy, hypo- or hyperthroidism, and a BMI of >25 kg/m2.. Patients using medications for other reasons: beta-blockers, diuretics, major psychotropic agents, oral steroids, daily nonsteroidal anti-inflammatory drugs, high-dose acetylsalicylic acid.

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Yilmaz 2008 Turkey	Nebivolol (neb) starting dose of 2.5 mg once daily titrated to achieve target DBP of <90 mmHg and SBP of <140 mmHg. Metoprolol succinate (extended release) starting dose of 25 mg once daily titrated to achieve target DBP of <90 mmHg and SBP of <140 mmHg. If after 2 weeks BP was not normalized, amlodipine (5-10 mg daily) was added to treatment. Duration: x 6 weeks.	Amlodipine was added if BP was not normalized after week 2.	Primary Outcome: Quality of sleep: Pittsburgh Sleep Quality Index (PSQI) which includes 7 component scores -- sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, daytime disfunction. Scores from each component are summed for a global PSQI score (1-21). Higher scores indicate lower quality of sleep. Score of <5 =poor sleeper. Measures at baseline and at week 6. Secondary Outcome: BP and heart rate measured at weeks 1, 2, 4, and 6.	Mean age: 40.7 Male: 20/39 (51%) Ethnicity: NR

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Yilmaz 2008 Turkey	DBP >90 mmHg: neb 2 (9%); met 0 (0%) SBP >140 mmHg: neb 7 (32%); met 8 (47%) median heart rate (bpm) neb 72.5; met 71.0 Mean global PSQI score at baseline neb 5.77 (poor sleepers 12 (55%); met 5.11 (poor sleepers 5 (29%)	Screened 56 Eligible 46 Enrolled 46 (neb 24; met 22)	7/0/39	Primary: Mean Global PSQI Score: neb: decrease from 5.77 to 4.55 (indicating imporved sleep) met: increased from 5.11 to 6.54 (indicating worsening sleep) (mean adjusted difference: -2.31; 95% CI: -3.10, - 1.51; *P*<0.001) End of treatment: neb: 7 (32%) poor sleepers met: 13 (76%) poor sleepers (*P*=0.006) Secondary: Target DBP and SBP were observed for all patients. Heart rate change from baseline: neb -1.08; met 1.22 (-2.31 CI 95%, *P*<0.001)

Evidence Table 1. Randomized controlled trials of beta blockers for hypertension

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Yilmaz 2008 Turkey	Patient recorded diary	No adverse events were reported during the couse of the study.	0 (0/39)

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Randomization described	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head-to-head controlled trials					
Walle 1994	NR	NR	Unclear	Mean age=58 years 43.3% male Race NR	60
Sundar 1991	NR	NR	n/a-crossover	Mean age=NR 100% male 100% Indian	NR
Steiner 1990	NR	NR	NR	Baseline characteristics NR	489 screened, 360 eligible

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Head-to-head controlled trials					
Walle 1994	Cardiiovascular diseases, such as angina pectoris, secondary hypertension, grade II or III AV block, heart failure, or a history of myocardial infarction (within 12 months); cerebrovascular ischemia: asthma/ chronic bronchitis; insulin-dependent diabetes; and malignancy or chronic disease requiring treatment	Yes	Yes	Yes	Yes
Sundar 1991	Patients with accociated conditions like moderate to severtr congestive infarction within 6 months, accelerated hypertension and those with severe gastrointestinal, renal or hepatie dysfunction were excluded	Yes	Yes	Yes	Yes
Steiner 1990	Patients could not have major concomitant medical or mental problems or significant changes in living conditions (e.g., recent death of spouse), or require concomitant therapy that could confound the study results	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential /high	Score	Funding
Head-to-head controlled trials						
Walle 1994	No 13 (21.7%) excluded due to protocol violations	Unclear	Yes No No No	No No	Fair	NR
Sundar 1991	Unclear	Unclear	Yes No No No	Unclear Unclear	Poor	NR
Steiner 1990	No; 16 (4.4%) were excluded due to protocol violations	Unclear	Yes No No No	NR	Fair	ICI Pharmaceuticals Group

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Control group standard of care	Length of follow-up
Head-to-head controlled trials		
Walle 1994	Yes	6 weeks
Sundar 1991	Yes	4 weeks
Steiner 1990	Yes	4 weeks

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Randomization described	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head-to-head controlled trials					
Dahlof 1988	NR	NR	n/a-crossover	Mean age=54.4 66.2% male Race NR	NR
Blumenthal 1988	NR	NR	NR	Mean age=42.5 years 100% male 84.6% white 62% antihypertensive treatment naïve	26
Buhler 1986	NR	NR	n/a - crossover	Mean age=53.3 years 76.1% male Race NR	138

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Head-to-head controlled trials					
Dahlof 1988	1. The patient had not followed the instructions to fill in and return the questionnaire on 3 occasions during the run-in period 2. The diastolic blood pressure <90mmHg or >105mmHg 3. Previous treatment with metoprolol or atenolol 4. AV-block 2 or 3 5. Non-compensated congestive heart failure 6. Insulin-treated diabetes 7. Bradycardia (heart rate <50 beats/min) 8. Bronchial asthma 9. Any serious concomitant illness or drug abuse which can interfere with the treatment 10. Unwillingness to participate in the study	Yes	Yes	Yes	Yes
Blumenthal 1988	NR	Yes	Yes	Yes	Yes
Buhler 1986	Patients were on other antihypertensive drugs, had contraindications for beta-blocker therapy, severe disease, or who were known for their poor compliance. Patients with impaired renal function, i.e., serum creatinine>150 umol/l, were also excluded.	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential /high	Score	Funding
Head-to-head controlled trials						
Dahlof 1988	No; excluded 3 patients (3.9%) due to AE's (1 patient in each group) and noncompliance (group NR)	n/a - crossover	Yes No No No	No No	Fair	NR
Blumenthal 1988	Unclear	NR	No No No No	NR NR	Poor	John D. and Catherine T. MacArthur Foundation, National Institutes of Health greants HL30675, HS31514, and AG04238, and a grant (RO7233) from the US Public Health Services
Buhler 1986	No 30 (22.4%) were excluded due to BP limits or nondrug related problems	Yes N=104 Mean age=53.3 82.7% male		No No	Fair	NR

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Control group standard of care	Length of follow-up
Head-to-head controlled trials		
Dahlof 1988	Yes	6 weeks
Blumenthal 1988	Yes	2 weeks
Buhler 1986	Yes	8 weeks

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Randomization described	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Placebo-controlled trials					
Oberman 1990 Wassertheil-Smoller 1991 Wassertheil-Smoller 1992 United States Trial of Antihypertensive Interventions and Management (TAIM)	NR	NR	NR	Mean age=49 56% male	878 randomized 697 analyzed
Perez-Stable 2000	Adequate: computer-generated list of random numbers	NR	No; statistically significant differences between the two groups on two tests of cognitive function	Fair Mean age=45.5; 66.5% male	312
Anonymous 1977 Greenberg 1984 Anonymous 1985 Miall 1987 Anonymous 1988a Anonymous 1988b Anonymous 1992 Lever 1993 Medical Research Council (MRC) UK	NR	NR	Yes	Mean age 52 52.1% male	515,000 screened 46,350 eligible 17,354 enrolled

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Placebo-controlled trials					
Oberman 1990 Wassertheil-Smoller 1991 Wassertheil-Smoller 1992 United States Trial of Antihypertensive Interventions and Management (TAIM)	History of myocardial infarction, stroke, or asthma, or a serum creatinine level of 177 mmol/d or greater, insulin-dependent diabetes, allergy to thiazides or beta-blockers, pregnancy, or likelihood of difficulty in complying with the interventions	Yes	NR	Yes	Yes
Perez-Stable 2000	Concomitant use of insulin, bronchodilators, antidepressants or antihypertensive medications within 1 month of screening; coronary artery disease, vascular heart disease, renal insufficiency, cerebrovascular disease, and secondary causes of hypertension	Yes	NR	Yes	Yes
Anonymous 1977 Greenberg 1984 Anonymous 1985 Miall 1987 Anonymous 1988a Anonymous 1988b Anonymous 1992 Lever 1993 Medical Research Council (MRC) UK	Secondary hypertension; already on antihypertensive treatment; cardiac failure; MI or stroke within previous 3 months, angina; intermittent claudication; diabetes; gout; asthma; other serious disease; pregnancy	Yes	Yes; assessed by an arbitrator ignorant of the treatment regimen	Yes	Yes

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential /high	Score	Funding
Placebo-controlled trials						
Oberman 1990 Wassertheil-Smoller 1991 Wassertheil-Smoller 1992 United States Trial of Antihypertensive Interventions and Management (TAIM)	No	NR	Attrition: 181(20.6%); compliance(% of patients taking > 80% of the pills): 92%; others NR	None	Fair	ICI Pharmaceuticals; A.H Robins; National Heart, Lung and Blood Institute
Perez-Stable 2000	No	NR	45% attrition; others NR	NR	Fair	Public Health Services Grants
Anonymous 1977 Greenberg 1984 Anonymous 1985 Miall 1987 Anonymous 1988a Anonymous 1988b Anonymous 1992 Lever 1993 Medical Research Council (MRC) UK	Yes	NR	Attrition due to primary and adverse events reported; others NR	NR	Fair	Duncan, Flockhart and Co Ltd; Imperial Chemical Industries Ltd; CIBA Laboratories; Merck Sharp and Dohme Ltd

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Control group standard of care	Length of follow-up
Placebo-controlled trials		
Oberman 1990 Wassertheil-Smoller 1991 Wassertheil-Smoller 1992 United States Trial of Antihypertensive Interventions and Management (TAIM)	Yes	6 months
Perez-Stable 2000	Yes	12 months
Anonymous 1977 Greenberg 1984 Anonymous 1985 Miall 1987 Anonymous 1988a Anonymous 1988b Anonymous 1992 Lever 1993 Medical Research Council (MRC) UK	Yes	5 years

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Randomization described	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head-to-head trials					
Brixius 2007	computer generated adequate	NR	Yes	mean age: group A 48.4; group B 47.2 Male: 100% Ethnicity: NR Yes	Screened: 50 Enrolled: 48
Yilmaz 2008 Turkey	NR	No Open-label	NR, only analyzed subjects' characteristics reported	Baseline characteristics for patients who completed the study only. Mean age: 40.7 Male: 51% Unknown	Screened: 56 Enrolled: 46

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Head-to-head trials					
Brixius 2007	Yes	Yes	NR (stated double-blind, no details given)	NR (stated double-blind, no details given)	NR (stated double-blind, no details given)
Yilmaz 2008 Turkey	Yes	Yes	No	No	No

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential /high	Score	Funding
Head-to-head trials						
Brixius 2007	Yes	Yes	No No Yes No	NR	fair	NR
Yilmaz 2008 Turkey	No, 3 patients were excluded from analysis	Yes	Yes No Yes No	No	Fair	Ulagay-Menarini Group, Istanbul, Turkey Menarini International, Florence Italy

Evidence Table 2. Quality assessments of randomized controlled trials of beta blockers for hypertension

Author Year Country	Control group standard of care	Length of follow-up
Head-to-head trials		
Brixius 2007	yes	28 weeks
Yilmaz 2008 Turkey	Yes	6 weeks

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Head-to-head trials			
Chieffo 1986 Italy Fair quality RCT	Patients with comorbid essential hypertension (WHO Classes I-II) and stable angina pectoris	Severe bradycardia (< 50 beats per minute); congestive heart failure; myocardial infarction less than three months before the start of the trial; asthma and renal insufficiency	Labetalol 200 mg + chlorthalidone 20 mg (lab+chl) daily (n=5) Atenolol 100 mg + chlorthalidone 25 mg (ate+chl) (n=5) x 8 weeks
Dorow 1990 Fair quality RCT Crossover	Outpatients aged between 41 and 67 years, suffering from angina pectoris due to coronary artery disease and concomitant reversible, chronic obstructive bronchitis; three angina attacks per week over the last three months (with or without therapy)	Unstable angina or angina at rest; myocardial infarction within the last 6 months; heart failure with or without digitalis treatment; arterial hypertension with supine diastolic blood pressure values under a thiazide diuretic of >/= 105 mm Hg; cardiac arrhythmias requiring treatment; bronchial asthma; restrictive airway disease; pulmonary hypertension; diseases that could impair the implementations of bicycle ergometry	Atenolol (ate) 50 mg daily Bisoprolol (bis) 5 mg daily x 6 months

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head-to-head trials				
Chieffo 1986 Italy Fair quality RCT	sl ntg	Patient daily record	Mean age=56.8 100% male Race nr	NR
Dorow 1990 Fair quality RCT Crossover	Diuretics Short-acting and other nitrates Bronchodilators Inhaled corticoids Antibiotics Mucolytics Expectorants	Method of measurement of 'Frequency of angina pectoris attacks' nr	Mean age: 55 % Male: 82.5 Race nr	% Smokers: 17.6 % Coronary artery disease: 100 % angina pectoris pretreatment: 80 % MI in case history: 20 % pathological exercise ECG: 100

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head-to-head trials				
Chieffo 1986 Italy Fair quality RCT	NR/NR/10	NR/NR/10 analyzed	Effect on angina(# patients with reduced frequency on both 'daily incidence of angina attacks' and 'dosage of sublingual nitroglycerin'): lab+chl=4/5(80%); ate+chl=3/5(60%)	NR
Dorow 1990 Fair quality RCT Crossover	NR/NR/40	0 withdrawn/1 lost/40 analyzed	Angina attacks/week(% decrease in mean): ate=(-82.8%); bis=(-64.3%)	NR

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head-to-head trials			
Chieffo 1986 Italy Fair quality RCT	NR	NR	Comorbid HTN
Dorow 1990 Fair quality RCT Crossover	NR	NR	

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Frishman 1979 United States Fair quality RCT	Patients with angina pectoris due to ischemic coronary artery disease as documented by coronary angiography or previous MI; positive treadmill exercise test showing at least a 1 mm ECG ST segment depression of the ischemic type in association with typical angina pectoris pain; at least 5 attacks of angina pectoris/2 weeks for three months with no evidence for an accelerated course	Co-existent valvular heart disease, congestive heart failure, hypertension, bronchial asthma requiring continued treatment with bronchodilators, severe bradycardia, intermittent claudication, and either myocardial infarction or a coronary artery bypass within 3 months	Pindolol (pin) 10-40 mg daily (n=23) Propranolol (pro) 40-240 mg daily (n=18) x 8 weeks

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Frishman 1979 United States Fair quality RCT	Nitroglycerin	Patient daily record Treadmill (protocol nr)	Mean age: 55 85.4% male Race nr	Diagnosis of coronary artery disease Coronary angiography: 80.5%

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Frishman 1979 United States Fair quality RCT	NR/NR/40	NR/NR/40 analyzed	Angina attacks/2 weeks(% reduction):pin=(-41.8%); pro=(-47.0%) Exercise tolerance(% increase in mets): pin=(+21.2%); pro=(+18.5%)	NR

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Frishman 1979 United States Fair quality RCT	Overall incidence: pin=4/23(17.4%); pro=17/18(94.4%) Pindolol Nasal stuffiness=1/23(4.3%) Nocturia=1/23(4.3%) Impotence=1/23(4.3%) Palpitations=1/23(4.3%) Propranolol Rash=1/18(5.5%) Blurred vision=2/18(11.1%) Fatigue=8/18(44.4%) Dyspnea on exertion=1/18(5.5%) Mild hypotension=5/18(27.8%)	NR	

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
van der Does 1999 Europe Fair quality RCT	Male or female (postmenopausal or using reliable contraceptive methods) treated or untreated patients (</=80 years) with chronic angina pectoris, stable for at least preceding 2 months (symptomatic upon exertion and responsive to ntg and/or rest); documented coronary heart disease either by previous angiography (>70% narrowing of a major coronary vessel) or MI (electrocardiogram or cardiac enzymes), or a previous positive exercise test with occurrence of angina and ST-segment depression; capable of performing upright bicycle ergometric exercise tests; not to be at risk while temporarily receiving placebo	Contraindications to study drugs/exercise testing; other forms of angina pectoris (vasospastic, unstable); MI/cardiac surgery within 3 months; main stem stenosis; ventricular aneurysm; marked left ventricular hypertrophy; hypertrophic subaortic stenosis; hemodynamically relevant vascular defects; decompensated cardiac failure; orthostasis; phlebothrombosis; disorders of impulse formation/conduction (resting heart rate <45 beats/min, bundle brach block, pacemaker); obstructive airways disease; insulin-dependent DM; relevant hepatic impairment; gross obesity; alcohol/drug abuse; epilepsy; concomitant drugs interfering with study objectives (e.g., other antianginal agents); other clinical study participation within 30 days	Carvedilol (car) 100 mg daily (n=247) Metoprolol (met) 200 mg daily (n=120) x 3 months

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
van der Does 1999 Europe Fair quality RCT	Nitrates	Erect bicycle ergometric exercise	Mean age: car=62; met=61 %male: car=72; met=71 Race nr	%smokers: car=14; met=19 %systemic hypertension: car=38; met=33 %diabetes mellitus: car=15; met=13 %dyslipidemia: car=32; met=31 %anterior MI: car=9; met=11 %posterior MI: car=18; met=17 %positive angiography: car=23; met=22 %1-vessel disease: car=13; met=10 %2-vessel disease: car=5; met=8 %3-vessel disease: car=5; met=3

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
van der Does 1999 Europe Fair quality RCT	nr/393 enrolled/368 randomized	36 withdrawn/lost nr/344 analyzed for efficacy	Per protocol analysis: car=231; met=113 Mean change in total exercise time(s): car=(+60); met=(+60) Mean change in time to angina(s): car=(+77); met=(+76)	Volunteered by subjects or observed by investigator were recorded regardless of their nature and regardless of whether a causal relation to study medication was assumed

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
van der Does 1999 Europe Fair quality RCT	car n=248; met n=120 Any adverse event: car=25%; met=30% <u>Most common AE's, n(%)</u> Dizziness: car=12(4.8), met=6(5.0) Bronchitis: car=9(3.6); met=3(2.5) Asthenia: car=8(3.2); met=3(2.5) Headache: car=8(3.2); met=4(3.3) Back pain: car=6(2.4); met=2(1.7)	AE withdrawals: car=18; met=6	

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Narahara 1990 United States Fair quality	Patients of either sex who were > 30 years of age; history of stable angina pectoris of > 3 months' duration; reproducible exercise-induced angina in conjunction with ≥ 1 mm of horizontal or downsloping ST-segment depression measured 0.08 second after the J point	Contraindications to beta blockade including sinus bradycardia (<50 beats/min), greater than first-degree atrioventricular block, congestive heart failure, asthma, peripheral vascular disease or insulin-dependent diabetes; women of child-bearing potential and patients with unstable angina pectoris or a myocardial infarction within the preceding 3 months	Betaxolol 20 mg once daily Betaxolol 40 mg once daily Propranolol 40 mg 4 times daily Propranolol 80 mg 4 times daily x 10 weeks

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Narahara 1990 United States Fair quality	Sublingual nitroglycerin	Patient diary used to measure (1) angina frequency; and (2) nitroglycerin consumption Treadmill exercise testing (modified Naughton protocol) used to measure (1) exercise duration; and (2) time to angina	Mean age=61 21.4% female 92.9% white	History of prior MI = 42% History of coronary angiography = 59% Coronary angiography patients with NYHA functional Class II = 82% Coronary angiography patients with NYHA functional Class III = 17%

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Narahara 1990 United States Fair quality	nr/nr/112	20(17.8%) withdrawn/lost to fu nr/90 analyzed for angina attacks and nitroglycerin tablet use; 82 analyzed for exercise variables	Mean number of angina attacks (% reduction) Betaxolol 20=60 Betaxolol 40=77 Propranolol 160=57 Propranolol 320=70 NS Nitroglycerin tablets/week (% reduction) Betaxolol 20=48 Betaxolol 40=73 Propranolol 160=59 Propranolol 320=55 NS Exercise duration (% increase in minutes) Betaxolol 20=14 Betaxolol 40=15 Propranolol 160=21 Propranolol 320=14 NS	NR

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Narahara 1990 United States Fair quality	Overall side effects (considered to be due to drug therapy): B20=50%; B40=37%; P160=42%; P320=45% # patients; sample sizes nr Fatigue: B20=1; B40=3; P160=4; P320=3 Increased sweating: B20=0; B40-3; P160=0; P320=0 Headache: B20=2; B40=0; P160=2; P320=0 Parasthesia: B20=0; B40=0; P160=0; P320=0 Diarrhea: B20=2; B40=0; P160=0; P320=0 Dyspepsia: B20=0; B40=2; P160=0; P320=0 Tinnitus: B20=2; B40=0; P160=0; P320=0 Angina: B20=0; B40=0; P16-=2; P320=0 Depression: B20=0; B40=2; P160=0; P320=0 Dyspnea: B20=0; B40=2; P160=0; P320=0 Abnormal vision: B20=0; B40=2; P160=0; P320=0	NR	

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Kardas 2007	Ischemic heart disease outpatients CCS class I-II, aged 40-75, beta-blockers-niave, whose mental state enabled conscious participation in the study.	Unstable angina pectoris, NYHA class III and IV heart failure, heart rate <60/min, II or III degree antrio-ventricular block, systolic blood pressure below 90 mmHg, symptomatic infection, and any conditions requiring help from others with drug administration.	Betaxolol 20 mg once daily metoprolol tartrate metropolol 50 mg twice daily for 8 weeks.

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Kardas 2007	Nitrates	MEMS, Medication Event Monitoring System used to measure patient complience. Drug effectiveness/ tollerance/ health-related quality of life. Patient diary used to measure (1) weekly number os chest pain episodes; and (2) weekly number of short-acting nitrates doses.	Mean age = 58.8 40.6% male ethnicity NR	NR

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Kardas 2007	NR/NR/112	13 withdrawn/ 0 loss to fu/96 analyzed for compliance. Analyzed 96 due to a MEMS container lost in 2 cases and failure to download compliance data from the MEMS cap in one case.	Betaxolol vs. Metoprolol 8 weeks Reduction in chest pain epidodes .42/week vs. .46/week (NS) Reduction in short-acting nitrate doses taken .30/week vs. .21/week (NS) Health Related Quality of Life-- improved general wellbeing 73% vs. 71.7% (n=41) sleep 31% vs. 34% mood 42% vs. 37% physical function 19% vs. 13% physical function 42.9% vs. 15.2% (p<0.01) sexual function 0.0% vs. 4.3% Tolerance and Adverse Effects 10.7% vs. 16.1% bradycardia 3.5% in both groups.	NR

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Kardas 2007	10.7% betaxolol vs. 16.1% metoprolol Bradycardia (3.5% in both groups) other adverse events NR	betaxolol vs. metoprolol 2/56 (4%) vs. 4/56 (7%)	

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Frishman 1989 United States Poor quality RCT	Patients with documented stable angina pectoris and mild to moderate hypertension	Patients with coexistent valvular heart disease, congestive heart failure, bronchial asthma, severe bradycardia (resting heart rate less than 50 beats/min), intermittent claudication, myocardial infarction within 3 months, and age above 70 years or under 18 years	Labetalol (lab) 200-1600 mg daily Propranolol (pro) 80-640 mg daily x 4 months

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Frishman 1989 United States Poor quality RCT	HCTZ 50 mg daily (if standing DBP > 100 mm Hg)	Treadmill ergometer exercise tests (Bruce protocol) Patient diary	Center 1 Mean age: lab=58; pro=57 Gender (%male): lab=66.7; pro=100 Race nr Center 2 Mean age: lab=51; pro=58 Gender(%male): lab=100; pro=100% Race nr	NR

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Frishman 1989 United States Poor quality RCT	NR/NR/41	12 withdrawn/1 lost to fu/34 analyzed for efficacy	Total exercise time (%D in sec) Center 1: lab=(+7); pro=(+12) Center 2: lab=(+23); pro=(+40) Time to angina onset(%D in sec) Center 1: lab=(+29); pro=(+38) Center 2: lab=(+58); pro=(+66) Number of patients with angina endpoint(D%) Center 1: lab=(-67); pro=(-63) Center 2: lab=(-38); pro=(-50)	Questioned generally about occurrence of adverse events specifically regarding occurrence of dyspnea, palpitations, sexual dysfunction, GI disturbances and dizziness

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Frishman 1989 United States Poor quality RCT	NR	NR	Center 1 measured exercise parameters at or close to peak drug effect Center 2 measured exercise parameters at or close to trough drug effect

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Placebo-controlled trials			
Destors 1989 Europe Fair Quality RCT	Male and female patients who were less than 70 years of age were considered for the study if they had coronary heart disease with chronic angina stabilized for at least 3 months. Women could be included if menopausal for at least 2 years or exhibiting coronary lesions at angiography. Demonstration of at least 8 attacks of angina during the last 14 days or 5 attacks of angina during the last 7 days of the 2-8 week washout period	Suffering exclusively at rest or had nocturnal attacks; angina pectoris not secondary to atherosclerosis; unstable angina pectoris; so called Prinzmetal's angina or myocardial infarction within the past 6 months; inability to assess pain and fill in diary cards; any contraindication to either active treatment; liver or kidney conditions likely to modify drug metabolism or all reasons preventing close compliance to study protocol	Bepridil (bep) 100-400 mg daily Propranolol (pro) 60-240 mg daily Placebo (pla) x 24 weeks

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Placebo-controlled trials				
Destors 1989 Europe Fair Quality RCT	sl short-acting trinitrin	Bicycle ergometer x wks 2, 4, 6, 8, 12, 16, 20 & 24 Patient diary cards x wks 8, 24	Mean age: pla=54.3; pro=56.1 % Male: pla=57.1; pro=73.1 Race nr	History of MI: pla=31.4%; pro=37.2% Positive ECG for exercise: pla=77.1%; pro=76.9% Positive ECG for attacks: pla=57.1%; pro=56.4% Angina duration(mos): pla=69.6; pro=66.6 Mean weekly attacks: pla=10.3; pro=12.4 Mean curative ntg tablets/wk: pla=10.6; pro=12.6 Mean preventive ntg tablets/wk: pla=2.6; pro=3.0 Mean attack-free days/wk: pla=1.2; pro=1.5 Mean exercise test duration(min): pla=9.3; pro=9.7

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Number screened/ eligible/ enrolled	Number withdrawn/lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Placebo-controlled trials				
Destors 1989 Europe Fair Quality RCT	NR/NR/191	38 withdrawals/15 lost to fu/analyzed 191	Angina attacks/week(% reduction) Week 8: pla=(-49%); pro=(-65%) Week 24: pla=(-77%); pro=(-71%) Ntg consumption(% reduction) Week 8: pla=(-57%); pro=(-73%) Week 24: pla=(-79%); pro=(-74%) Number of attack-free days Week 8: pla=190; pro=193 Week 24: pla=270; pro=204 Total work(mean % increase): Week 8: pla=13%; pro=48% Week 24: pla=20%; pro=50% Maximum workload(mean % increase): Week 8: pla=6%; pro=27% Week 24: pla=14%; pro=30% Exercise duration(mean % increase): Week 8: pla=7%; pro=22% Week 24: pla=8%; pro=24%	NR

Evidence Table 3. Randomized controlled trials of beta blockers for angina

Author Year Country Study Design	Adverse Effects Reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Placebo-controlled trials			
Destors 1989 Europe Fair Quality RCT	Number of patients with: Hypotension: pla=1; pro=4 Bronchospasm: pla=1; pro=1 Allergic reaction: pla=0; pro=1 Raynaud phenomenon: pla=0; pro=1 Fatigue: pla=2; pro=14 Psychiatric problems: pla=1; pro=2 Gastrointestinal problems: pla=2; pro=10 Other: pla=1; pro=6 Any: pla=6; pro=23 Severe coronary events(cardiac death, MI, angina deterioration): pla=2(5.7%); pro=8(10.2%) Development of heart failure/AV block/rhythm disturbances: pla=0; pro=5	Death due to MI(# pts): pla=0; pro=1 CVA(# pts): pla=1; pro=1 Severe clinic events(# pts): pla=1; pro=2 Adverse reaction(# pts): pla=0; pro=1	

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head-to-head controlled trials					
Frishman 1989 United States	NR	NR	Not clear	Good mean age=56 91.2% male	34
van der Does 1999 Europe	Block randomization (sets of 6); method of sequence generation nr	NR	Yes	Good mean age >55 higher %male	393 enrolled 368 randomized
Narahara 1990 United States	nr	nr	yes	yes	112

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Head-to-head controlled trials					
Frishman 1989 United States	Coexistent valvular heart disease, congestive heart failure, bronchial asthma, severe bradycardia (resting heart rate less than 50 beats/min), intermittent claudication, myocardial infarction within 3 months, and age above 70 years or under 18 years	Yes	NR	Yes	Yes
van der Does 1999 Europe	Contraindications to study drugs or exercise testing; other forms of angina pectoris (vasospastic, unstable); myocardial infarction or cardiac surgery within 3 months; main stem stenosis; ventricular aneurysm; marked left ventricular hypertrophy; hypertrophic subaortic stenosis; hemodynamically relevant vascular defects; decompensated cardiac failure; orthostasis; phlebothrombosis; disorders of impulse formation/conduction (e.g., resting heart rate <45 beats/min, bundle brach block, pacemaker); obstructive airways disease; insulin-dependent diabetes mellitus; relevant hepatic impairment; gross obesity; alcohol or drug abuse; epilepsy; concomitant drugs interfering with the study objectives (e.g., other antianginal agents); participation in another clinical study within 30 days	Yes	Yes	Yes	Yes
Narahara 1990 United States	Contraindications to beta blockade including sinus bradycardia (<50 beats/min), greater than first-degree atrioventricular block, congestive heart failure, asthma, peripheral vascular disease or insulin-dependent diabetes; women of child-bearing potential and patients with unstable angina pectoris or a myocardial infarction within the preceding 3 months	Yes	Yes	Yes	Yes

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding
Head-to-head controlled trials						
Frishman 1989 United States	No	NR	Attrition reported; other nr	No	Poor	In part by Schering-Plough
van der Does 1999 Europe	No	NR	Attrition reported; other nr	NR	Fair	Boehringer Mannheim
Narahara 1990 United States	No	nr	Yes No No No	No No	Fair	Lorex Pharmaceuticals

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Control group standard of care	Length of follow-up
Head-to-head controlled trials		
Frishman 1989 United States	Yes	4 months
van der Does 1999 Europe	Yes	3 months
Narahara 1990 United States	Yes	10 weeks

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Dorow 1990	NR	NR	N/A-crossover	Sample of patients cormorbid with chronic obstructive bronchitis	40
Frishman 1979 United States	NR	NR	Baseline comparisons nr. Run-in mean attack frequencies (95% CI): pin=18.4(17.4-19.4); pro=28.5(26.4-30.6)	Good mean age=55 85.4% male	40 enrolled
Chieffo 1986 Italy	NR	NR	NR	Cormorbid hypertension and angina Good mean age=56.8 100% male	10 enrolled
Kardas 2007	NR	NR	Unclear: baseline comparability excluded 16 (14%) noncompleters. Other variables such as diagnosis of CAD, proir-MI, etc. not reported.	40% male*, mean age =56.8 *This study included a lower proportion of males than other studies of this type.	112 randomized

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Dorow 1990	Unstable angina or angina at rest; myocardial infarction within the last 6 months; heart failure with or without digitalis treatment; arterial hypertension with supine diastolic blood pressure values under a thiazide diuretic of >/= 105 mm Hg; cardiac arrhythmias requiring treatment; bronchial asthma; restrictive airway disease; pulmonary hypertension; diseases that could impair the implementations of bicycle ergometry	Yes	nr	Yes	Yes
Frishman 1979 United States	Co-existent valvular heart disease, congestive heart failure, hypertension, bronchial asthma requiring continued treatment with bronchodilators, severe bradycardia, intermittent claudication, and either myocardial infarction or a coronary artery bypass within 3 months	Yes	NR	Yes	Yes
Chieffo 1986 Italy	Severe bradycardia (< 50 beats per minute); congestive heart failure; myocardial infarction less than three months before the start of the trial; asthma and renal insufficiency	Yes	NR	Yes	Yes
Kardas 2007	Unstable angina pectoris, NYHA class III and IV heart faiilure, heart rate <60/min., II or III degree atrio-ventricular block, systolic blood pressure <90 mmHg, symptomatic infection, and any contradictions requiring help of others with drug administration.	Yes	No -- open study	No -- open study	No -- open study

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding
Dorow 1990	Yes	N/A	Attrition and compliance reported; others nr	None	Fair	NR
Frishman 1979 United States	Yes	NR	NR	NR	Fair	Sandoz, Inc.
Chieffo 1986 Italy	Yes	NR	NR	NR	Fair	NR
Kardas 2007	No; 16/112 (14%) excluded	NR	Yes No Yes No	Differential: Attrition 16% for betaxolol vs. 12% High: Somewhat; 16/112 (14%) excluded from primary analysis	Fair	Medical University of Lodz and from Sanofi-Synthelabo Warsaw, Poland

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Control group standard of care	Length of follow-up
Dorow 1990	Yes	1 year
Frishman 1979 United States	Yes	8 weeks
Chieffo 1986 Italy	Yes	8 weeks
Kardas 2007	Yes	8 weeks

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Placebo-controlled trials					
Destors 1989 Europe	NR	NR	Yes	Good mean age=55.3 66.5% male	191 enrolled

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Placebo-controlled trials					
Destors 1989 Europe	Suffering exclusively at rest or had Nocturnal attacks; angina pectoris Not secondary to atherosclerosis; unstable angina pectoris; so called Prinzmetal's angina or myocardial infarction within the past 6 months; inability to assess pain and fill in diary cards; any contraindication to either active treatment; liver or kidney conditions likely to modify drug metabolism or all reasons preventing close compliance to study protocol	Yes	Yes	Yes	Yes

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: Differential/high	Score	Funding
Placebo-controlled trials						
Destors 1989 Europe	Yes	NR	Attrition and compliance reported; others nr	7.8% at week 24	Fair	NR

Evidence Table 4. Quality assessments of randomized controlled trials of beta blockers for angina

Author, Year Country	Control group standard of care	Length of follow-up
Placebo-controlled trials		
Destors 1989 Europe	Yes	24 weeks

Evidence Table 5. Quality assessments of randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Anonymous (MACB Study Group) 1995	NR	NR	Yes	Median age=64 85.5%male	967
Sjoland 1995	**NR**	NR	No; patients in met group significantly older than those in pla group (*P*=0.02)	Mean age NR 86.6% male	618

Evidence Table 5. Quality assessments of randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Anonymous (MACB Study Group) 1995	Simultaneous valve surgery	Minimal	NR	Yes	Yes
Sjoland 1995	Simultaneous valve surgery = 261(19%) No informed consent = 254 (18%) Need beta blockade = 194 (14%) Age over 75 = 170 (12%) Systolic blood pressure<100 mm Hg = 57 (4%) Severe obstructive pulmonary disease = 62 (4%) In other randomized trials = 61 (4%) Death = 42 (3%) Heart rate < 45 beats/min, severe heart failure, poor peripheral circulation, advanced atrioventricular block or previous participation in study = 87 (6%) Other = 387 (28%)	Yes	NR	Yes	Yes

Evidence Table 5. Quality assessments of randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Anonymous (MACB Study Group) 1995	Yes	NR	Attrition=38.9%; others NR	NR	Fair	NR
Sjoland 1995	No	NR	Attrition=36.1%; others NR	NR	Poor	NR

Evidence Table 5. Quality assessments of randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Control group standard of care	Length of follow-up
Anonymous (MACB Study Group) 1995	Yes	2 years
Sjoland 1995	Yes	2 years

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Placebo-controlled trials			
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	RCT	Patients referred for CABG	Simultaneous valve surgery

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Placebo-controlled trials				
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	Metoprolol (met) 200 mg daily *(n=480)* Placebo *(n=487)* x 2 years Treatment interval: 5-21 days post-CABG	Aspirin 250 mg daily Dipyridamole TID *Angina*: Long-acting nitrates, Calcium channel blockers *Hypertension:* thiazide diuretic, calcium channel blocker, ACE inhibitor *Supraventricular arrhythmias:* digitalis, disopyramide, calcium antagonist *Ventricular arrhythmias:* class I anti-arrhythmic drug	Endpoints: Ischemic events including death, myocardial infarction, development of unstable angina pectoris, need for coronary artery bypass grafting or percutaneous transluminal coronary angioplasty	Median age: met=64; pla=64 %male: met=84; pla=87 Race: NR

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Placebo-controlled trials			
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	*Previous history of (%):* Angina: met=20.4; pla=20.1 Functional class I: met=0.4; pla=0.4 Functional class II: met=2.5; pla=2.5 Functional class III: met=11.9; pla=12.1 Functional class IV: met=6.0; pla=5.5 Duration of angina (median months): met=36; pla=39 MI: met=11.5; pla=12.5 Hypertension: met=6.9; pla=6.2 Diabetes: met=2.7; pla=2.3 CHF: met=2.9; pla=2.7 CABG: met=0.8; pla=1.0 PTCA: met=1.5; pla=1.0 Smokers: met=2.3; pla=2.5 Ex-smokers: met=12.7; pla=12.5	2365/2365/967	Total withdrawn: met=165(34%); pla=212(44%) Lost nr Analyzed: met=480; pla=487

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo-controlled trials				
Anonymous (MACB Study Group) 1995 Sweden *Fair quality*	Mortality: met=16(3.3%); pla=9(1.8%) Infarct development: met=9(1.9%); pla=10(2.1%) Development of unstable angina pectoris: met=14(2.9%); pla=17(3.5%) Need for CABG: met=2(0.4%); pla=1(0.2%) Need for PTCA=1(0.2%); pla=2(0.4%) Total endpoints: met=42(8.8%); pla=39(8.0%)	NR	NR	Bradycardia: met=12(2%); pla=4(0.8%) (p=0.05) Hypotension: met=6(1%); pla=11(2%) (NS) Congestive heart failure: met=13(3%); pla=6(1%) (NS) Poor peripheral circulation: met=8(2%); pla=13(3%) Atrioventricular block II/III: met=1(0.2%); pla=1(0.2%) Severe obstructive pulmonary disease: met=6(1%); pla=4(0.8%)

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Study design	Eligibility criteria	Exclusion criteria
Sjoland 1995 Sweden *Poor quality*	RCT	All CABG patients at 15 regional hospitals in 3 year period	n = 1398 excluded Simultaneous valve surgery = 261(19%) No informed consent = 254 (18%) Need beta blockade = 194 (14%) Age over 75 = 170 (12%) Systolic blood pressure<100 mm Hg = 57 (4%) Severe obstructive pulmonary disease = 62 (4%) In other randomized trials = 61 (4%) Death = 42 (3%) Heart rate < 45 beats/min, severe heart failure, poor peripheral circulation, advanced atrioventricular block or previous participation in study = 87 (6%) Other = 387 (28%)

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sjoland 1995 Sweden *Poor quality*	n= 967 metoprolol (met): 100 mg/day x 2 wks, then 200 mg/day x 2 yrs vs. placebo (pla) x 2 yrs	Calcium antagonists, long-acting nitrates, diuretics for heart failure, digitalis, other treatment for heart failure, antihypertensives, antiarrhythmics, acetylsalicylic acid, anticoagulation	Exercise test after 2 years	Mean age ≥ 65 = (46%) Mean age < 65 =(54%) % male = 85 Race: NR

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Sjoland 1995 Sweden *Poor quality*	History: angina pectoris = 949/967 (98%) myocardial infarction = 558/967 (58%) CHF = 129/967 (13%) Hypertension = 334/967 (35%) Diabetes mellitus = 115/967 (12%) Claudication = 105/967 (11%) Cerebrovascular disease = 68/967 (7%) Smoking = 113/967 (12%) Previous smoking = 592/967 (61%) Angina functional class (lo-hi): 1 = 18/967 (2%) 2 = 118/967 (12%) 3 = 554/967 (57%) 4 = 263/967 (27%)	2291 (74 died before screen) 2365 eligible CABG 967 enrolled	Withdrawn = 193/967 (20%) Lost (admin) = 148/967 (15%) Lost (nr) = 8/967 (1%) Analyzed = 618/967 (64%)

Evidence Table 6. Randomized controlled trials of beta blockers for coronary artery bypass graft

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Sjoland 1995 Sweden *Poor quality*	Exercise capacity (median): met = 130W pla = 140W (*P*=0.02) Angina pectoris at exercise: met = 48/306 (16%) pla = 33/311 (11%) Terminated exercise due to chest pain: met =18/307 (6%) pla = 10/311 (3%) Subjective symptom means: Effort (1-10) : met = 7.6; pla = 7.4 Dyspnoea (0-10): met = 6.6; pla = 6.5 Chest pain (0-10): met = 1.1; pla = 0.6 (*P*=0.001)	NR	Cardiac events (total): met = 19/307 (6%) pla = 19/311 (6%) Hypotension: met = 6/307 (2%) pla = 4/311 (1%) Bradycardia: met = 7/307 (2%) pla = 1/311 (0.3%)	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Head-to-head controlled trials			
Wilcox 1980 UK *Fair quality*	RCT	Clinical diagnosis of suspected MI within the previous 24 hours	Already taking a beta blocker; severe heart failure; sinus bradycardia of under 40 beats per minute; in second or third degree heart block; systolic BP of >90 mm Hg; history of asthma or diabetes; residence too far away.
Jonsson 2005 Norway	Open RCT	Age 18-80 w/chest pain for more than 30 mins consistent with acute MI if admitted to hospital w/in 24hrs after onset with diagnosis confimred by significant increase in cardiac enzymes with or without EKG changes.	Use of beta blockers during 3 mos preceding trial, history of cardiomyopathy, myopericarditis, cardiac surgery (w/in 1 mo of trial), bradycardia, hypotension, AV block grade 2-3, severe COPD, hemodynamically significant valvular defects including aortic stenosis, SBP <100 or >220 mmHg or DBP >120 mmgHg, Killip class 4 shock or heart failure, renal failure w/serum creatinine >160 mmol/L, hepatic impairment or platelet count <100,000 or white cell count <2000. Patients <18 or >80 yrs also excluded as were patients with any routine regulatory reason (participating in another study, drug contraindication, risk of teratogen effect, alcohol or drug abuse, psychatric disorder, serious concomitant disease , cancer or inability to give consent.)

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Head-to-head controlled trials			
Wilcox 1980 UK *Fair quality*	Propranolol (pro) 120-160 mg daily Atenolol (ate) 100 mg daily Placebo x one year Treatment initiated within 24 hours post-MI	NR	Clinic visits at 3-month intervals Cause of death was established from hospital and general practitioners' records and from postmortem reports
Jonsson 2005 Norway	atenolol 12.5mg bid titrated to 50mg bid by 6 wks carvedilol 6.25mg bid titrated to 25mg bid by 6 wks	Statins Aspirin Warfarin Diuretics ACE inhibitor/ARB	Hospital and clinic assessments weekly weeks 1-6; clinic assessment month 3 and 12 CV endpoints evaluated by investigators and controlled by blinded endpoint committee

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Head-to-head controlled trials				
Wilcox 1980 UK *Fair quality*	Mean age(% patients) <35 yrs: pro=3.8; ate=3.9; pla=2.3 -45 yrs: pro=12.9; ate=10.2; pla=16.3 -55 yrs: pro=33.3; ate=35.4; pla=31.0 -65 yrs: pro=32.6; ate=27.6; pla=31.0 > 65 yrs: pro=17.4; ate=22.8; pla=19.4 % male: Pro=84%; Ate=89%; Pla=81% Race: NR	*Hypertension:* Pro=11%; Ate=10%; Pla=15% *Angina:* Pro=27%; Ate=31%; Pla=24% *Infarction:* Pro=21%; Ate=16%; Pla=19% Drugs being taken for cardiovascular system: Pro=14%; Ate=14%; Pla=20% Drugs taken for other purposes: Pro=14%; Ate=14%; Pla=11%	662 screened/388 eligible/388 randomized	Withdrawn=171(44.1%) /lost to fu NR /analyzed=388
Jonsson 2005 Norway	Carvedilol 59.5 (SD 11.2) yrs 85% male 93% white Atenolol 61.7 (SD 11.4) yrs 71% male 93% white	*Previous MI:* Car=6%; Ate=6% *Angina:* Car=55%; Ate=54% *Hypertension:* Car=20%; Ate=19% *Hyperlipidemia:* Car=9%; Ate=11% *Additional medications:* aspirin: Car 89%; Ate 95% (*P*=0.044) warfarin + aspirin: Car 7%; Ate 1% (*P*=0.022) diuretics: Car 8%; Ate 21% (*P*=0.004) NSD between groups for use of warfarin (4% both groups), ACE inhibitors/ARBs (27;33%) or statins (97%; 98%)	nr/nr/232	11/nr/232 (safety analysis; unclear if this is the same for efficacy analysis)

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Head-to-head controlled trials		
Wilcox 1980 UK *Fair quality*	Mortality *At 6 weeks:* pro=10(7.5%); ate=11(8,6%); pla=15(11.6%) *At 1 year:* pro=17(12.9%); ate=19(14.9%); pla=19(14.7%)	Side effects separately recorded as either volunteered or elicited
Jonsson 2005 Norway	CV events Time to first serious CV event - unadjusted analysis Car vs Ate RR 0.88 (95% CI -.59 to 1.30; *P*=0.524) Adujsted for diuretic use Car vs Ate RR 1.0 (95% CI 0.6 to 1.5; *P*=0.990) LVEF at 12 mos Car 57.1%; Ate 56.0% (*P*=NS)	Clinical exams and information on all AEs registered at every visit

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Head-to-head controlled trials			
Wilcox 1980 UK *Fair quality*	NR	Withdrawals due to(# pts/%): *Hypotension:* pro=14(10.6%); ate=18(14.2%); pla=2(1.6%) Bradycardia: pro=8(6.1%); ate=9(7.1%); pla=3(2.3%) 2nd degree heart block: pro=3(2.3%); ate=1(0.8%); pla=2(1.6%) 3rd degree heart block: pro=1(0.7%); ate=4(3.1%); pla=2(1.6%) Heart failure: pro=7(5.3%); ate=3(2.4%); pla=8(6.2%) Asthma: pro=1(0.7%); ate=0; pla=0 Other: pro=10(7.5%); ate=16(12.6%); pla=23(17.8%)	
Jonsson 2005 Norway	No serious AEs reported *Cold hands/feet:* Car 20%; Ate 33.3% (*P*=0.025) *Other AEs:* NSD between groups for the following: dizziness, dyspnea, fatigue, muscle pain, flatulence, insomnia, atrial fibrillation, depression, nausea, coughing, ancle edema, anxity, impotence, nightmare occurrence, hyperhydrosis, constipation, diarrhea, skin reaction, dyspepsia	NR	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Mrdovic 2007	RCT	Consecutive patients who presented with clinical and electrocardiographic signs of acute anterior wall ST elevation myocardial infarction (STEMI) and LV EF of ≤ 45% on the echocardiogram performed within the first 72 hrs from the onset of symptoms.	Contradictions for beta blocker therapy including Killip class 3 or 4 heart failure, systolic arterial hypotension of <90 mm Hg, bradycardia of <50 beats per minute, second- or third-degree atrioventricular block, chronic obstructive pulmonary disease requiring bronchodilation therapy, and peripheral arterial disease with symptoms at rest. Also excluded were those already treated with adrenergic blockers or agonists or calcium-channel blockers.

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Mrdovic 2007	Inhospital: metoprolol tartrate 50 mg bid carvedilol 12.5 mg bid Postdischarge: metopolol tartrate 100 mg bid carvedilol 25 mg bid	Carvedilol vs. Metoprolol Concomitant therapy: streptokinase 65.8% vs. 60.0% asprin 89.7% vs. 89.9% intravenous metropolol 23.2% vs. 25.9% digitalis 18.1% vs. 25.3% diuretics 40% vs. 44.3% inotropes 5.2% vs. 10.1% statins 51.6% vs. 48.1% ace inhibitors 98.7% vs. 99.3%	Patients were reviewed at 6-month intervals for the assessment of tolerability and adverse cardiac events. Follow-up period continued until 233 primary endpoints were reached. Primary end point: fime to first composite cardiac adverse event (t-CAE) including all-cause mortality; rehospitalization for cardiovascular event; revascularization with percutaneous coronary intervention or bypass surgery; postinfarction angina pectoris with documented electorcardiopraphic signs of ischemia; and heart failure requiring additional treatment with digitalis, diuretics, or inotropic agents. Secondary end point: time to composite hard events (t-CHE) including cardiovascular death and nonfatal reinfarction. Health related quality of life: Short Form-36 (SF-36) questionnaire with 36 items and 8 domains. Each group of domains was reduced to a summary measure.

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Mrdovic 2007	Carvedilol 60.5 (SD 10.4) yrs 70% male Ethnicity NR Metoprolol 62.9 (SD 10.5) yrs 69% male Ethnicity NR	Diabetes Car= 26.5%; Met=27.1% (*P*=0.97) Hypertension Car=63.9%; Met=67.1% (*P*=0.34) Hyperlipidemia Car=55.5%; Met=44.3% (*P*=0.037)	493/318 /313	Withdrawn: Inhospital - car.=8; met.=22 (*P*=0.011) During follow up - car.=10; met.=16 (*P*=0.22) Lost to fu: car.=7; met.=0 Analysed: car.=155; met.=158

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Mrdovic 2007	Carvedilol vs. metoprolol Primary end point: time to first composite cardiac adverse event (t-CAE) all-cause death 8 (5.4%) vs. 14 (9.8%) *P*=0.21 postinfarction angina 29 (19.6%) vs. 39 (27.3%) *P*=0.16 HF 20 (13.5%) vs. 28 (19.6%) P=.21 rehospitalizatoin 11 (7.4%) vs. 17 (11.9%) *P*=0.23 revascularization 30 (20.3) vs. 37 (25.9%) *P*=0.33 Secondary end point: time to composite hard events (t-CHE) cardiovascular death 7 (4.7%) vs. 12 (8.4%) *P*=0.26 nonfatal reinfarction 9 (6.1%) vs. 12 (8.4%) *P*=0.47 Health-related quality of life (HRQL) (adjusted for age and baseline differences) general health 54 (SD 9) vs 50 (SD 14) *P*=0.037 physical functioning 70 (SD 22) vs. 62 (SD 23) *P*=0.011 role physical 68 (SD 30) vs. 60 (SD 28) *P*=0.058 vitality 58 (SD 23) vs. 50 (SD 23) *P*=0.008 social functioning 77 (SD 27) vs. 70 (SD 26) *P*=0.036 role emotional 85 (SD 24) vs. 80 (SD 28) *P*=0.13 mental health 56 (SD 18) vs. 51 *P*=0.035 bodily pain 91 (SD 19) vs. 88 (SD 21) *P*=0.32 PCS 52 (SE 4) vs. 51 (SE 4) *P*=0.086 MCS 53 (SE 4) vs. 52 (SE 5) *P*=0.16	Patients were reviewed at 6-month intervals for tolerability and adverse cardiac events.

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Mrdovic 2007	Only patients who were withdrawn from the study due to an AE are included. carvedilol vs. metoprolol In hospital: 8 vs. 22 total sample: progression of HF (n=19) hypotension (n=5) second or third degree atrioventricular block (n=5) bronchial obstruction (n=1) (OR car. 0.98, CI 0.14-0.63, *P*=0.011) During follow-up: 10 vs. 16 were withdrawn because of adverse effects or clinical deterioration (OR 0.59, CI 0.26-1.36, *P*=0.22).	Inhospital: car=8 (5%) vs. met.=22 (14%) total sample: HF n=19 hypotension n=5 second- or thrid-degree atrioventricular block n=5 bronchial obstruction n=5 Follow up: car=10 (6%) vs. met.=16 (10%) Total number of withdrawls car=18 (12%) vs. met=36 (23%) (OR for carvedilol .39, CI 0.21-0.73, *P*=0.003)	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Acebutolol vs placebo			
Boissel 1990 France *Fair quality*	RCT	At least 2 of the following risk factors: (1) Typical chest pain of ≥ 1 hour in duration, typical Q waves and significant release of cardiac enzyme(s) (2) admitted for this acute event > 2 and < 22 days before (3) presented ≥ 7 of the secondary risk factors of the selection algorithm, including ≥ 1 "major" secondary risk factor (history of dyspnea when walking on flat ground, documented atrial fibrillation, ventricular fibrillation, ventricular tachycardia, overt heart failure or sinusal tachycardia during the reference event, recurrent AMI or angina pectoris before the eighth day)	Heart rate <45 beats/min; complete auriculoventricular block and acute heart failure that required treatment with ≥ 2 drugs of different classes (e.g., diuretics and vasodilators); contraindication to beta blocking treatment; age > 75 years; death; malignancy; valvular disease; coma; asthma; chronic bronchopneumopathy; Raynaud syndrome; participation in another study; patients enrolled in APSI before

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Acebutolol vs placebo			
Boissel 1990 France *Fair quality*	Acebutolol 400 mg daily Placebo x 1 year Treatment initiated within 2-22 days post-MI	NR	Primary outcome: Total death

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Acebutolol vs placebo				
Boissel 1990 France *Fair quality*	Mean age=62.9 years 73% male Ethnicity nr	Angina pectoris=41.5% Unstable angina=28.9% Congestive heart failure=27.1% Renal failure=3.6% Diabetes mellitus=14.6% Cigarette smoker (actual or past)=65.5% Systemic hypertension=32.9% Atrial flutter or fibrillation=13.5% Ventricular flutter or fibrillation=5% Number of secondary risk factors (median)=8	nr/nr/607	Withdrawn=211 (34.8%) /0 lost to fu /analyzed=607

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Acebutolol vs placebo		
Boissel 1990 France *Fair quality*	Acebutolol (n=298) vs placebo (n=309) Total mortality: 17 (5.7%) vs 34 (11%); *P*=0.019 Vascular death: 12 (4%) vs 30 (9.7%); *P*=0.006 Reinfarction: 6 (2%) vs 4 (1.3%); *P*=NS Fatal or nonfatal reinfarction: 9 (3%) vs 11 (3.6%); *P*=NS Acute pulmonary edema: 20 (6.7%) vs 15 (4.9%); *P*=NS Fatal or non-fatal cardiac failure: 22 (7.4%) vs 22 (7.1%); *P*=NS Ventricular flutter or ventricular fibrillation: 1 (0.3%) vs 0; *P*=NS Ventricular flutter, ventricular fibrillation, or fatal arrhythmia: 0 vs 3 (1%); *P*=NS Other vascular events: 35 (11.7%) vs 28 (9.1%); *P*=NS Other nonvascular events: 51 (17.1%) vs 70 (22.7%); *P*=NS	nr

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Acebutolol vs placebo			
Boissel 1990 France *Fair quality*	Acebutolol (n=298) vs placebo (n=309) Angina pectoris: 98 (32.9%) vs 92 (29.8%); *P*=NS Heart failure: 137 (46%) vs 105 (34%); *P*=0.003 Conduction or rhythm disturbance: 102 (34.2%) vs 101 (32.7%); *P*=NS Sinus bradycardia: 48 (16.1%) vs 16 (5.2%); *P*<0.001 Sinus tachycardia: 8 (2.7%) vs 26 (8.4%); *P*=0.002 Atrioventricular block: 17 (5.7%) vs 15 (4.9%); *P*=NS Right bundle branch: 11 (3.7%) vs 16 (5.2%); *P*=NS Left bundle branch: 4 (1.3%) vs 7 (2.3%); *P*=NS Flutter or atrial fibrillation: 16 (5.4%) vs 12 (3.9%); *P*=NS Extrasystola or ventricular tachycardia: 16 (5.4%) vs 26 (8.4%); *P*=NS Other arrhythmia: 24 (8.1%) vs 29 (9.4%); *P*=NS	Acebutolol (n=298) vs placebo (n=309) Withdrawals due to adverse events: 12 (4%) vs 11 (3.5%); *P*=NS	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Carvedilol vs placebo			
Basu 1997 UK *Fair quality*	RCT	Chest pain; ECG changes; serum concentration of creatine kinase; MB isoform consistent with diagnosis	Already on ACE or beta blockers; contraindications to ACE or beta blockers; Killip class IV heart failure; cardiogenic shock; severe bradycardia; hypotension; second to third degree heart block; left bundle branch block; severe valvular disease; insulin-dependent DM; renal failure; known malignancy; other severe disease; pregnancy

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Carvedilol vs placebo			
Basu 1997 UK *Fair quality*	Carvedilol (car) 2.5-50 mg daily Placebo (pla) x 6 months Initial dose loaded intravenously	Aspirin - 100% Heparin - 97% Oral/iv nitrates - 97%	Patients were reviewed at 3-month intervals Exercise test (Bruce protocol) Endpoints: cardiac death, reinfarction, unstable angina, heart failure, emergency coronary revascularization, ventricular arrhythmias requiring intervention, cerebrovascular accident and initiation of additional cardiovascular drug therapy other than sublingual nitrates for angina

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Carvedilol vs placebo				
Basu 1997 UK *Fair quality*	Mean age: car=60; pla=60 % male: car=84; pal=84.5 Race: NR	*Site of MI:* Anterior - Car=51%; Pla=49% Inferior - Car=49%; Pla=51% *Type of MI:* Q-wave - Car=80%; Pla=80% Non-Q-wave - Car=20%; Pla=20% *Heart failure at entry (Killip II/III):* Car=45%; Pla=28% *Thrombolysed:* Car=99%; Pla=96% *Median time to thrombolysis:* Car=3.8 hours; Pla=3.9 hours *Smoker:* Car=67%; Pla=53.5% *Non-smoker:* Car=33%; Pla=46% *Previous IHD:* Car=20%; Pla=25% *NIDDM:* Car=12%; Pla=18% *Median time to infusion:* Car=16.8 hours; Pla=16.7 hours	416 screened/NR/151 enrolled	146 analyzed (car=75; pla=71)

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Carvedilol vs placebo		
Basu 1997 UK	Serious cardiac events: car=18(24%); pla=31(43.7%) Deaths/reinfarctions: car=11(14.7%); pla=6(8.4%)	NR
Fair quality		

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Carvedilol vs placebo			
Basu 1997 UK	Dizziness(% patients): car=6.5%; pla=1.4%	Withdrawals due to non-cardiac adverse events(# pts): car=4(5.3%); pla=3(4.2%)	
Fair quality			

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Anonymous, 2001; McMurray 2005 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	RCT	>18 years; stable, definite MI occurring3-21 days prior to randomization; left-ventricular ejection fraction of 40% or less; receipt of concurrent treatment with ACE inhibitors for at least 48 hours and stable dose for 24+ hours unless proven intolerance to ACE inhibitors; heart failure appropriately treated with diuretics and ACE inhibitors during acute phase	Required continued diuretics or inotropes; uncontrollable heart failure; unstable angina; uncontrolled hypertension; bradycardia; unstable insulin-dependent DM; continuing indication for beta blockers for any condition other than heart failure; requiring ongoing therapy with inhaled beta agonists or steroids

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Anonymous, 2001; McMurray 2005 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	Carvedilol (car) up to 50 mg daily Placebo (pla) x 1.3 years (mean) of follow-up	ACE inhibitors(% patients)=98 Reperfusion therapy(% patients)=46	Patients were reviewed every 3 months during the first year, and every 4 months thereafter

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Anonymous, 2001; McMurray 2005 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	*Carvedilol:* Mean age 63 73% male *Placebo:* Mean age 63 74% male	*Smoking history:* Current - Car=33%; Pla=32% Previous - Car=27%; Pla=25% Never - Car=39%; Pla=43% *Medical history:* Previous MI - Car=31%; Pla=29% Previous angina - Car=57%; Pla=54% Previous hypertension - Car=55%; Pla=52% Previous DM - Car=21%; Pla=23% Other vascular disease - Car=17%; Pla=16% Previous revascularization - Car=12%; Pla=11% Hyperlipidemia - Car=32%; Pla=33% SIte of MI: Anterior - Car=59%; Pla=54% Inferior - Car=21%; Pla=21% Other - Car=20%; Pla=25% Medications at time of randomization: ACE inhibitor - Car=98%; Pla=97% Aspirin - Car=86%; Pla=86%	NR/NR/1959 randomized	Permanent withdrawals(excluding death): car=192(20%); pla=175(18%)/lost to fu nr/1959 analyzed

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Anonymous, 2001; McMurray 2005 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	Co-primary endpoints(# patients/%) All-cause mortality: car=116(12%); pla=151(15%) (*P*=0.031) All-cause mortality or cardiovascular-cause hospital admission: car=340(35%); pla=367(37%) (NS) Secondary endpoints(# patients/%) Sudden death: car=51(5%); pla=69(7%) (NS) Hospital admission for heart failure: car=118(12%); pla=138(14%) (NS) Other endpoints(# patients/%) Cardiovascular-cause mortality: car=104(11%); pla=139(14%) (*P*=0.024) Death due to heart failure: car=18(2%); pla=30(3%) (NS) Non-fatal MI: car=34(3%); pla=57(6%) (NS) All-cause mortality or non-fatal MI: car=139(14%); pla=192(20%) (*P*=0.002) Atrial fibrillation/flutter: car=2.3%; plac=5.4%; HR 0.41 (95% CI 0.25-0.68; *P*=0.0003) Ventricular fibrillation/flutter/tachycardia: car=0.9%; pla=3.9%; HR 0.24 (95% CI 0.11-0.49; *P*<0.0001) Cardiac arrest in first 30 days of the trial: car=0.5%; pla=0.7%; HR 0.72 (95% CI 0.23-2.25; *P*=0.56) Composite endpoint in first 30 days (all cause mortality, nonfatal MI, or cardiac arrest) Car=31, 3.2%; pla 53, 5.4%; HR 0.58, 95% CI 0.38-0.91, *P*=0.02)	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous, 2001; McMurray 2005 International RCT *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)* Fair quality	NR	NR First 30 days of the trial: car=2.4%; pla=2.6% (NS)	Original primary endpoint (all-cause mortality) amended during the trial to co-primary endpoints of all-cause mortality (alpha=0.005) and all-cause mortality+cardiovascular hospitalization(alpha=0.045) apparently due to advice by Data Safety Monitoring Board (DSMB) that a blinded interim analysis had shown that power to detect pre-specified total mortality effect size was under threat

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Metoprolol vs placebo			
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	RCT	Ages 45-74; hospitalized for acute MI	History of CABG; permanent pacemaker; contraindication to beta blocker therapy; conditions likely to require beta blocker therapy; administration of any beta blocker within 3 days before the start of pre-entry evaluation; planned therapy with aspirin, sulfinpyrazone clofibrate;=, or dipyridamole; life threatening conditions other than CHF; conditions likely to affect protocol compliance; history of adverse reaction to metoprolol or its analogues.
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	RCT	Geographic location; chest pain of acute onset and 30 minutes' duration or ECG signs of acute MI with estimated onset of infarction within previous 48 hours; age 40-74;	Contraindications to beta blockade; need for beta blockade; administrative considerations

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Metoprolol vs placebo			
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	Metoprolol (met) 200 mg daily Placebo (pla) x 1 year Treatment interval: 5-15 days post-MI		Interim visits conducted at 1, 3, 7 and 12 months
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	Metoprolol (met) 15 mg intravenously; 200 mg orally Placebo (pla) Treatment interval(mean): 11.3 hours Initial dose loaded intravenously (3 injections); then administered orally x 3 months	*Arrhythmias:* iv lidocaine or procainamide *CHF:* furosemide 40-80 mg iv, then oral *Chest pain:* iv morphine; sl ntg; oral anticoagulants	Physician examination at 1-week and 3 months after inclusion

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Metoprolol vs placebo				
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	Mean age = 58 % Male = 83% % White = 90.5%	*Previous medical history:* MI = 14.5% Angina = 25% CHF = 2% Hypertension = 36% Diabetes = 7.5% Location of infarct: Anterior = 50.3% Inferior = 56% Anterior & inferior = 2% High lateral = 2.5% True subendocardial = 2.5%	NR/NR/2395 enrolled	Withdrawn: met=381(31.9%); pla=355(29.6%)/lost to fu NR/analyzed=2395
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	*Entire sample:* Mean age: met=60; pla=60 % male: met=75.6; pla=76.2 Race nr *Subgroup of patients with indirect signs of mild-to-moderate CHF (met n=131; pla n=131)* Mean age: met=63; pla=63 % male: met=75; pla=76 Race nr	*Clinical history:* Previous infarction - Met=21.2%; Pla=22.7% Angina pectoris - Met=35.7%; Pla=34.7% Hypertension - Met=29.1%; Pla=29.7% Smoking - Met=49.7%; Pla=50.3% *Clinical status at entry:* Pulmonary rales (24) - Met=11.6%; Pla=9% ECG signs of infarction (1) - Met=49.9%; Pla=47.8% Heart rate >100 beats/minute (1) - Met=4.7%; Pla=6.2% Systolic BP <100 mm Hg (2) - Met=3.3%; Pla=4.4% *Dyspnea at onset of pain (29) - Met=28.8%; Pla=30.8%*	2802 screened/2619 eligible/1395 randomized (met n=698; pla n=697)	Withdrawn: met=131(19.1%); pla=131(19.1%)/lost to fu NR /1395 analyzed

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Metoprolol vs placebo		
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	Total mortality (# patients/%) *</= 90 days:* met=23(1.9%); pla=37(3.1%) *</= 210 days:* met=42(3.5%); pla=54(4.5%) *</= 365 days:* met=65(5.4%); pla=62(5.2%) *</= 540 days:* met=86(7.2%); pla=93(9.8%)	NR
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	Entire sample: Mortality: met=40/698(5.7%); pla=62/697(8.9%); Odds ratio=0.62(95% CI 0.40-0.96) Reinfarction: met=35/698(5%); pla=54/697(7.7%); Odds ratio=0.63(95% CI 0.39-0.99) Subgroup with mild-to-moderate CHF: Mortality: met=13/131(10%); pla=25/131(19%); Odds ratio=0.47(95% CI 0.21-1.0); *P*=0.036 Reinfarction: met=9/131(7%); pla=10/131(8%); NS	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Metoprolol vs placebo			
Anonymous 1987 USA *Lopressor Intervention Trial* *Fair quality*	*Overall incidence:* met=34.6%; pla=23.8% Incidence of (%): Body as a whole: met=9.1; pla=6.2 Cardiovascular: met=17.2; pla=9.6 Digestive: met=4.3; pla=3.3 Endocrine: met=0; pla=0 Haemic/lymphatic: met=0.2; pla=0.2 Metabolic/nutritional: met=1.2; pla=0.5 Musculoskeletal: met=0.3; pla=0.4 Nervous system: met=8.7; pla=7.7 Respiratory: met=4.1; pla=2.7 Skin/appendages: met=1.3; pla=1.5 Special senses: met=2.8; pla=1.3 Urogenital system: met=1.6; pla=1.0	*Overall withdrawal due to adverse events(%):* met=13.1; pla=5.8	
Hjalmarson, 1981 Herlitz, 1984 Herlitz, 1997 Sweden *Goteborg Metoprolol Trial* *Good quality*	NR	Withdrawals due to overall adverse events: met=22(3.2%); pla=22(3.2%) Withdrawals due to(# pts/%): Hypotension: met=29(4.2%); pla=13(1.9%) (*P*=0.018) Bradycardia: met=18(2.6%); pla=5(0.7%) (*P*=0.011) Heart failure: met=4(0.6%); pla=7(1.0%) (NS)	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Metoprolol vs placebo			
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	RCT	Residence within catchment area; admission to coronary care unit within 48 hours from onset of symptoms and development of acute MI; sinus rhythm without complete bundle branch block.	Systolic BP <100 mm Hg; sever cardiac failure not responding to digitalis or diuretics; severe intermittent claudication; obstructive pulmonary disease; need for beta-adrenoceptor blockade; other major disease; unwillingness to participate.
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	RCT	Admission to CCU at Ulster Hospital	Delay from onset of pain exceeded 6 hours; initial rhythm VF; initial rhythm agonal; systolic BP >90 mm Hg associated with heart rate <100 beats min-1; clinical pulmonary edema or CHF; sinus or junctional bradycardia (<60 min-1), with systolic BP >90 mmHg and not responding to patient's legs elevated; received a beta-adrenergic blocking drug or a type I antiarrhythmic drug during previous 48 hours; atrio-ventricular block greater than first degree; previous admission to the study.

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Metoprolol vs placebo			
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	Metoprolol (met) 200 mg daily Placebo (pla) x 36 months Treatment interval: 48 hours post-MI	*Angina:* non-beta-andrenergic blocking antianginal agents	Interim visits conducted every 3 months
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	Metoprolol (met) 15 mg iv, followed by 200 mg oral daily dosage Placebo (pla) x 1 year Treatment interval: 48 hours post-MI	NR	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Metoprolol vs placebo				
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	Mean age: met=60; pla=59 % male: met=78; pla=83 Race = NR	Smokers: Met=53%; pla=60% Ex-smokers: Met=19%; Pla= 18% Previous MI: Met=24.5%; Pla=26.5% DM before MI: Met=10%; Pla=6% Cerebrovascular incidence before MI: Met=5%; Pla=3% Site of infarction: Anterior: Met=44%; Pla=51% Inferior: Met=38%; Pla=31% Unknown: Met=18%; Pla=18%	nr/nr/301	73(24.2%) withdrawn/lost to fu nr/301 analyzed
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	Age ≤65 = 548 >65 = 252 % Male 71.5% Race: NR	Previous MI = 26.75% Hypertension = 11.5 % Smoking habit = 47% Previous history of angina = 46.25% Previous history of dyspnoea = 28.38% Initial ventricular ectopic activity = 22.88% Initial supraventricular ectopic activity = 5%	1556 screened/800 eligible/800 enrolled	Withdrawn nr/lost to fu nr/800 analyzed

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Metoprolol vs placebo		
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	Sample size: met n=154; pla n=147 Total mortality (# patients/%): pla=31(21.1%); met=25(16.2%) (NS) Cardiac mortality (# patients/%): pla=29(19.7%); met=20(13.0%) (NS) Sudden death (# patients/%): pla=21(14.3%0; met=9(5.9%) (*P*<0.05) Reinfarction (# patients/%): pla=31(21.1%); met=18(11.7%) (*P*<0.05)	NR
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	Total mortality (# patients/%) At 3 months: met=37/416(8.9%); pla=35/384(9.1%)(NS) At one year: met=52/416(12.5%); pla=53/384(13.8%)(NS) Sudden death (# patients/%) At 3 months: met=4/416(1.0%); pla=3/384(2.1%)(NS) At one year: met=8/416(1.9%); pla=18/384(4.7%) (*P*<0.05)	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Metoprolol vs placebo			
Olsson, 1985 *Stockholm Metoprolol Trial* *Fair quality*	NR	Withdrawals due to (# patients/%): Uncontrolled angina: pla=16(10.9%); met=6(3.9%) (*P*<0.05) Heart failure: pla=1(0.7%); met=7(4.5%) (*P*<0.05) Symptomatic bradycardia: pla=1(0.7%); met=1(0.6%) (NS) Hypotension: pla=0; met=2(1.3%)	
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* *Fair quality*	# patients (%) Hypotension: met=20/416(4.8%); pla=14/384(3.6%) (NS) Heart failure: met=47/414(11.4%); 35/378(9.3%) (NS)	NR	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Pindolol vs placebo			
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	RCT	Clinical diagnosis of acute MI within previous 21 days; had to meet 2 of the following criteria: retrosternal severe chest pain of 20+ minutes duration, resistant to nitroglycerine and startinh in previous 48 hours; pulmonary edema without previously known valvular disease; shock without suspicion of acute hypovolaemia or intoxication; transient elevation of glutamine oxaloaecetic acid transminase or asptarate amino transferase in serum to values exceeding the normal limits for the laboratory on at least 2 readings with a maximum approximately 24 hours after the estimated onset of infarction, coupled with absent or less pronounced elevation of glutamine pyruvic acid transaminase or alinine amino transferase in serum; ECG series with presence of Q waves and/or presence of the disappearance of localized ST-elevation combined with development of T-inversion in at least 2 of the routine 12 leads; clinical course complicated by electrical and/or mechanical complications.	Uncontrolled heart failure; unrelated heart disease; persistent heart block of second or third degree; persistent bradycardia <50 beats/minute; obstructive airways disease; uncontrollable insulin dependent diabetes; known hypersensitivity to beta blocking drugs; other diseases serious enough to worsen the short-term prognosis irrespectively of the MI; pregnancy; necessity to use beta blocking drug or calcium antagonists; unable to return for regular control.

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Pindolol vs placebo			
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	Pindolol (pin) 15-20 mg daily Placebo (pla) x 24 months Treatment interval: up to 21 days post-MI	NR	Follow-up visits: months 1, 3, 6, 12, 18 and 24 Primary endpoint: death

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Pindolol vs placebo				
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	*Mean Age:*Pin=58; Pla=58 % male: Pin=83; Pla=83 Australian: Pin=48%; Pla=48% Swedish: Pin=52%; Pla=51.5%	*History:* Smoking: Pin=48%; Pla=43% Hypertension: Pin=24%; Pla=28% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) Angina pectoris: Pin=36%; Pla=32% Functional limitation: Pin=30%; Pla=30% Prior MI: Pin=18%; Pla=16% Diabetes: Pin=5%; Pla=8% (values indicated are those with a 10% or greater variation between patients randomized to pin. or pla.) *Anterior or lateral infarction:* Pin=47%; Pla=46% *Other site of infarction:* Pin=53%; Pla=54% *Medication used at time of randomization:* Digitalis: Pin=31%; Pla=34% Diuretics: 74%; Pla=75% Vasodilators (nitrates): Pin=23%; Pla=22% Antiarrhythmics: Pin=54%; Pla=51% Anticoagulants: Pin=72%; Pla=71% *Medication used at time of discharge:* Digitalis: Pin=31%; Pla=32% Diuretics: Pi46%; Pla=42% Nitrates: Pin=39%; Pla=35%	2500 screened/529 eligible/529 enrolled	126(23.8%) withdrawn/lost to fu nr/529 analyzed (pin n=263; pla n=266)

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Pindolol vs placebo		
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	*(# patients/%)* *Total mortality:* pla=47(17.7%); pin=45(17.1%) (NS) *Cardiac death:* pla=43(16.2%); pin=40(15.2%) (NS) *Cardiac sudden death:* pla=31(11.7%); pin=28(10.6%) (NS) *Non-cardiac death:* pla=4(1.5%); pin=5(1.9%)	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Pindolol vs placebo			
Australian & Swedish Study 1983 Australia, Sweden *Fair quality*	Overall incidence: pin=89(33.8%); pla=45(16.8%) (*P*=0.0001)	Withdrawals due to adverse events (# patients/%): pin=50(19%); pin=22(8.3%) (*P*=0.0003) Withdrawals due to: Cardiac failure: pin=20(7.6%); pla=11(4.1%) Hypotension: pin=3(1.1%); pla=1(0.4%) Reinfarction: pin=1(0.4%); pla=3(1.1%)	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Propranolol vs placebo			
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	RCT Single-blind	Age <76; history of at least 30 minutes of ischemic pain within 18 hours of potential therapy; new or presumably new ECG changes	Cardiogenic shock; advanced cardiac or other disease that would interfere with prognosis; participation in conflicting protocol; inability to participate because of geographical or psychological reasons; recent major surgery or MI; permanent cardiac pacemaker; previous participation in the protocol; failure or inability to give informed consent

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Propranolol vs placebo			
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Propranolol (pro): initial dose infused intravenously (0.1 mg per kg of body weight); subsequent oral dosing initiated at 20 mg and increased with an HR target of 45-60 BPM Placebo (pla) x 7 days	NR	Follow-up visits: months 3 and 6 Telephone vital status interview: 6-month intervals thereafter

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Propranolol vs placebo				
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Mean age: pro=54.9; pla=54.6 % male: pro=72.4; pla=74.1 % white: pro=82.1; pla=83.7	Mean age = 54.7 Male = 73.2% White = 83% Current smokers = 50% White collar workers = 39% High school or higher education = 61.3% Regular drinkers = 22% Medical history before recent infarction: Hypertension requiring medication = 44% Documented previous infarction = 14.5% Angina >3 weeks before recent infarction = 39% CHF in previous 3 weeks = 5% Diabetes = 19% Previous cardiac arrest = 0.7% Previous cardiac surgery = 5% Previous cardiac arrythmias = 7%	Screened=7597/Eligible=2408/Eligible after application of exclusion criteria=1589/Eligible for Group A (no contraindications to beta blocker therapy)=879 (pro n=134; pla n=135; hyaluronidase=131)	Overall patient withdrawals nr/lost to fu=1(treatment group nr)/analyzed=269

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Propranolol vs placebo		
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Mortality(after 36-months of follow-up): pro=24/134(17.9%); pla=20/135(14.8%) Treatment period=10 days Beta blockade at 3 months(% pts): pla=37%; pro=53% Beta blockade at 6 months(% pts): pla=40; pro=54	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Propranolol vs placebo			
Roberts, 1984 Rude, 1986 Roberts, 1988 United States *Multicenter Investigation of the Limitation of Infarct Size (MILIS)* *Fair-poor quality*	Cardiac failure (%): pla=23; pro=19	NR	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Propranolol vs placebo			
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	RCT	Men and women aged 30-69; hospitalized with symptoms and ECG and enzymatic changes compatible with acute MI	Chronic obstructive lung disease; severe CHF; bradycardia; life-threatening illness other than CHF; need for beta blocking drugs

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Propranolol vs placebo			
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	Propranolol (pro) 180 mg (82% of patients) or 240 mg (18% of patients) *(n=1916)* Placebo (pla) *(n=1921)* Treatment initiated 5-21 days post-MI	*% patients* Vasodilator: pro=47.8; pla=47.1 Diuretic: pro=40.8; pla=42.3 Tranquilizer: pro=28.0; pla=30.4 Digitalis: pro=26.9; pla=26.3 Aspirin: pro=21.5; pla=21.6 Antiarrhythmic: pro=20.7; pla=25.6 Potassium: pro=16.3; pla=17.7 Antihypertensive, excluding diuretic: pro=11.8; pla=13.4 Anticoagulant: pro=9.8; pla=8.5 Dipyridamole: pro=6.2; pla=5.5 Insulin: pro=4.8; pla=4.2 Hormonal: pro=4.5; pla=4.4 Oral hypoglycemic: pro=5.5; pla=3.2 Sulfinpyrazone: pro=4.3; pla=5.0	Clinic visits at 3-month intervals Deaths classified by blinded mortality classification subcommittee (relative/witness report; death certificates; attending physician; hospital records; autopsy)

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Propranolol vs placebo				
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	*Propranolol:* Mean age: 54.7 84% male *Placebo:* Mean age: 54.9 85.1% male	*Mean systolic BP mm Hg:* Pro=112.3; Pla=111.7 *Mean diastolic BP mm Hg:* Pro=72.5; Pla=72.3 *Mean heart rate, beats per minute:* Pro=76.2; Pla=75.7 *Mean cholesterol, mg/dL:* Pro=212.7; Pla=213.6 *Mean weight, kg:* Men - Pro=80.2; Pla=79.8 Women - Pro=67.4; Pla=66.5 *Current smoker*: Pro=57.4%; Pla=56.9% *Medical history:* Prior MI - Pro=13.9%; Pla=13.2% Hypertension - Pro=41.1%; Pla=40.1% Angina pectoris - Pro=35.8%; Pla=36.5% CHF - Pro=9%; Pla=9.4% DM - Pro=11.7%; Pla=11.3% *Taking propranolol or other beta blocker:* Pro=7.2%; Pla=6.8% *In-hospital events occurring before randomization:* Atrial fibrillation - Pro=6.8%; Pla=5.7% CHF - Pro=14.3%; Pla=14.9% Vetricular tachycardia - Pro=23%; Pla=23.2% Use of antiarrhythmic drug - Pro=45.8%; Pla=46% *Medications being used at time of randomization:* Antiarrythmic - Pro=16.6%; Pla=17.9% Anticoagulant - Pro=13.9%; Pla=15.1% Antiplatlet - Pro=7.1%; Pla=6.8% Diuretic - Pro=16.1%; Pla=18% Vasodilator - Pro=36%; Pla=36.3% Digitalis - Pro=12.5%; Pla=13% Oral hypoglycemic - Pro=2.2%; Pla=1.8%	Screened: 16,400 Eligible/enrolled (total=3,837): pro=1916; pla=1921	Overall number withdrawn nr/12(0.3%) lost to fu/3837 analyzed (pro n=1916; pla n=1921)

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Propranolol vs placebo		
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	*NNT; RR (95% CI)* ***Total mortality:*** NNT=39; RR=0.73(0.59-0.91) ***Deaths due to:*** ***Cardiovascular disease:*** NNT=44; RR=0.74(0.59-0.93) ***Sudden arteriosclerotic heart disease:*** NNT=78; RR=0.72(0.53-0.99) ***Non-sudden arteriosclerotic heart disease:*** NNT=97; RR=0.73(0.52-1.03) ***Other cardiovascular disease:*** NNT=1882(harm); RR=1.14(0.43-3.03) ***Noncardiovascular disease:*** NNT=322; RR=0.65(0.31-1.36)	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Propranolol vs placebo			
Anonymous, 1982 Goldstein, 1983 Anonymous, 1983 Lichstein, 1983 Furberg, 1984 Jafri, 1987 United States *Beta-blocker Heart Attack Trial (BHAT)* *Fair quality*	% patients with complaints: Shortness of breath: pro=66.8; pla=65.5 Bronchospasm: pro=31.3; pla=27.0 (*P*<0.005) Rapid heartbeat: pro=10.8; pla=15.1 (*P*<0.001) Cold hands, feet: pro=10.0; pla=7.7 (*P*<0.025) Tiredness: pro=66.8; pla=62.1 (*P*<0.005) Reduced sexual activity: pro=43.2; pla=42 Depression: pro=40.7; pla=39.8 Nightmares: pro=39.7; pla=36.9 Faintness: pro=28.7; pla=26.6 Insomnia: pro=21.1; pla=18.8 Blacking out: pro=9.1; pla=10.3 Hallucinations: pro=5.9; pla=4.5 Diarrhea: pro=5.5; pla=3.6 (*P*<0.01)	% patient withdrawals due to: CHF: pro=4; pla=3.5 (NS) Hypotension: pro=1.2; pla=0.3 (*P*<0.005) Pulmonary problems: pro=0.9; pla=0.7 (NS) Sinus bradycardia: pro=0.7; pla=0.3 (NS) New or extended MI: pro=0.4; pla=0.4 (NS) Serious ventricular arrhythmia: pro=0.3; pla=1.0 (*P*<0.025) Heart block: pro=0.1; pla=0.1 (NS) Syncope: pro=0.1; pla=0.1 (NS) Tiredness: pro=1.5; pla=1.0 (NS) Disorientation: pro=0.6; pla=0.6(NS) Depression: pro=0.4; pla=0.4 (NS) Faintness: pro=0.5; pla=0.2 (NS) Nightmares: pro=0.1; pla=0.2 (NS) Insomnia: pro=0.2; pla=0.0 (NS) Reduced sexual activity: pro=0.2; pla=0.0 (*P*<0.05) GI problems: pro=1.0; pla=0.3 (*P*<0.01) Dermatologic problems: pro=0.3; pla=0.1 (NS) Cancer: pro=0.2; pla=0.1 (NS)	

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Study design	Eligibility criteria	Exclusion criteria
Propranolol vs placebo			
Hansteen 1982 Norway *Fair quality*	RCT	MI according to WHO criteria, screened on fourth day after MI, only those with increased risk of death were included.	Contraindications to beta blockade; uncontrolled heart failure
Baber 1980 Multinational *Fair quality*	RCT	Diagnosis of anterior MI based on ECG abnormalities od an anterior infarction described as "very probable" on WHO ECG criteria; either a typical history or serum enzyme levels (AST and LDH) at least twice the accepted upper limit of normal or three times if CK was used.	Bronchospasm; atrioventricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Propranolol vs placebo			
Hansteen 1982 Norway *Fair quality*	Propranolol (pro) 160 mg daily Placebo (pla) x 12 months Treatment interval: 4-6 days post-MI	NR	Follow-up visits: months 2, 6 and 12
Baber 1980 Multinational *Fair quality*	Propranolol (pro) 120 mg daily Placebo (pla) x 9 months Treatment interval: 2-14 days post-MI	NR	Follow-up visits: months 1, 3, 6 and 9

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Propranolol vs placebo				
Hansteen 1982 Norway *Fair quality*	Mean age: Pro= 58; Pla=58.8 % male: Pro=84.5%; Pla=85.5%	*No previous CHD:* Pro=51.4%; Pla=48.6% *Angina pectoris:* Pro=30.6%; Pla=31.9% *Previous MI:* Pro=18%; Pla=19.5% *Hypertension (treated):* Pro=22.3%; Pla=18.15 *Intermittent claudication: Pro=8.6%; Pla=5.7%* *CVD:* Pro=3.2%; Pla=2.5% *Drug treatment before admission:* *Digitalis:* Pro=6.1%; Pla=5.7% *Diuretics:* Pro=19.1%; Pla=16% *Other antihy*pertensives: Pro=7.9%; Pla=6.4% Daily smoker: Pro=58.3%; Pla=64.9% *Ex-smoker:* Pro=28.1%; Pla=24.2%	4929 screened/eligible nr/560 enrolled	Withdrawals: pro=70(25.2%); pla=72(25.5%)/lost to fu nr/560 analyzed
Baber 1980 Multinational *Fair quality*	*Mean age:* Pro=55; Pla=54.8 *% male:* Pro=86%; Pla=83% *Previous angina:* Positive: Pro=35%; Pla=40% *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%	*Previous angina:* Positive: Pro=35%; Pla=40% Angina more than 3 months: Pro=15%; Pla=19% *Previous infarct:* *History of cardiac failure:* *Concurrent disease:* Hypertension: Pro=13%; Pla=15% Peripheral artery disease: Pro=1%; Pla=2% Diabetes: Pro=3%; Pla=4% *Smokers:* Pro=64%; Pla=65%	nr/nr/720	Total withdrawals: pla=88(24%); pro=82(23%)/lost to fu nr/720 analyzed

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Outcomes	Method of adverse effects assessment?
Propranolol vs placebo		
Hansteen 1982 Norway *Fair quality*	pro n=278; pla n=282 # patients/% Sudden death: pro=11(3.9%); pla=23(8.1%) (*P*=0.038) Type 1: pro=9(3.2%); pla=17(6.0%) (NS) Type 2: pro=1(0.3%); pla=3(1.1%)(NS) Type 3: pro=1(0.3%); pla=3(1.1%)(NS) Fatal reinfarction: pro=11(3.9%); pla=10(3.5%) (NS) Other cardiac deaths: pro=0; pla=2(0.7%)(NS) Other deaths: pro=3(1.1%); pla=2(0.7%)(NS) Total deaths: pro=25(8.9%); pla=37(13.1%) (NS) Total cardiac deaths: pro=22(7.9%); pla=35(12.4%) (NS) Non-fatal reinfarctions: pro=16(5.7%); pla=21(7.4%) (NS) Total no of cardiac events: pro=38(13.7%); pla=56(19.8%) (NS)	NR
Baber 1980 Multinational *Fair quality*	pla n=365; pro n=355 # pts/% Cardiac deaths: pla=18(4.9%); pro=19(5.4%) Non-cardiac deaths: pla=2(0.5%); pro=3(0.8%) Cardiac deaths after withdrawal: pla=7(1.9%); pro=6(1.7%) Total deaths: pla=27(7.4%); pro=28(7.9%) Non-fatal reinfarctions: pla=14(3.8%); pro=15(4.2%)	NR

Evidence Table 7. Randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Propranolol vs placebo			
Hansteen 1982 Norway *Fair quality*	Overall incidence(% pts): pro=57; pla=51 Most common adverse events(# pts/%): Bradycardia: pro=88(31.6%); pla=13(4.6%) (*P*<0.05) Heart failure: pro=18(6.5%); pla=25(8.9%) Hypotension: pla=23(8.2%); pla=9(3.2%) (*P*<0.05) Bronchospasm: pro=10(3.6%); pla=10(3.5%) Cold hands/feet: pro=31(11.1%); pla=30(10.6%) Dizziness/asthenia: pro=38(13.7%); pla=19(6.7%)	*# patients/%* *Withdrawals due to:* Atrioventricular or sinoatrial block: pro=3(1.1%); pla=3(1.1%) Sinus bradycardia: pro=7(2.5%); pla=1(0.3%) Heart failure: pro=22(7.9%); pla=16(5.7%) Hypotension: pro=1(0.3%); pla=1(0.3%) Bronchospasm: pro=1(0.3%); pla=1(0.3%) Intermittent claudication: pro=2(0.7%); pla=0 Cold hands/feet: pro=1(0.3%); pla=0 Nightmares: pro=3(1.1%); pla=3(1.1%) Dizziness/asthenia: pro=2(0.7%); pla=1(0.3%) Other symptoms: pro=3(1.1%); pla=2(0.7%) Reinfarction: pro=6(2.2%); pla=4(1.4%)	
Baber 1980 Multinational *Fair quality*	NR	Reinfarction: pla=9(2.5%); pro=10(2.8%) Cardiac failure: pla=22(6.0%); pro=22(6.2%) Cardiac failure alone: pla=17(4.6%); pla=10(2.8%) Angina: pla=13(3.6%); pro=7(1.9%) Arrhythmias: pla=11(3.0%); pro=7(1.9%) Adverse reaction: pla=5(1.4%); pro=12(3.4%) Other: pla=38(10.4%); pro=42(11.8%)	

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head-to-head controlled trials					
Wilcox 1980 UK	NR	adequate; numbered packs	Yes	Mean age NR 84.7% male	388 randomized
Jonsson 2005 Norway	Adequate (sealed envelopes; method of generation of envelopes NR)	NR	Yes	Mean age=60.1 yrs 67% male	232 randomized
Mrdovic 2007	Adequate (random numbers table)	no (use of numbered identical envelopes)	Statistically significant differences for three of 27 baseline varialbes. Age: car=60.5 years vs. met=62.9 years. Metropolol patients less likely to have hyperlipidemia and more likley to have Killip 4 HF as inhospital complication	Mean age=61.7 yrs 67% male yes	493 randomized

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat analysis
Head-to-head controlled trials						
Wilcox 1980 UK	Already taking a beta blocker; severe heart failure; sinus bradycardia of under 40 beats per minute; in second or third degree heart block; systolic BP of >90 mm Hg; history of asthma or diabetes; residence too far away.	Yes	Yes	Yes	Yes	Yes
Jonsson 2005 Norway	Use of beta blockers during 3 mos preceding trial, history of cardiomyopathy, myopericarditis, cardiac surgery (w/in 1 mo of trial), bradycardia, hypotension, AV block grade 2-3, severe COPD, hemodynamically significant valvular defects including aortic stenosis, SBP <100 or >220 mmHg or DBP >120 mmgHg, Killip class 4 shock or heart failure, renal failure w/serum creatinine >160 mmol/L, hepatic impairment or platelet count <100,000 or white cell count <2000.	Yes	Yes	Yes	No	Unclear for efficacy; Yes for safety
Mrdovic 2007	Contradictions for beta blocker therapy including Killip class 3 or 4 heart failure, systolic arterial hypotension of <90 mm Hg, bradycardia of <50 beats per minute, second- or third-degree atrioventricular block, chronic obstructive pulmonary disease requiring bronchodilation therapy, adn peripheral arterial disease with symptoms at rest. Also excluded were those already treated with adrenergic blockers or agonists or calcium-channel blockers.	Yes	No	No	No	No, excluded 22/313 (7%).

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Head-to-head controlled trials							
Wilcox 1980 UK	NR	Attrition=44.1%; others NR	NR	**Fair**	Imperial Chemical Industries Ltd.	N/A	1 year
Jonsson 2005 Norway	NR	NR	No	**Fair**	Roche; Glaxo Smith Kline	N/A	1 year
Mrdovic 2007	Unclear	Yes NR NR NR	7 (4%) for carvedilol vs. 0 for metoprolol. No No	**Fair**	Ministry of Science, Belgrade Serbia	N/A	mean 13.4 months

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Acebutolol vs placebo					
Boissel 1990 France	Adequate	Adequate	Significant between-group differences for 7 of >266 baseline variables	Mean age=62.9 years 73% male Ethnicity nr	607 randomized

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat analysis
Acebutolol vs placebo						
Boissel 1990 France	Heart rate <45 beats/min; complete auriculoventricular block and acute heart failure that required treatment with ≥ 2 drugs of different classes (e.g., diuretics and vasodilators); contraindication to beta blocking treatment; age > 75 years; death; malignancy; valvular disease; coma; asthma; chronic bronchopneumopathy; Raynaud syndrome; participation in another study; patients enrolled in APSI before	Yes	Yes	Yes	Yes	Yes

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Acebutolol vs placebo							
Boissel 1990 France	NR	Yes No Yes No	No No	**Fair**	NR	Yes	Mean follow-up=271 days

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Carvedilol vs placebo					
Basu 1997 UK	NR	NR	Yes	84% male Mean age=60	151 randomized
Anonymous 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	Adequate; Permuted blocks with stratification by center	NR	Yes	73.5% male Mean age=63 mean LVEF=32.9%	1959 recruited

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat analysis
Carvedilol vs placebo						
Basu 1997 UK	Already on ACE or beta blockers; contraindications to ACE or beta blockers; Killip class IV heart failure; cardiogenic shock; severe bradycardia; hypotension; second to third degree heart block; left bundle branch block; severe valvular disease; insulin-dependent DM; renal failure; known malignancy; other severe disease; pregnancy	Yes	Yes	Yes	Yes	Yes
Anonymous 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	Required continued diuretics or inotropes; uncontrollable heart failure; unstable angina; uncontrolled hypertension; bradycardia; unstable insulin-dependent DM; continuing indication for beta blockers for any condition other than heart failure; requiring ongoing therapy with inhaled beta agonists or steroids	Yes	Yes	Yes	Yes	Yes

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Carvedilol vs placebo							
Basu 1997 UK	NR	NR	None	**Fair**	NPH Cardiac Research Fund; Boehringer Mannheim GmbH	Yes	6 months
Anonymous 2001 *Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN)*	NR	NR	NR	**Fair**	GSK	Yes	mean of 1.3 years

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Metoprolol vs placebo					
Anonymous 1987 USA *Lopressor Intervention Trial*	NR	NR	Yes	Mean age=58 83% male	2395 randomized
Herlitz 1984 Herlitz 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Adequate; computer-generated randomization lists in blocks of 10	NR	Yes	Mean age=60 75.5% male	1395 randomized
Olsson 1985 *Stockholm Metoprolol Trial*	NR	NR	Yes	Mean age=59.5 80.5% male	301 randomized

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat analysis
Metoprolol vs placebo						
Anonymous 1987 USA *Lopressor Intervention Trial*		Yes	Yes	Yes	Yes	Yes
Herlitz 1984 Herlitz 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	Contraindications to beta blockade; need for beta blockade; administrative considerations	Yes	Yes	Yes	Yes	Yes
Olsson 1985 *Stockholm Metoprolol Trial*	Systolic BP <100 mm Hg; sever cardiac failure not responding to digitalis or diuretics; severe intermittent claudication; obstructive pulmonary disease; need for beta-adrenoceptor blockade; other major disease; unwillingness to participate.	Yes	Yes	Yes	Yes	Yes

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Metoprolol vs placebo							
Anonymous 1987 USA *Lopressor Intervention Trial*	NR	Attrition=30.7%; others NR	NR	**Fair**	CIBA-GEIGY	Yes	1.5 years
Herlitz 1984 Herlitz 1997 Sweden *Goteborg Metoprolol Trial* Fair quality	NR			**Good**	NR	Yes	1 year
Olsson 1985 *Stockholm Metoprolol Trial*	NR	Attrition=24.2%; others NR	NR	**Fair**	AB Hassle	Yes	3 years

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	Adequate; block randomization	NR	Yes	Mean age NR 71.5% male	800 randomized

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat analysis
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality		Yes	Yes	Yes	Yes	Yes

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Salathia 1985 Northern Ireland *Belfast Metoprolol Trial* Fair quality	NR	NR	NR	**Fair**	Astra Pharmaceuticals	Yes	1 year

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Pindolol vs placebo					
Australian & Swedish Study 1983 Australia, Sweden	NR	NR	Yes	Mean age=58 83% male	529 randomized
Propranolol vs placebo					
Anonymous 1982, 1983 Goldstein 1983 Lichstein 1983 Furberg 1984 Jafri 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	NR	NR	Yes	Mean age=54.8 84.4% male 88.8% white	3837 randomized
Hansteen 1982 Norway	Adequate; blocks of 10	NR	No; Mean heart size higher in pro group	Mean age NR 85% male	560 randomized

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat analysis
Pindolol vs placebo						
Australian & Swedish Study 1983 Australia, Sweden	Uncontrolled heart failure; uNRelated heart disease; persistent heart block of second or third degree; persistent bradycardia <50 beats/minute; obstructive airways disease; uncontrollable inslulin dependent diabetes; known hypersensitivity to beta blocking drugs; other diseases serious enough to worsen the short-term prognosis irrespectively of the MI; pregnancy; necessity to use beta blocking druga or calcium antagonists; unable to return for regular control.	Yes	Yes	Yes	Yes	Yes
Propranolol vs placebo						
Anonymous 1982, 1983 Goldstein 1983 Lichstein 1983 Furberg 1984 Jafri 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	Chronic obstructive lung disease; severe CHF; bradycardia; life-threatening illness other than CHF; need for beta blocking drugs	Yes	Deaths classified by blinded mortality classification subcommittee	Yes	Yes	Yes
Hansteen 1982 Norway	Cotraindications to beta blockade; uncontrolled heart failure	Yes	NR	Yes	Yes	Yes

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Pindolol vs placebo							
Australian & Swedish Study 1983 Australia, Sweden	NR	Attrition=23.8%; Compliance=54% took 90% or more	NR	**Fair**	Sandoz Ltd.	Yes	24 months
Propranolol vs placebo							
Anonymous 1982, 1983 Goldstein 1983 Lichstein 1983 Furberg 1984 Jafri 1987 United States *Beta-blocker Heart Attack Trial (BHAT)*	NR	NR	Lost to fu: pro=4(0.2%); pla=8(0.4%)	**Fair**	National Heart, Lung, and Blood Institute	Yes	mean of 25 months
Hansteen 1982 Norway	NR	Attrition=25.3%; Compliance(% taken > 95%): 80	NR	**Fair**	Imperial Chemical Industries Ltd.	Yes	12 months

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Baber 1980 Multinational	NR	NR	Yes	Mean age=54.9 84.5% male	720 randomized

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat analysis
Baber 1980 Multinational	Bronchospasm; atriovenyricular block greater than first degree; sinus bradycardia; persistent heart failure; beta blockade at the time of infarction.	Yes	NR	Yes	Yes	Yes

Evidence Table 8. Quality assessments of randomized controlled trials of beta blockers for post myocardial infarction

Author, Year Country	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding	Control group standard of care	Length of follow-up
Baber 1980 Multinational	NR	Attrition=23.5%; others NR	NR	**Fair**	ICI Pharmaceuticals	Yes	9 months

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Bisoprolol		
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	25.4% NYHA Class III: 95% IV: 5%	Age 18-75, CHF, dyspnea or fatigue corresponding to NYHA III or IV, ambulatory, clinically stable past 3 weeks and no heart failure past 6 weeks. Mandatory background medication diuretic and vasodilator therapy. Ejection fraction <40%. Etiology of heart failure: (1) idiopathic dilated cardiomyopathy with no known cause, (2) ischemia with documented history, (3) hypertension with history of therapy, (4) valvular heart disease repaired >6 months and nonischemic dilated cardiomyopathy with significant mitral valve insufficiency.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Bisoprolol		
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	CHF due to hypertrophic or restrictive cardiomyopathy with predominant left ventricular diastolic dysfunction; or secondary to mitral or aortic valve disease surgically repaired <6 months, or not repaired. MI <3 months. Awaiting bypass surgery or transplantation. Disabling permanent dyspnea at rest, insulin-dependent diabetes, asthma, renal insufficiency, hypothyroidism or hyperthyroidism, short life expectancy due to severe illness or malignancy. Resting heart rate <65 bpm; systolic blood pressure <100 or >160 mm Hg. No digitalis or amiodarone treatment <6 weeks before or 2 months after inclusion. Beta-adrenergic agonist or antagonist drugs and phosphodiesterase inhibitors prohibited.	Bisoprolol (bis) 5 mg vs. placebo (pla) for 1+ years Initial dose 1.25 mg/day titrated over 1 month. Clinician choice for dose levels at 1.25 mg (17%), 2.5 mg (30%) , 3.75 mg (2%) or 5 mg (51%) per day.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Bisoprolol				
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	Diuretic: 100% Vasodilator: ACEIs: 90% Calcium antagonists: 6% Other: 40% Digitalis: 57% Antiarrhythmic: Amiodarone: 20% Other: 6% Anticoagulant: 39% Antiplatelet: 26%	*Primary:* Total mortality. *Secondary*: Bisoprolol tolerability (premature withdrawals, NYHA functional status, number of nonlethal critical events. Followup every 3 months, mean duration 1.9 years.	Mean age 59.6 82.5% Male Race NR	CHF etiology: IDC: 36% Ischemia: 55% Hypertension: 5% Valvular disease: 4% History of acute episodes of heart failure: 56% History of MI: 47% Mean LVEF: 25.4%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Bisoprolol				
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	Total screened & eligible: NR Enrolled: 641 bis (n= 320) pla (n= 321)	Total withdrawn: 157/641 (24.5%) Bis 75/320 (23.4%) Pla 82/321 (25.5%) 1 patient lost to follow-up. Analyzed=641	Primary (All Deaths): Bis: 53/320 (16.6%) Pla: 67/321 (20.9%) (NS) Sudden death: Bis: 15/320 (4.7%) Pla: 17/321 (5.3%) (NS) Secondary: NYHA class improvement: Bis: 68/320 (21%) Pla: 48/321 (15%) (*P*<0.03) NYHA class deterioration: Bis: 41/320 (13%) Pla: 35/321 (11%) (NS) Heart failure: Bis: 11/320 (3.4%) Pla: 22/321 (6.9%) (NS) Subgroup deaths, no MI history: Bis: 18/151 (12%) Pla: 42/187 (22.5%) (*P*=0.01)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Bisoprolol			
Anonymous 1994 *The Cardiac Insufficiency Bisoprolol Study (CIBIS I)* 70 centers in 9 European countries Fair quality	NR, except Bis: 2 sinus bradycardia, 2 atrioventricular blockade	NR Non CV events: Bis: 44/320 (13.7%) Pla: 54/321 (16.8%)	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	27.5% NYHA Class III: 83% IV: 17%	Age 18-80, CHF diagnosis >3 months previous, dyspnea on exertion, orthopnea or paroxysmal nocturnal dyspnoea, and fatigue, corresponding to NYHA III or IV; ambulatory, clinically stable past 6 weeks or 3 months for acute MI. CV therapy unchanged past 2 weeks. Mandatory medication diuretic and ACE inhibitor or other vasodilator if ACEI intolerant. Ejection fraction <35%.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	Uncontrolled hypertension, MI or unstoppable angina pectoris in past 3 months, revascularization in past 6 months, previous or scheduled heart transplant, atrioventricular block > first degree without pacemaker, resting heart rate < 60 bpm, systolic blood pressure <100, renal failure, reversible obstructive lung disease or planned therapy with beta-adrenoreceptor blockers. No treatment with beta blockers (also eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs except amiodarone during trial.	Bisoprolol (bis) 10 mg. vs. placebo (pla) for 1+ years Initial dose 1.25 mg/day titrated weekly for 3 weeks to 5 mg (13%), then 4-week intervals to 7.5 mg (11%) and 10 mg/day (43%). No run-in period.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	Diuretic: 99% Vasodilator: -ACE inhibitors: 96% -Calcium antagonists: 2% - Nitrates: 58% Digoxin: 52% Antiarrhythmic: - Amiodarone: 15% Anticoagulant: 31% Antiplatelet: 41%	*Primary:* Total mortality. *Secondary:* All-cause hospital admission, all CV deaths, combined endpoint, permanent treatment withdrawals. Followup every 3 months, mean duration 1.3 years. Study stopped early with significant results.	Mean age 61 80.5% Male Race NR	CHF etiology: - Primary dilated cardiomyopathy: 12% - Ischemia: 50% - Other heart failure: 39%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	Total screened & eligible: NR Enrolled: 2647 Bisoprolol (n= 1327) Placebo (n= 1320)	Total: 69/2647 (2.6%) Bis: 41/1327 (3.1%) Pla: 28/2647 (2.1%) 6 patients lost to follow-up. Analyzed=2.647	Primary - Total mortality: Bis: 156/1327 (12%) Pla: 228/1320 (17%) (*P*<0.0001) - Sudden death: Bis: 48/1327 (3.6%) Pla: 83//1320 (6.3%) (*P*=0.0011) Subgroup analysis of mortality: - Ischemic etiology Bis: 75/662 (11.3%) Pla: 121/654 (18.5%) (*P*<0.001) Secondary: - All CV deaths Bis: 119/1327 (9.0%) Pla: 161/1320 (12.2%) (*P*=0.0049) - All-cause hospital admission Bis: 440/1327 (33.2%) Pla: 513/1320 (38.9%) (*P*=0.0006) Subgroup analysis of hospital admission: - for worsening heart failure Bis: 159/1327 (12.0%) Pla: 232/1320 (17.6%) (*P*=0.0001) - for stroke Bis: 31/1327 (2.3%) Pla: 16/1320 (1.2%) (*P*=0.04) - for ventricular tachycardia and fibrillation Bis: 6/1327 (0.5%) Pla: 20/1320 (1.5%) (*P*=0.006) - for hypotension: Bis: 3/1327 (0.2%) Pla: 11/1320 (0.8%) (*P*=0.03) - for bradycardia: Bis: 14/1327 (1.1%) Pla: 2/1320 (0.2%) (*P*<0.004)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous 1999 *The Cardiac Insufficiency Bisoprolol Study (CIBIS II)* Good quality	NR	NR	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Carvedilol		
Bristow 1996 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	23% NYHA class II: 46% II: 52% IV: 2%	Age 18-85, ejection fraction ≤ 35%, symptomatic ischemic or dilated cardiomyopathy heart failure, symptoms present ≥ 3 months, walk test 150-450 m, stability (no change in NYHA class and absence of hospitalization) ≥ past 1 month, any digoxin use started ≥ 2 months prior and stable dose ≥ past 1 month, resting heart rate ≥ 68 bpm.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Carvedilol		
Bristow 1996 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	Uncorrected valvular disease, hypertrophic or postpartum cardiomyopathy, uncontrolled symptomatic or sustained ventricular tachycardia, acute MI within 3 months, planned or likely revascularization or transplantation within 6 months after screening. Also, sick sinus syndrome, 2nd- or 3rd-degree heart block not treated with pacemaker, symptomatic peripheral vascular disease limiting exercise testing, sitting systolic blood pressure <85 mm Hg or >160 mm Hg, CV accident within last 3 months, cor pulmonale, obstructive pulmonary disease requiring oral bronchodilator or steroid therapy, and other selected disorders and sensitivities. Excluded drugs: alcohol intake >100 g/day, use of investigational drug within 30 days, CCBs, amiodarone within 3 months, and others.	Carvedilol (car) 12.5 mg, 25 mg, 50 mg daily Placebo (pla) x 6 months 3-week screening phase. 2-week run-in with open-label car. to establish tolerability prior to randomization. 2-week titration phase.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Carvedilol				
Bristow 1996 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	ACE inhibitors: 94% Digitalis: 92% Loop-activity diuretics: 95% Thiazide diuretics: 18% Vasodilators: 35%	*Primary:* Improvement in submaximal exercise, using 6-minute walk test and 9-minute self-powered treadmill test. *Secondary:* Changes in quality of life, NYHA class, EF, need for hospitalization due to heart failure and other CV causes, and signs and symptoms of heart failure.	Mean age 59.5 76% Male 78% White	Ischemic cause: 52%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Carvedilol				
Bristow 1996 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	Screened: NR Eligible for run-in: 376 Enrolled: 345 car. 50 mg (n=89) car. 25 mg (n=89) car.12.5 mg (n=83) placebo (n=84)	Total: 52/345 (15%) Lost to QOL assessment: 38/345 (11%) Lost to hospitalization assessment: 23/345 (6.7%) Lost to exercise result: NR Analyzed=345	No effect on exercise duration. No effect on NYHA class. Crude mortality at 6 months: car 25 bid: 1/89 (1.1%)(*P*≤0.001) car 12.5 bid: 6/89 (6.7%) (*P*=0.07) car 6.25 bid: 5/83 (6.0%) (*P*≤0.05) Pla: 13/84 (15.5%) (*P* values vs. placebo) Sudden death Car (all)=6/261(2.3%); pla=6/84(7.1%) CV Hospitalizations Total: car 25 bid: 9/82 (11.0%) car 12.5 bid: 11/82 (13.4%) car 6.25 bid: 9/80 (11.3%) Pla: 17/78 (21.8%) (no linear trend) (all car. vs. pl, *P*=0.03) QOL mean score change: car 25 bid: -5.5 car 12.5 bid: -7.3 car 6.25 bid: -7.9 Pla: -7.3 (NS)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Carvedilol			
Bristow 1996 *Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)* Fair quality	**Dizziness:** All car: 83/261 (31.8%) car 25 bid: 34/89 (38.2%) car 12.5 bid: 29/89 (32.6%) car 6.25 bid: 20/83 (24.1%) pla: 19/84 (22.6%) (linear trend, *P*=0.01) (all car vs. pla, *P*=0.11) **Cardiac failure:** All car: 56/261 (21.4%) car 25 bid: 22/89 (24.7%) car 12.5 bid: 23/89 (25.8%) car 6.25 bid: 11/83 (13.3%) pla: 19/84 (22.6%) (linear trend, *P*=0.34) (all car vs. pla, *P*=0.82) Edema or weight gain: All car: 30/261 (11.5%) car 25 bid: 9/89 (10.1%) car 12.5 bid: 10/89 (11.2%) car 6.25 bid: 11/83 (13.3%) pla: 5/84 (6.0%) (linear trend, *P*=0.60) (all car vs. pla, *P*=0.14) **Bradycardia:** All car: 21/261 (8.0%) car 25 bid: 10/89 (11.2%) car 12.5 bid: 10/89 (11.2%) car 6.25 bid: 1/83 (1.2%) pla: 1/84 (1.2%) (linear trend, *P*=0.001) (all car vs. pla, *P*=0.03) **Hypotension:** All car: 17/261 (6.5%) car 25 bid: 6/89 (6.7%) car 12.5 bid: 6/89 (6.7%) car 6.25 bid: 5/83 (6.0%) Pla: 4/84 (4.8%) (linear trend, *P*=0.60) (all car vs. pla, *P*=0.56)	Withdrawals due to any adverse events: car(all)=18%; pla=11%	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Packer 1996 *PRECISE* Fair quality	22% NYHA class II: 40% III: 56% IV: 4%	Chronic heart failure (dyspnea or fatigue ≥3 months), LVEF ≤35% despite ≥2 months treatment with diuretics and ACEI.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Packer 1996 *PRECISE* Fair quality	Uncorrected primary valvular disease, active myocarditis or obstructive or restrictive cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; heart rate <68 bpm; significant hepatic, renal or endocrine disease; drug or alcohol abuse; or any condition that could limit survival. Patients receiving CCBs, alpha- or beta-adrenergic agonist or antagonists or specific antiarrhythmic drugs.	Carvedilol (car) 50 mg daily vs. placebo (pla) for 6 months Begin 6.25 mg bid titrated over 2-6 weeks (50 mg bid for weight ≥85 kg) - 87% reached target, avg 28 mg/day.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Packer 1996 *PRECISE* Fair quality	Digitalis: 90% Loop-active diuretic: 99% ACEI: 97% Direct-acting vasodilator: 29%	*Primary:* Exercise tolerance on 6-minute corridor walk and 9-minute treadmill. Secondary: global assessment, NYHA class, LVEF, quality of life	Mean age 60.3 73% Male Race NR	Cause of heart failure - CAD : 52% - Nonischemic dilated cardiomyopathy: 48%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Packer 1996 *PRECISE* Fair quality	Screened: NR Eligible for run-in: 301 Enrolled: 278 car (n= 133) pla (n= 145)	49/278 (18%) withdrawn Lost to follow-up for NYHA class and global assessment: 9% Lost to follow-up for AE report: 10/278 (4%) Analyzed: 278	Primary: 6-minute exercise test increase: car: 17 m pla: 6 m (NS) No difference in 9-minute treadmill test. Secondary: NYHA class III/IV improvement: car: 28/130 (21.5%) pla: 9/130 (6.9%) (*P*=0.014) NYHA class deterioration: car: 3% vs. pla: 15% (*P*=0.001) No difference in QOL scores. LVEF change: car: +8% pla: +3% (*P*<0.001) Deaths (ITT): car: 6/133 (4.5%) pla: 11/145 (7.6%) (NS) CV hospitalization (ITT): car: 22/133 (16.5%) pla: 37/145 (25.5%) (NS)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Packer 1996 *PRECISE* Fair quality	Dizziness: car: 31/129 (24.0%) pla: 16/139 (11.5%) (*P*<0.01) Heart failure: car: 15/129 (11.6%) pla: 31/139 (22.3%) (*P*<0.025) Weight gain: NR Bradycardia: car: 7/129 (5.4%) pla: 1/139 (0.7%) (*P*<0.025) Hypotension: car: 8/129 (6.2%) pla: 3/139 (2.2%) (NS)	Withdrawals due to any adverse event: car=7(5.3%); pla=11(8.3%)	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Colucci 1996	Mild 23%	Age 18-85 with chronic symptomatic heart failure (dyspnea or fatigue) ≥3 months), LVEF ≤35% despite ≥2 months treatment with diuretics and ACEI.
U.S. Carvedilol Heart Failure Study Group (Mild)	NYHA class II: 85% III: 15%	

Fair quality

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood of revascularization or transplantation within 12 months; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival. Patients receiving amiodarone within 3 months before screening.	Carvedilol (car) 50 mg daily vs. placebo (pla) for 12 months (mean 7 months) Begin 12.5 mg bid titrated (50 mg bid for weight ≥85 kg) - 85% achieved max dose. Terminated early with significant results.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	Background therapy held constant if possible, adjusted for AE	*Primary:* progression of heart failure. *Secondary:* LVEF, NYHA class, heart failure score, global assessments, quality of life, 9-minute self-powered treadmill test, and heart size	Mean age 55 85% Male Race NR	Cause of heart failure: Ischemic: 42% Nonischemic: 58%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	Screened: NR Eligible for run-in: 389 Enrolled: 366 car (n=232) pla (n=134)	Withdrawals=8.5%; Lost to fu NR; Analyzed=366	Primary: Clinical progression of heart failure: car: 25/232 (10.8%) pla: 28/134 (20.9%) (*P*=0.008) All deaths: car: 2/232 (0.9%) pla: 5/134 (3.7%) (*P*=0.048) CV deaths: car: 0 pla: 4/134 (3.0%) (*P*<0.01) Hospitalization for heart failure: car: 9/232 (3.9%) pla: 8/134 (6.0%) (NS) Secondary: NYHA class improved: car: 12% vs. pla: 9% NYHA class worsened: car: 4% vs. pla: 15% (overall change favors car, *P*=0.003) QOL score mean change: car: -4.9 vs. pla: -2.4 (NS) No difference in exercise test.	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Colucci 1996 *U.S. Carvedilol Heart Failure Study Group (Mild)* Fair quality	dizziness: car: 81/232 (34.9%) pla: 27/134 (20.1%) (*P*<0.01) cardiac failure: car: 26/232 (11.2%) pla: 22/134 (16.4%) (NS) weight increase: car: 29/232 (12.5%) pla: 10/134 (7.5%) (NS) bradycardia: car: 30/232 (12.9%) pla: 1/134 (0.7%) (*P*<0.001) hypotension: car: 21/232 (9.1%) pla: 4/134 (3.0%) (*P*<0.05)	nr	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	22% NYHA class II: 1% III: 86% IV: 14%	Age 22-85; symptoms of heart failure (dyspnea or fatigue) ≥3 months); LVEF ≤35% despite ≥2 months treatment with diuretics and ACEI; able to walk less than 150 m on 6-minute corridor walk test assigned to severe protocol (relaxed to <350 m due to slow enrollment).

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood heart transplantation within 6 months; sick sinus syndrome or advanced heart block without pacemaker; any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival.	Carvedilol (car) 50 mg daily Placebo (pla) x 6 months, mean 3 months.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	Diuretic: 98% ACEI: 93% Digoxin: 90%	*Primary:* quality of life *Secondary:* mortality, CV hospitalizations, global assessments, NYHA class, LVEF, 6-minute walk exercise test	Mean age 60 58% Male Race: 71% White 21% Black 8% Other	Cause of heart failure: Ischemic: 45% Nonischemic: 55%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	Screened: NR Eligible for run-in: 131 Enrolled: 105 car (n= 70) pla (n= 35)	Reported withdrawn: 12/105 (11%) (4 deaths, 2 transplants. 5 AE) Reports 1 lost to follow-up. Final sample sizes often NR. Lost to LVEF test: 50/105 (52%). Lost to follow-up in 2 months: 35/105 (33%) Lost to follow-up in 6 months: 92/105 (88%)	[carry-forward analysis] Primary: QOL score improvement: car=11.6; pla=8.8 Secondary: No difference in NYHA class. No difference in CV hospitalization. No difference in deaths. 6-minute exercise test increase: car: 19.0 m pla: 28.4 m (NS)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group* Poor quality	[sample size NR - unreliable] dizziness: car: 24.3% pla: 31.4% worsening heart failure: car: 10.0% pla: 22.9% weight gain: car: 10.0% pla: 5.7%	*Withdrawals due to:* Bradycardia/heart block: car=3(1.4%); pla=0 Dizziness/hypotension: car=3(1.4%); pla=0 Worsening heart failure: car=5(2.4%); pla=2(0.9%)	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Richards 2001	29%	Chronic stable heart failure due to ischemic heart disease; LVEF <45%; NYHA functional class II or III or previous NYHA class II-IV
Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	NYHA class II: 30% III: 54% IV: 16%	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	Current NYHA class IV; heart rate below 50 beats per minute; sick sinus syndrome; second or third degree heart block; systolic BP <90 mm Hg or >160/100 mm Hg; treadmill exercise duration <2 minutes or >18 minutes; coronary event or procedure within previous 4 weeks; primary myocardial or valvular disease; current treatment with beta-blocker, beta-agonist or verapamil; insulin-dependent DM; obstructive airways disease; hepatic disease; any other life-threatening non-cardiac disease.	Carvedilol (car) 50 mg daily Placebo (pla) x 12 months Begin 6.25 mg bid titrated over2-5 weeks. At 6 months, avg. 46 mg daily.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	ACEI: 85% Diuretic: 76% Digoxin: 79%	*Primary:* Change in LVEF and treadmill exercise duration (Naughton protocol 2-min. stages) *Secondary:* Change in LV dimension, 6-minute walk distance, symptoms of heart failure, frequency of death, hospital admission, and worsening heart failure Clinical assessment at 5 weeks and 3 months, then every 3 months.	Mean age 67 80% male Race NR	Previous MI: 88.6% Previous hospital admission for CHF: 42% Previous highest NYHA class: II: 26.5% III: 30% IV: 43% Current NYHA class: I: 30% II: 54% III: 16% Current treatment for heart failure: ACEI: 85.5% Diuretic: 75.6% Digoxin: 38%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	Screened: NR Eligible for run-in: 442 Enrolled: 415 car (n= 207) pla (n= 208)	Total withdrawn at 6 months: 43/415 (10%)/lost to fu NR/analyzed=415	*Primary:* *No significant i*mprovement in treadmill duration *Secondary:* *No significant improvement in* 6-min. walk distance NYHA class (12 months) improved: car 26%; pla 28% no change: car=58%; pla=58% worse: car 16%; pla 13% Total mortality: car: 20/208 (9.6%) pla: 26/207 (12.6%) (NS) Sudden death: car: 10/208 (4.8%) pla: 11/207 (5.3%) (NS) All hospital admissions: car: 99/208 (47.6%) pla: 120/207 (58.0%) (NS) All CV hospitalizations: car: 70/208 (33.7%) pla: 83/207 (40.1%)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group Study* Good quality	nr	*Withdrawals due to:* Dizziness/Hypotension: car: 3/207 (1.4%) pla: 0 (NS) Worsening heart failure: car: 5/207 (2.4%) pla: 2/208 (0.9%) (NS) Bradycardia/Heart block: car: 3/207 (1.4%) pla: 0 (NS)	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	29.5% NYHA Class I: 11.1% II: 60.3% III: 28.5%	Stable chronic heart failure (defined as freedom from an acute cardiovascular event for 3 months; freedom from all-cause admission for 1 month; stable treatment for heart failure for at least 2 weeks) with objective evidence of left ventricular systolic dysfunction (ECG wall motion index cutoff of 1.3 or less; corresponding to an LVEF of <40%) due to coronary artery disease (defined as history of myocardial infarction, coronary revascularisation, or coronary artery disease on arteriography); NYHA Class I-III
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	19.8% NYHA Class NR	Patients with severe chronic heart failure as a result of ischemic or nonischemic cardiomyopathy

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	Patients younger than 40 years and women of child-bearing age; resting heart rate less than 60 beats per minute; sitting systolic blood pressure less than 85 mm Hg; unstable angina; arrhythmias; uncontrolled hypertension; obstructive pulmonary disease; poorly controlled diabetes; or clinically relevant renal or hepatic disease; those receiving non-dihydropiridine calcium-channel blockers; beta blockers, or antiarrhythmic agents other than amiodarone	Carvedilol (car) 6.25-50 mg daily Placebo (pla) x 4 months maintenance
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	Heart failure that was caused by uncorrected primary valvular disease or a reversible form of cardiomyopathy; had received or were likely to receive a cardiac transplant; had severe primary pulmonary, renal, or hepatic disease; or had a contraindication to beta-blocker therapy; coronary revascularization, acute myocardial or cerebral ischemic event, sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation within the previous two months; use of an alpha-adrenergic blocker, a calcium-channel blocker, or a class I antiarrhythmic drug within the previous four weeks or a beta-blocker within the previous two months; systolic blood pressure lower than 85 mm Hg; heart rate lower than 68 beats per minute; serum creatinine concentration higher than 2.8 mg per deciliter; serum potassium concentration lower than 3.5 mmol per liter or higher than 5.2 mmol per liter; increase of more than 0.5 mg per deciliter in the serum creatinine concentration or a change in body weight of more than 1.5 kg during the screening period	Carvedilol (car) 50 mg daily *(n=1156)* Placebo (pla) *(n=1133)*

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	Angiotensin-converting enzyme inhibitors treatment compulsory	*Primary:* Change in LVEF in hibernators versus non-hibernators *Secondary:* (1) LVEF change in carvedilol versus placebo, irrespective of hibernation status; (2)relation between volume of hibernating myocardium and change in LVEF; (3) change in contractile dysfunction in hibernators versus non-hibernators; (4) change in number of segments with reversible exercise-induced myocardial perfusion defects on carvedilol versus placebo; (5) *composite of death or worsening of heart failure in carvedilol vs placebo*	Age: 62.5 % male: 90 % white: 91.1	Current smokers: 16.7% Diabetes: 22.3% Previous MI: 90.2% Previous CABG: 45.2% NYHA Class I: 11.1% II: 60.3% III: 28.5% LVEF (mean): 29.5%
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	Usual medications for heart failure	*Primary: A*ll-cause mortality *Secondary:* (1) Combined risk of death/hospitalization for any reason; (2) combined risk of death or hospitalization for CV reason; (3) combined risk of death/hospitalization for HF; (4) patient global assessment	Age: pla=63.4; car=63.2 %male: pla=80; car=79 Race NR	% ischemic cause: pla=67; car=67 % left ventricular ejection fraction: pla=19.8; car=19.9 % heart failure hospitalization within past year: pla=65; car=66

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	489 screened/440 eligible/387 enrolled	82(21.2%) withdrawn/lost to fu NR/305 analyzed	Exercise time (seconds): car=405; pla=427 (NS) Death: car=8/188(4.3%); pla=6/188=3.2%(NS) Composite of all-cause mortality and worsening heart failure: car=44/187(23.5%); pla=37/188(19.7%) (NS)	nr
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	3106 screened/eligible NR/2289 randomized	withdrawn: pla=84; car=70/0 lost/analyzed(ITT): pla=1133; car=1156	*n (hazard ratio; 95%CI)* All-cause mortality: pla=190; car=130 (0.65; 0.52-0.81) Death/hospitalization for any reason: pla=507; car=425 (0.76; 0.67-0.87) Death/hospitalization for CV reason: pla=395; car=314 (0.73; 0.84-0.63) Death/hospitalization for HF: pla=357; pla=271 (0.69; 0.81-0.59) No. of pts hospitalized, n(%) Worsening HF: pla=268(23.7); car=198(17.1) CV reason: pla=314(27.7); car=246(21.3) For any reason: pla=432(38.1); car=372(32.2) More than once: pla=188(16.6); car=152(13.1)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Cleland, 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)* Fair quality	Overall adverse events: frequent in both groups (rates NR) Dizziness, fatigue, syncope and bradycardia were more typical with carvedilol than with placebo (rates NR)	nr	
Eichhorn 2001 Packer, 2001, 2002 Krum 2003 *The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial* Fair quality	Serious adverse events: pla=516(45.5%); car=451(39.0%)	One-year withdrawal rates: pla=18.5%; car=14.8%	Study stopped early based on the finding of a significant beneficial effect of carvedilol on survival that exceeded the prespecified interim monitoring boundaries Mortality reduction equivalent for age, gender, LVEF, cause of HF subgroups

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Hori 2004 Japan	LVEF=30% NYHA class II/III=78%	Patient who had ischemic or nonischemic cardiomyopathy with stable symptoms (NYHA functional class II or III); LVEF ≤ 40%; age between 20 and 79 years
The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial *Fair quality*		

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	Valvular heart disease, hypertrophic obstructive cardiomyopathy, cardiogenic shock, systolic blood pressure < 90 mm Hg, bradycardia (<60/min), grade II or III atrioventricular block, life-threatening arrhythmia, unstable angina, resting angina, cor pulmonale, asthma, Raynaud phenomenon, and intermittent claudication; myocardial infarction or coronary artery bypass grafting had occurred within the preceding 3 months	Run-in Open carvedilol 2.5 mg daily x 1-2 weeks; then open carvedilol 5 mg daily x ≥ 2 weeks Treatment Carvedilol 5 mg daily Carvedilol 20 mg daily Placebo x 24-48 weeks

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	Diuretics, digitalis, ACE inhibitors, calcium channel blockers, vasodilators, anti-arrhythmic agents	*Primary:* Improvement of global assessment of CHF by attending physician (markedly improved, moderately improved, mildly improved, no change, worsened, unassessable) *Secondary:* all-cause death or hospitalization for cardiovascular disease (CVD), CVD hospitalization, hospitalization for worsening CHF, changes of LVEF, and changes of NYHA class	Mean age=60 77% male 100% Japanese	Nonischemic etiology of heart failure=73% NYHA class II/III=78% LVEF=30% Systolic BP (mm HG)=119 Diastolic BP (mm Hg)=72 Heart rate (beats/min)=80 Body weight=61 kg Other medications ACE-inhibitors=76% Diuretics=86% Digitalis=65%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	nr/nr/190 enrolled	16 (8.4%) withdrew after run-in (prior to randomization; number withdrawn following randomization NR/lost to fu NR/analyzed=173	Placebo (n=49) vs carvedilol 5 mg (n=47) vs carvedilol 20 mg (n=77); *P* value for carvedilol 5 mg vs placebo comparison; *P* value for carvedilol 20 mg vs placebo comparison Primary Global improvement (proportion of patients with moderate or marked improvement): 36.7% vs 44.7% vs 59.7%; *P*=NS; *P*<0.05 Secondary Death or CVD hospitalization: 24.5% vs 8.5% vs 5.2%; *P*=0.024; *P*=0.002 CVD hospitalization: 24.5% vs 4.3% vs 3.9%; *P*=0.003; *P*<0.001 Worsening CHF: 20.4% vs 2.1% vs 2.6%; *P*=0.004; *P*<0.001 Other CVD reasons for hospitalizations: 6.1% vs 2.1% vs 1.3%; *P*=0.229; *P*=0.116 Change in LVEF units (mean): 6.6 vs 8.7 vs 13.2; *P*=NS; *P*<0.05 NYHA class Improved: 48.9% vs 80.9% vs 70.8%; *P*<0.001; *P*<0.05 No change: 40.4% vs 17.0% vs 27.8%; *P*<0.05; *P*=NS Worsened: 10.6% vs 2.1% vs 1.4%; *P*=NS; *P*=NS	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial* *Fair quality*	Incidence: 63.3% vs 51.1% vs 59.7%; *P*=NS; *P*=NS	NR	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Metoprolol		
Anderson 1985 USA Fair quality	28% NYHA class avg: 2.8	Idiopathic dilated cardiomyopathy confirmed by ECG

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Metoprolol		
Anderson 1985 USA Fair quality	Unstabilized overt cardiac failure; alcohol abuse; secondary cardiomyopathies; firm exclusions to beta blocker treatment (asthma, advanced heart block, allergy)	Metoprolol (met) 100 mg daily Placebo (pla) x 19 months Begin 12.5 mg bid titrated over 2 weeks to target - median dose 25 mg bid.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Metoprolol				
Anderson 1985 USA	Digitalis: 87% Diuretic: 80% Vasodilators: 40% Antiarrhythmics: 35% Anticoagulant (warfarin): 12%	*Primary:* Survival *Secondary:* Exercise duration (Naughton protocol)	Mean age 51 66% male Race NR	NR
Fair quality				

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Metoprolol				
Anderson 1985 USA Fair quality	Screened: NR Eligible: 50 Enrolled: 50 met (n=25) pla (n=25)	Dropout from treatment group: 5/25 (20%) Overall, 2 patients lost to follow-up Analyzed=50	Primary Deaths: met: 5/25 (20%) pla: 6/25 (24%) (NS) Secondary Exercise duration: met: 9.4 min pla: 8.2 min (NS)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Metoprolol			
Anderson 1985 USA Fair quality	NR	NR	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	22% NYHA class I: 3% II: 45% III: 49% IV: 4%	16-75 years; symptomatic dilated cardiomyopathy; state of compensated heart failure by means of conventional treatment; systolic BP ≥90 mm Hg; heart rate ≥45 beats per minute

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	Treatment with beta blockers, calcium channel blockers, inotropic agents or high doses of tricyclic antidepressant drugs; significant CAD shown by angiography; clinical or histological signs of ongoing myocarditis; other life-threatening diseases; obstructive lung disease; excessive alcohol consumption; drug abuse; insulin-dependent diabetes; pheochromocytoma; thyroid disease	Metoprolol (met) 100-150 mg daily (higher target for higher weight) vs. placebo for 18 months and 12 months Run-in period 2-7 days. Begin 10 mg titrated over 6+ weeks to target - mean dose 108 mg/day.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	Digitalis: 78% ACEI: 79% Nitrates: 14% Antiarrhythmics: 16% Frusemide: 75%	*Primary* Combined - total deaths and need for transplantation. *Secondary* Exercise duration (Naughton protocol in North America, bicycle exercise protocol in Europe begin 20W +10W increments); also LVEF, QOL, and NYHA change; and hospital readmissions. At 45 days, 3, 6, 12 and 18 months.	Mean age 49 73% male Race NR	Current smokers: 18%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	Screened: NR Eligible: 417 Enrolled: 383 met (n=194) pla (n=189)	Withdrawn from study medication at 12 months: 54/383 (14%) Lost to LVEF measure: 44% Lost to QOL measure: 71% Lost to hospital followup: 6% Analyzed=383	Primary Total deaths or need for transplantation: met: 25/194 (12.9%) pla: 38/189 (20.1%) (NS) All-cause mortality: met=23(11.8%); pla=21(11.1%) Sudden death: met: 18/194 (9,3%) pla: 12/189 (6.3%) (NS) Secondary Exercise capacity at 6 and 12 months: met: +80s and +76s pla: +47s and +15s (Difference at 12 months, *P*=0.046) NYHA class improvement: data NR Quality of life: data NR Hospitalization patients: met: 37/184 (20.1%) pla: 49/177 (27.7%) (NS) Hospitalization episodes: met: 51/184 (27.7%) pla: 83/177 (46.9%) (*P*<0.05)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Waagstein 1993 *Metoprolol in Dilated Cardiomyopathy (MDC) Trial* Fair quality	NR	*Withdrawals due to:* Progressive heart failure: met: 7/194 (3.6%) pla: 13/189 (6.9%) (NS) All "related" adverse events: met=1(0.5%); pla=3(1.6%)	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 Deedwania 2005 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality	28% NYHA class II: 41% III: 55% IV: 4%	Age 40-80; symptomatic heart failure (NYHA class II-IV) for 3 months or more and receiving optimum standard therapy; stable clinical condition during 2 week run-in phase; LVEF of <40%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 Deedwania 2005 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality	Acute MI or unstable angina within 28 days; indication or contraindication for treatment with beta-blockade or drugs with beta-blocking properties; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty; implanted cardioversion defibrillator (expected or performed); CABG or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second or third degree; unstable decompensated heart failure; supine systolic BP >100 mm Hg; any serious disease that might complicate management and follow-up according to protocol; use of calcium antagonists; use of amiodarone within 6 months; poor compliance.	Metoprolol (met) 200 mg/day vs. placebo for 1 year 2-week placebo run-in. Begin 12.5 mg (NYHA class III/IV) or 25 mg daily, titrated over 6 weeks to target.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 Deedwania 2005 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality	Diuretics: 90% ACEI: 89% Angiotensin I: 7% ACEI or Angiotensin II: 96% Digitalis: 64% Aspirin:46% Lipid-lowering agents: 26%	*Primary:* Total mortality, and combined total mortality and all-cause hospitalization (time to first event) *Secondary:* Worsening heart-failure mortality or hospitalization (time to first event), other CV events, NYHA class change, and QOL substudy.	Mean ages: <60: 34% 60-69: 35% ≥70: 31% 77% male 94% White 5% Black 1% Other	Current daily smoker: 14.4% Heart failure: Ischemic: 65% Nonischemic: 35% Previous MI: 48% Atrial fibrillation: 16.6% Hypertension: 44% DM: 24.6%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 Deedwania 2005 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality	Screened: NR Eligible (recruited): 4427 Enrolled: 3991 met (n=1990) pla (n=2001)	Total withdrawn: 589/3991 (15%) 0 lost to follow-up of vital status. Analyzed=3991	Primary All cause mortality: met=145(7.3%); pla=217(10.8%) (*P*=0.0009) Total mortality or All-cause hospitalization: met: 641/1990 (32.2%) pla: 767/2001 (38.3%)(*P*<0.001) Sudden death: met=3.9%; pla=6.5% (*P*=0.0002) Death or heart transplantation: met: 150/1990 (7.5%) pla: 218/2001 (10.9%) (*P*<0.001) Cardiac death or nonfatal MI: met: 139/1990 (7.0%) pla: 225/2001 (11.2%) (*P*<0.001) Secondary All hospitalization (patients): met: 1021/1990 (51.3%) pla: 1149/2001 (57.4%) (*P*=0.005) CV hospitalization (patients): met: 394/1990 (19.8%) pla: 494/2001 (24.7%) (*P*<0.001) NYHA class improvement favors met group (*P*=0.003). Subgroup: diabetic patients Total mortality risk reduction met vs pla: 18% (95% CI 44% to -19%; *P*>0.2 All hospitalization risk reduction met vs pla: 37% (95% CI, 53 to 15; *P*=0.0026)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 Deedwania 2005 *Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)* Fair quality		Withdrawals due to: Dizziness: met: 12/1990 (0.6%) pla: 6/2001 (0.3%) (NS) Heart failure: met: 78/1990 (3.9%) pla: 117/2001 (5.8%) (*P*<0.01) Weight increase: NR Bradycardia: met: 16/1990 (0.8%) pla: 5/2001 (0.2%) (*P*<0.025) Hypotension: met: 12/1990 (0.6%) pla: 5/2001 (0.2%) (NS) Any adverse event: met=9.8%; pla=11.7%	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	28.5% NYHA Class: I: 6.8% II: 69.2% III: 23.5% IV: 0.5%	Symptomatic heart failure (Class II-IV); 6-minute walk distance of <500 m; LVEF<40%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	NR	*Stage 1:* Candesartan: 4-16 mg daily Enalapril: 20 mg daily Candesartan 48 mg and enalapril 20 mg *Stage 2:* Addition of Metoprolol CR (met CR) 25-200 mg daily or placebo

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	Stage I medications	*Primary:* 1) 6-minute walk distance 2) neurohumoral parameters *Secondary:* 1) NYHA functional class 2) Quality of life (Minnesota Living With Heart Failure questionnaire)	Mean age=61.5 82.1% male 87.1% white	Heart failure duration: 7-12 mo: 12.4% >12 mo: 87.6% Previous MI: 63.6% Diabetes: 25.3% Smoker Current: 15% Former: 61% Never: 23.9% NYHA Class: I: 6.8% II: 69.2% III: 23.5% IV: 0.5% LVEF(mean): 28.5%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	nr/468/426	nr/nr/426	6-minute walk distance change (meters): met CR=(-1); pla=(-3) Quality of life: met CR=pla (data NR) NYHA functional class: met CR=pla (data NR) All-cause deaths: met CR=8(3.7%); pla=17(8%) (NS) Sudden death due to worsening heart failure: met CR=0.5%; pla=3(1.4%) Hospitalizations due to heart failure: met CR=15(7%); pla=5(2.3%)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)* Fair quality	NR	Overall discontinuation due to intolerability: met CR=11%; pla=12% Permanent discontinuation due to: Symptomatic hypotension: met CR=4(1.9%); pla=2(0.9%) Worsening heart failure: met CR=7(3.3%); pla=5(2.4%) Symptomatic bradycardia: met CR=0; pla=0	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Waagstein 2003 Europe *Fair quality*	28.5% NYHA Class I=0 IIa=13.3% IIb=49.1% IIIa=29.1% IIIb=8.5%	Symptomatic patients of either sex, 18- to 80-years old, with stable CHF (NYHA class II-III). Patients were prospectively stratified into an ischemic heart disease (IHD) group and a dilated cardiomyopathy (DCM) group. DCM was diagnosed based on the presence of LV dilation and EF ≤ 0.40 without significant coronary artery obstruction; IHD was diagnosed based on LV dilation, EF ≤ 0.40, and the presences or a history of at least one significant coronary obstruction

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Waagstein 2003 Europe *Fair quality*	Coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the previous 6 months or who were scheduled for or expected to require these treatments during the 6-month study; patients who had a major ischemic event (acute MI or unstable angina) within the previous 6 months and those with large anterior aneurysms, acute myocarditis, primary valvular heart disease, exercise-limiting angina pectoris or severe systemic disease; excessive consumption of alcohol (≥ 100 g of pure alcohol/day or ≥ 700 gram/week), resting systolic blood pressure > 190 mmHg or diastolic > 100 mmHg, systolic blood pressure <95 mmHg (unless considered occasional), heart rate < 50 beats/min, second- or third-degree atrioventricular (AV) block, sick sinus syndrome, sinoatrial block or atrial fibrillation (which makes equilibrium radionuclide angiography difficult to perform; pacemaker for third-degree AV block or a ventricular inhibited (VVI) pacemaker programmed with a fixed heart rate above the spontaneous heart rate	Metoprolol 150 mg daily Placebo x 6 months

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Waagstein 2003 Europe *Fair quality*	ACE inhibitors, diuretics and digitalis in patients with overt heart failure ACE inhibitors and digoxin could be used, as long as the dosage remained unchanged for at least 2 weeks before the study period; diuretic doses could be altered as clinically indicated	Maximal exercise capacity (bicycle tests-protocol NR) Self-assessment NYHA classification	Mean age=56.7 80% male Ethnicity NR	Weight=79.1 kg Height=173.1 cm Heart rate=78.1 beats/min Systolic blood pressure=121.5 mmHg Diastolic blood pressure=76.5 mmHg NYHA Class I=0 IIa=13.3% IIb=49.1% IIIa=29.1% IIIb=8.5% Previous MI=48.5% Previous CABG=18.8% Previous PTCA=9.7% ACE inhibitor=91.5% Diuretics=77.6% Digoxin=57% Mean EF=0.285 Mean duration of exercise=515.6 seconds

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Waagstein 2003 Europe *Fair quality*	nr/nr/172 enrolled/169 randomized/165 started double-blind medication	3 (1.7%) withdrew prior to randomization, 31 (18.3%) withdrew following randomization/1(0.6%) lost ot fu/165 analyzed	Metoprolol (n=71) vs placebo (n=65) EF at 6 months (estimates from a graph) EF at rest: 0.36 vs 0.29; P<0.001 EF at exercise: 0.37 vs 0.32; P<0.001 Maximal exercise on bicycle test: data NR; P=NS Death during study or within 3 weeks after discontinuing study medication: 4.6% vs 3.8%; P=NS Hospital/emergency room admission for cardiovascular reasons: data NR; P=NS Improvement in NYHA class: 42% vs 33%; P=NS	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Waagstein 2003 Europe *Fair quality*	NR	11.6% vs 12.6%; *P*=NS	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Nebivolol		
Edes 2005 (ENECA)	neb. vs. placebo LVEF mean 25.41, 26.41 NYHA class II 52.24%, 45.24% NYHA class III 45.52%, 47.62% NYHA class IV 2.24%, 7.14%	Hospitalized patients or outpatients aged < 65; NYHA class II, III, IV CHF; a stable clinical course; an LVEF ≤35%; and stable basic medication for CHF with ACE inhibitors and/or ARBs, diuretics, and/or digitalis for a minimum of 2 weeks prior to inclusion.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Nebivolol		
Edes 2005 (ENECA)	Acute corinary syndrome; a MI within the last 3 months; PTCA or coronary artery bypass surgery within the last month; obstructive or hypertrophic cardiomyopathy; hemodynamically relevant congenital or valvular heart disease; tachyarrhythmia resistant therapy (>100/min); bradycardia. Patients were also excluded if they received beta-blocker therapy in the 4 weeks prior to the beginining of the trial or known intolerance or hypersensitivity to nebibolol.	nebivolol: maximum tolerated dose or maximum of 10 mg/day. Placebo: maximum tolerated does or maximum of 10 mg/day. 8 months

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Nebivolol				
Edes 2005 (ENECA)	intervention as add on therapy. standard medications: ACE inhibitors, diuretics and digitalis	Primary: LVEF Secondary: NYHA score, Quality of Life (Minnesota Living w/ Heart Failure Questionnaire - higher score = higher disability), hospitalization rate, survivial rate (Kaplan-Meier), safety parameters (adverse events, vital signs, and laboratory parameters) 8 months	neb. vs. placebo age= 71.87, 72.19 male=70.15%, 76.98% ethnicity=99.2%, 98.4% caucasian	neb. vs. placebo height (cm) 168.73, 170.3 weight (kg) 74.56, 75.59 BMI 26.11, 26.02 previous MI 59.7%, 57.14% atrial fibrillation 26.52%, 25.40% diabetes 24.63%, 26.98% NYHA class II 52.24%, 45.24% NYHA class III 45.52%, 47.62% NYHA class IV 2.24%, 7.14% LVEF mean 25.41, 26.41

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Nebivolol				
Edes 2005 (ENECA)	354/NR/260	24/1/260	neb. vs. plecebo Secondary outcomes: NYHA improvement by 1 class: 33/134 (24.6%), 34/126 (26.9%); improvement by 2 classes: 2/134 (1.4%), 3/126 (1.5%) (NS) Quality of life: mean score decreased 9.13 vs. 11.01 points (NS) mean time to first hospitalization: 15.92 days, 15.77 days (NS) survival rate: 67.47%, 62.89% (NS) Adverse Events: 81 (60.45%) patients, 78 (61.90%) patients total mortality rate: 7/134 (5.2%), 7/126 (5.5%)	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nebivolol			
Edes 2005 (ENECA)	159/260 patients (360 total events neb.=186 vs. placebo=174) AEs with highest freq.: worsening of CHF (14 vs. 16), ventricular tachycardia (5 vs. 7), atrial fibrillation 4 vs. 8). most frequent drug related: (neb. vs. placebo) bradycardia (9 vs. 2) hypotension (8 vs. 4) dizziness (5 vs. 2) Percentage of severe advers events: neb 12.9; pla 15.03 (NS)	NR	

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Mean EF NYHA Class	Eligibility criteria
Flather 2005 (SENIORS)	neb. vs. placebo NYHA class I 3%, 2.7% NYHA class II 56.5%, 56.3% NYHA class III 38.7%, 38.7% NYHA class IV 1.8%, 2.3% Ejection fraction: < 35%: 64.3%, 64.8% > 35%: 35.7%, 35.2%	Patients ≥ 70 years old, clinical history with CHF with at least one of the following: documented hospital admission within previous 12 months with discharge diagnosis of CHF, documented left ventricular EF ≤ 35% w/in previous 6 months.

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria	Interventions (drug, regimen, duration)
Flather 2005 (SENIORS)	New drug therapy for heart failure 6 weeks prior to randomization, any change in cardiovascular drug therapy 2 weeks prior to randomization, heart failure due primarily to valvular heart disease, contraindication or previous intolerance to beta-blockers (e.g., heart rate <60 beats/min or systolic blood pressure <90 mmHg), curent use of beta-blockers, significant hepatic or renal dysfunction, cerebrovascular accidents within previous 3 months, and being on a waiting list for percutaneous coronary intervention or cardiac surgery or other major medical conditions that may have reduced survival during the period of the study.	Nabivolol titrated to 10 mg once daily. Placebo titrated to 10 mg once daily. Duration: NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Allowed other medications/interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Flather 2005 (SENIORS)	Angiotensin converting enzyme inhibitor neb 81.7%; pla 82.6% Angiotensin II antagonist neb 6.2%; pla 7.1% Aldosterone antagonist neb 28.8%; pla 26.4%	Primary: all cause mortality cardiovascular hospital admission (time to first event) Secondary: all cause hospital admissions cardovascular mortality NYHA Class assessment 6 minute walk test at 6 months follow-up at 4, 6 months and at 3 month intervals.	Mean Age:76.1 male: 63% ethnicity: NR	neb. vs. placebo NYHA class I 3%, 2.7% NYHA class II 56.5%, 56.3% NYHA class III 38.7%, 38.7% NYHA class IV 1.8%, 2.3% Ejection fraction: ≤ 35%: 64.3%, 64.8% > 35%: 35.7%, 35.2% Heart rate (beats/min) 79.2, 78.9 smoker: 4.9%, 5.4% prior MI 43.8%, 43.7% Hypertension 61.1%, 62.3% Atrial fibrillation: 33.8%, 35.5% DM: 26.9%, 25.3%

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment?
Flather 2005 (SENIORS)	nr/nr/2135	7/nr/2128	# events nebivolol vs. placebo Primary outcome: all cause mortality or cardiovascular hospital admission: 332 (31.1%), 375 (35.3%) P=0.039 Cardovascular hospitalizations contributing to primary outcome: 256 (24%), 276 (26%) (NS) Secondary outcomes: Death (all cause) 169 (15.8%), 192 (18.1%) (NS) NYHA Class assessment: data NR 6 minute walk test at 6 months: data NR quality of life: data NR	NR

Evidence Table 9. Placebo controlled trials of beta blockers for heart failure

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Flather 2005 (SENIORS)	First 15 advers categories by incidence overall neb. vs. placebo cardiac failure, aggravated 24%; 25% dizziness: 15.6%; 13.4% hypotension: 7.7%; 7.2% atrial fibrillation: 7.3%; 7% dyspnoea: 6.6%; 7.4% bradycardia: 11.1%; 2.6% dyspnoea, exacerbated: 6.2%; 6.8% fatigue: 6.7%; 5.8% angina pertoris: 4.9%; 6.8% hypertension: 5.2%; 5.8% headache: 5.8%; 4.9% oedema lower limb 5.2%; 2.3% nasopharyngitis: 4.0%; 3.2% unstable angina: 2.9%; 4.2% anaemia: 3.5%; 3.6%	neb 1.6% (18/1067); pla .37% 4/1061 enrolled: 2135	

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	Adequate; computer generated	NR	Differences in: - history of MI Bis: 169 (53%) pla: 134 (42%) (*P*<0.005) - diastolic blood pressure Bis: 79.5 mm Hg Pla: 77.9 mm Hg (*P*=0.03)	Mean Age: 59.6 Male: 82.5% Ethnicity: NR	Screened NR 641 randomized
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Adequate; computer generated random numbers	Adequate; centralized	Yes	Mean age: 61 Male: 80.5% Ethnicity: NR	Screened NR 2647 randomized

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	CHF due to hypertrophic or restrictvie cardiomyopathy with predominant left ventricular diastolic dysfunction; or secondary to mitral or aortic valve disease surgically repaired <6 months, or not repaired. MI <3 months. Awaiting bypass surgery or transplantation. Disabling permanent dyspnea at rest, insulin-dependent diabetes, asthma, renal insufficiency, hypothyroidism or hyperthyroidism, short life expectancy due to severe illness or malignancy. Resting heart rate <65 bpm; systolic blood pressure <100 or >160 mm Hg. No digitalis or amiodarone treatment <6 weeks before or 2 months after inclusion. Beta-adrenergic agonist or antagonist drugs and phosphodiesterase inhibitors prohibited.	Yes	Yes, blinded independent committee	Yes, allocation centrally controlled; titration blinded	Yes
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Uncontrolled hypertension, MI or unstoppable angina pectoris in past 3 months, revascularization in past 6 months, previous or scheduled heart transplant, atrioventricular block > first degree without pacemaker, resting heart rate < 60 bpm, systolic blood pressure <100, renal failure, reversible obstructive lung disease or planned therapy with beta-adrenoreceptor blockers. No treatment with beta blockers (also eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs except amiodarone during trial.	Yes	Yes, blinded independent committee	Yes	Yes

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	Yes	Yes	Attrition=157/641 (24.5%); others NR	No	Fair	NR
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Yes	Yes	Attrition=69/2647 (2.6%); others NR	No	Good	NR

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
Anonymous 1994 The Cardiac Insufficiency Bisoprolol Study (CIBIS I) Fair quality	Yes	Mean 1.9 years
Anonymous 1999 The Cardiac Insufficiency Bisoprolol Study (CIBIS II)	Yes	Mean 1.3 years

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
MOCHA Bristow1996 Multicenter Oral Carvedilol Heart Failure Assessment	NR	NR	Yes	Mean age: 59.5 Male: 76% Caucasian: 78%	Screened: NR Eligible for run-in: 376 Enrolled: 345
PRECISE Packer1996	NR	NR	Yes	Mean age: 60.3 years Male: 73% Ethnicity: NR	Screened: NR Eligible for run-in: 301 Enrolled: 278

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
MOCHA Bristow1996 Multicenter Oral Carvedilol Heart Failure Assessment	Uncorrected valvular disease, hypertrophic or postpartum cardiomyopathy, uncontrolled symptomatic or sustained ventricular tachycardia, acute MI within 3 months, planned or likely revascularization or transplantation within 6 months after screening. Also, sick sinus syndrome, 2nd- or 3rd-degree heart block not treated with pacemaker, symptomatic peripheral vascular disease limiting exercise testing, sitting systolic blood pressure <85 mm Hg or >160 mm Hg, CV accident within last 3 months, cor pulmonale, obstructive pulmonary disease requiring oral bronchodilator or steroid therapy, and other selected disorders and sensitivities. Excluded drugs: alcohol intake >100 g/day, use of investigational drug within 30 days, CCBs, amiodarone within 3 months, and others.	Yes	NR	Yes	Yes
PRECISE Packer1996	Uncorrected primary valvular disease, active myocarditis or obstructive or restrictive cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; heart rate <68 bpm; significant hepatic, renal or endocrine disease; drug or alcohol abuse; or any condition that could limit survival. Patients receiving CCBs, alpha- or beta-adrenergic agonist or antagonists or specific antiarrhythmic drugs.	Yes	NR	Yes	Yes

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
MOCHA Bristow1996 Multicenter Oral Carvedilol Heart Failure Assessment	Yes	NR	Attrition=52/345 (15%); others NR	No	Fair	SmithKline Beecham Pharmaceuticals
PRECISE Packer1996	Unclear	NR	Attrition=49/278 (18%); others NR	No	Fair	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
MOCHA Bristow1996 Multicenter Oral Carvedilol Heart Failure Assessment	NR	6 months
PRECISE Packer1996	NR	6 months

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	NR	Yes	Mean age: 55 Male: 85% Ethnicity: NR	Screened: NR Eligible for run-in: 389 Enrolled: 366
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	NR	NR	Yes	Mean age: 60 years (range 22-85) Male: 58% Ethnicity: - Caucasian: 71% - Black: 21% - Other: 8%	Screened: NR Eligible for run-in: 131 Enrolled: 105
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Adequate; computer generated	Adequate; centralized	Yes	Mean age 67 80% male Race NR	Screened: NR Eligible for run-in: 301 Enrolled: 278

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood of revascularization or transplantation within 12 months; sick sinus syndrome or advanced heart block (without pacemaker); any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival. Patients receiving amiodarone within 3 months before screening.	Yes	NR	Yes	Yes
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	Uncorrected primary valvular disease, nondilated or hypertrophic cardiomyopathy; MI, stroke, unstable angina or CABG within 3 months; symptomatic or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or implantable defibrillator within 3 months; likelihood heart transplantation within 6 months; sick sinus syndrome or advanced heart block without pacemaker; any condition other than heart failure that could limit exercise; systolic blood pressure >160 or <85 mm Hg or diastolic blood pressure >100 mm Hg; clinically significant hepatic or renal disease, or any condition that could limit survival.	Yes	NR	Yes	Yes
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Current NYHA class IV; heart rate below 50 beats per minute; sick sinus syndrome; second or third degree heart block; systolic BP <90 mm Hg or >160/100 mm Hg; treadmill exercise duration <2 minutes or >18 minutes; coronary event or procedure within previous 4 weeks; primary myocardial or valvular disease; current treatment with beta-blocker, beta-agonist or verapamil; insulin-dependent DM; obstructive airways disease; hepatic disease; any other life-threatening non-cardiac disease.	Yes	Yes	Yes	Yes

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	Yes	NR	Attrition=31(8.5%); others NR	NR	Fair	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	No	NR	Attrition=12(11.4%); others NR	Unclear; 87.6% of patients did not complete final QOL assessment	Poor	SmithKline Beecham Pharmaceuticals & Boehringer Mannheim Therapeutics
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Yes	NR	Attrition=14.9%; others NR	NR	Good	SmithKline Beecham - independently initiated conducted, analyzed by ANZ Heart Failure Research Collaborative

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
Colucci 1996 U.S. Carvedilol Heart Failure Study Group	NR	Mean 7 months
Cohn 1997 *U.S. Carvedilol Heart Failure Study Group*	NR	Mean 3 months
Richards 2001 Anonymous 1995, 1997 *Australia/New Zealand Heart Failure Research Collaborative Group*	Yes	Mean 19 months

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Cleland 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Adequate; random numbers table	Adequate; centralized	Unclear; baseline characteristics provided for only 78.8% of all randomized patients	Good mean age=62.5 90% male	489 screened 387 randomized
COPERNICUS Eichhorn 2001 Packer 2001 Packer 2002 Krum 2003	NR	NR	Yes	Good mean age >55 higher proportion male	3106 screened 2289 randomized

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Cleland 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Patients younger than 40 years and women of child-bearing age; resting heart rate less than 60 beats per minute; sitting systolic blood pressure less than 85 mm Hg; unstable angina; arrhythmias; uncontrolled hypertension; obstructive pulmonary disease; poorly controlled diabetes; or clinically relevant renal or hepatic disease; those receiving non-dihydropiridine calcium-channel blockers; beta blockers, or antiarrhythmic agents other than amiodarone	Yes	Yes	Yes	Yes
COPERNICUS Eichhorn 2001 Packer 2001 Packer 2002 Krum 2003	Heart failure that was caused by uncorrected primary valvular disease or a reversible form of cardiomyopathy; had received or were likely to receive a cardiac transplant; had severe primary pulmonary, renal, or hepatic disease; or had a contraindication to beta-blocker therapy; coronary revascularization, acute myocardial or cerebral ischemic event, sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation within the previous two months; use of an alpha-adrenergic blocker, a calcium-channel blocker, or a class I antiarrhythmic drug within the previous four weeks or a beta-blocker within the previous two months; systolic blood pressure lower than 85 mm Hg; heart rate lower than 68 beats per minute; serum creatinine concentration higher than 2.8 mg per deciliter; serum potassium concentration lower than 3.5 mmol per liter or higher than 5.2 mmol per liter; increase of more than 0.5 mg per deciliter in the serum creatinine concentration or a change in body weight of more than 1.5 kg during the screening period	Yes	Yes	Yes	Yes

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Cleland 2003	No	Unclear	Attrition=21.2%; others NR	NR	Fair	Hoffman-La Roche
Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)						
COPERNICUS	Yes	NR	attrition reported; others NR	None	Fair	Roche; GlaxoSmithKline
Eichhorn 2001 Packer 2001 Packer 2002 Krum 2003						

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
Cleland 2003 *Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success (CHRISTMAS)*	Yes	189 days (mean)
COPERNICUS Eichhorn 2001 Packer 2001 Packer 2002 Krum 2003	Yes	Mean 10.4 months

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial*	NR	NR	yes	100% Japanese	190 enrolled 16 (8.4%) withdrawn following run-in phase 174 randomized
Packer 1996 Colucci 1996 Yancy 2001 *U.S. Carvedilol Heart Failure Study Group*	NR	NR	Yes	Good mean age >55 higher proportion male	Screened NR 1094 randomized
Anderson 1985	Inferior; pairs	NR	Yes	Mean age 51 66% male Race NR	Screened: NR Eligible: 50 Enrolled: 50
Waagstein 1993	Computer-generated with "block size of 4," stratified	NR	Yes	Mean age 49 73% male Race NR	Screened: NR Eligible: 417 Enrolled: 383

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial*	Valvular heart disease, hypertrophic obstructive cardiomyopathy, cardiogenic shock, systolic blood pressure < 90 mm Hg, bradycardia (<60/min), grade II or III atrioventricular block, life-threatening arrhythmia, unstable angina, resting angina, cor pulmonale, asthma, Raynaud phenomenon, and intermittent claudication; myocardial infarction or coronary artery bypass grafting had occurred within the preceding 3 months	Yes	NR	NR	NR
Packer 1996 Colucci 1996 Yancy 2001 *U.S. Carvedilol Heart Failure Study Group*	Major CV event or surgical procedure within 3 months of study entry; uncorrected, primary valvular disease; active myocarditis; sustained ventricular tachycardia or advanced heart block not controlled by antiarrhythmic intervention or a pacemaker; systolic blood pressure of more than 160 or less than 85 mm Hg or diastolic blood pressure of more than 100 mm Hg; a heart rate of less than 68 beats per minute; clinically important hepatic or renal disease; or any condition other than heart failure that could limit exercise or survival; concomitant use of calcium-channel blockers α- or β-adrenergic agonists or antagonists or class IC or III antiarrhythmic agents	Yes	Yes	Yes	Yes
Anderson 1985	Unstabilized overt cardiac failure; alcohol abuse; secondary cardiomyopathies; firm exclusions to beta blocker treatment (asthma, advanced heart block, allergy)	Yes	NR	NR	NR
Waagstein 1993	Treatment with beta blockers, calcium channel blockers, inotropic agents or high doses of tricyclic antidepressant drugs; significant CAD shown by angiography; clinical or histological signs of ongoing myocarditis; other life-threatening diseases; obstructive lung disease; excessive alcohol consumption; drug abuse; insulin-dependent diabetes; pheochromocytoma; thyroid disease	Yes	Yes	NR	NR

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial*	No (1 patient that did not received any medication was excluded from ITT)	NR	No No No No	NR	Fair	NR
Packer 1996 Colucci 1996 Yancy 2001 *U.S. Carvedilol Heart Failure Study Group*	Yes	NR	AE withdrawals reported; others NR	none	fair	SmithKline Beecham Pharmaceuticals and Roche Laboratories Two investigators/authors are employees and stock holders of SKB
Anderson 1985	Yes	NR	Attrition=5/50(10%); others NR	No	Fair	Univ. of Utah SOM and LDS Hospital, Salt Lake City
Waagstein 1993	Yes for primary endpoint Nor for other	NR	Attrition=14.1%; others NR	High loss for secondary endpoints except hospitalization.	Fair	Astra Pharmaceutical divisions and Ciba-Geigy Corp., Swedish Heart & Lung Foundation & Swedish Medical Research Council

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
Hori 2004 Japan *The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) Trial*	Yes	mean follow-up NR
Packer 1996 Colucci 1996 Yancy 2001 *U.S. Carvedilol Heart Failure Study Group*	Yes	12 months
Anderson 1985	NR	Mean 19 months
Waagstein 1993	NR	12 months and 18 months (n=211/383)

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
MERIT-HF Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002	Adequate; computer generated	Adequate; centralized	Yes	Mean ages: <60: 34% 60-69: 35% ≥70: 31% 77% male White: 94% Black: 5% Other: 1%	Screened: NR Eligible (recruited): 4427 Enrolled: 3991
Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	NR	NR	yes	Mean age=61.5 82.1% male 87.1% white	Screened: NR Eligible: 468 Enrolled: 426

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
MERIT-HF Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure	Acute MI or unstable angina within 28 days; indication or contraindication for treatment with beta-blockade or drugs with beta-blocking properties; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty; implanted cardioversion defibrillator (expected or performed); CABG or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second or third degree; unstable decompensated heart failure; supine systolic BP >100 mm Hg; any serious disease that might complicate management and follow-up according to protocol; use of calcium antagonists; use of amiodarone within 6 months; poor compliance.	Yes	Yes	NR	NR
Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	NR	yes	yes	yes	yes

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
MERIT-HF Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002	Yes	NR	Attrition=589/3991 (15%); others NR	No	Fair	Project leader, coordinator, medical advisor, and acknowledgement to Astra Hassle, Sweden
Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure Anonymous 2000 *The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)*	yes	NR	Compliance (>80% of study medication): met CR=93%; pla=92%; others NR	NR	Fair	NR

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
MERIT-HF	Yes	1 year (mean)
Anonymous 1999 Goldstein 1999 Hjalmarson 2000 Goldstein 2001 Ghali 2002 Gottlieb 2002		
Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure Anonymous 2000	yes	24 weeks
The Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD)		

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Waagstein 2003 Europe	NR	NR	yes	Mean age=56.7 80% male Ethnicity NR	Screened: NR Eligible: NR Enrolled: 172
Edes 2005 (ENECA)	NR	patients were allocated a patient number in ascending order	yes	neb. vs. placebo age= 71.87, 72.19 male=70.15%, 76.98% ethnicity=99.2%, 98.4% caucasian	Screened: 354 Eligible: NR Enrolled: 260

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Waagstein 2003 Europe	Coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the previous 6 months or who were scheduled for or expected to require these treatments during the 6-month study; patients who had a major ischemic event (acute MI or unstable angina) within the previous 6 months and those with large anterior aneurysms, acute myocarditis, primary valvular heart disease, exercise-limiting angina pectoris or severe systemic disease; excessive consumption of alcohol (≥ 100 g of pure alcohol/day or ≥ 700 gram/week), resting systolic blood pressure > 190 mmHg or diastolic > 100 mmHg, systolic blood pressure <95 mmHg (unless considered occasional), heart rate < 50 beats/min, second- or third-degree atrioventricular (AV) block, sick sinus syndrome, sinoatrial block or atrial fibrillation (which makes equilibrium radionuclide angiography difficult to perform; pacemaker for third-degree AV block or a ventricular inhibited (VVI) pacemaker programmed with a fixed heart rate above the spontaneous heart rate	yes	NR	NR	NR
Edes 2005 (ENECA)	Acute corinary syndrome; a MI within the last 3 months; PTCA or coronary artery bypass surgery within the last month; obstructive or hypertrophic cardiomyopathy; hemodynamically relevant congenital or valvular heart disease; tachyarrhythmia resistant therapy (>100/min); bradycardia. Patients were also excluded if they received beta-blocker therapy in the 4 weeks prior to the beginining of the trial or known intolerance or hypersensitivity to nebibolol.	yes	stated double-blind, but no details given	stated double-blind, but no details given	stated double-blind, but no details given

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Waagstein 2003 Europe	no (4 patients excluded from ITT due to never taking study medication)	NR	yes no no no	no no	Fair	Medical Research Council (Project 02529), the Swedish Heart-Lung Foundation and AstraZeneca
Edes 2005 (ENECA)	yes	yes	yes no no no	no no	Fair	Berlin-Chemie AG, Menarini Group, Berlin, Germany

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
Waagstein 2003 Europe	Yes	6 months
Edes 2005 (ENECA)	yes	12 months

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Flather 2005 (SENIORS)	master randomization list carried out by phone adequate	yes	yes	Mean age:76.1 male: 63% ethnicity: NR Yes	Screened: NR Eligible: NR Enrolled: 2135

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Flather 2005 (SENIORS)	New drug therapy for heart failure 6 weeks prior to randomization, any change in cardiovascular drug therapy 2 weeks prior to randomization, heart failure due primarily to valvular heart disease, contraindication or previous intolerance to beta-blockers (e.g., heart rate <60 beats/min or systolic blood pressure <90 mmHg), curent use of beta-blockers, significant hepatic or renal dysfunction, cerebrovascular accidents within previous 3 months, and being on a waiting list for percutaneous coronary intervention or cardiac surgery or other major medical conditions that may have reduced survival during the period of the study.	yes	NR	NR	yes

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Flather 2005 (SENIORS)	analysis excluded 7 patients	yes	yes no yes no	no no	Fair	Menarini Ricerche SpA

Evidence Table 10. Quality assessments of placebo-controlled trials of beta blockers for heart failure

Author Year Country	Control group standard of care	Length of follow-up
Flather 2005 (SENIORS)	yes	mean 21 months

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Sanderson 1999 China	RCT	Patients with typical symptoms of heart failure and reduced LV ejection fraction (<0.45)	Valvular heart disease as the etiology of LV dysfunction, active myocarditis, unstable angina, a documented history of sustained ventricular tachycardia or symptomatic nonsustained ventricular tachycardia or second- or third degree atrioventricular block; chronic obstructive lung diseases, asthma, long-term alcohol or drug abuse or chronic renal failure (serum creatine >200 μmol/liter), hepatic hematological, neurological or collagen vascular disease
Kukin 1999	RCT Open	Patients with chronic heart failure secondary to ischemic heart disease, valvular myopathy, or idiopathic cardiomyopathy; symptomatic (NYHA class II, III, or IV) and had documented systolic dysfunction, with a radionuclide gated blood pool scan ejection fraction </= 35%; taking stable outpatient doses of digoxin and ACEIs or angiotensin II receptor antagonists for >/= 6 weeks and a stable dose of diuretics for >/= 2 weeks	Obstructive valvular disease, acute myocardial infarction within 6 weeks, or active angina

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sanderson 1999 China	Metoprolol (met) 100 mg daily (n=26) Carvedilol (car) 50 mg daily (n=25) x 12 weeks	Frusemide ACE inhibitor Angiotensin II receptor antagonist	Minnesota Heart Failure Symptom Questionnaire NYHA Functional Class assessment 6-min corridor walk test at weeks 4, 8 and 12	Mean age: met=60.4; car=58.7 %male: met=88.5; car=68.0 100% Chinese
Kukin 1999	Metoprolol (met) (n=30) or Carvedilol (car) (n=37) at a target dose of 50 mg daily for patients weighing < 85 kg and 100 mg daily for patients weighing > 85 kg x 6 months	Digoxin ACEIs Angiotensin II receptor antagonists Diuretics	Minnesota Living with Heart Failure questionnaire (Minn LwHFQ) 6-minute corridor walk tests Maximal exercise bicycle tests at 4 and 6 months	Mean age: met=55; car=60 %male: met=66.7; car=70.3 Race NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Author Year Country	Number withdrawn/ lost to fu/ analyzed
Sanderson 1999 China	Mean NYHA class: met=2.7; car=2.6 Mean symptom questionnaire score: met=13.1; car=17.2 Mean ETT (6-min walk, feet): met=1164; car=1122 *Etiology* IDC%: met=38.5; car=52 ICM%: met=19.2; car=24 HTHD%: met=42.3; car=24	NR/NR/51	Sanderson 1999 China	met=3; car=5/nr/nr
Kukin 1999	*Etiology* Ischemic%: met=33.3; car=48.6 Idiopathic%: met=60; car=43.2 Valvular%: met=6.7; car=8.1 NYHA II%: met=23.3; car=16.2 NYHA III%: met=70; car=72.9 NYHA IV%: met=6.7; car=10.8 Minn LwHFQ mean: met=52; car=52 6-min walk test mean (ft): met=1228; car=1133	NR/NR/67	Kukin 1999	14 withdrawn/0 lost/53 analyzed

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse effects reported
Sanderson 1999 China	Symptom questionnaire score mean: met=4.8; car=8.1 NYHA functional class mean: met=2.1; car=2.2 ETT(6-min walk, feet) mean: met=1263; car=1194	NR	NR
Kukin 1999	*NYHA class (#pts at baseline/month 6)* I: met=0/1; car=0/0 II: met=5/11; car=5/9; III: met=17/11; car=22/21 IV: met=1/0; car=3/0 *Minn LwHFQ at 6 months (mean change in points):* met=(-15); car=(-15) *6-minute walk (mean change in ft. at 6 months):* met=(+81); car=(+63)	NR	NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Sanderson 1999 China	
Kukin 1999	NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Metra 2000	RCT	Patients with chronic heart failure caused by an ischemic or nonischemic cardiomyopathy; NYHA class II, III, or IV symptoms for >/= 6 months; LV ejection fraction </= 0.35 by radionuclide ventriculography, and a peak VO2 </= 25 mL/kg-1/min-1 by cardiopulmonary exercise testing; concomitant treatment with furosemide and an ACEI (or angiotensin-receptor blocker if the ACEI was not tolerated) and had constant doses of background medicaiton as an outpatient for 1 week before the study	Patients with unstable angina, an acute myoardial infarction, or a coronary revascularization procedure within 3 months; history of alcohol abuse; primary valve disease; congenital heart disease; systolic blood pressure <90 mm Hg; concomitant disease that might adversely influence prognosis or impair exercise capacity; contraindications to b-blocker therapy; concomitant treatment with other β-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Metra 2000	Weight <75 kg/Weight >/= 75 kg Metoprolol tartrate (met): 100/200 mg daily (n=75) Carvedilol (car): 50/100 mg daily (n=75) x 44 months	Frusemide ACE inhibitor Angiotensin II receptor antagonist	LVEF Bicycle exercise testing 6-minute walk test Minnesota Living with Heart Failure Questionnaire (Minn LwHFQ) NYHA functional classification administered every 3 months Death and urgent transplantation	Age= met=58; car=55 Gender(%male): met=90.7; car=90.7 Race NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Author Year Country	Number withdrawn/ lost to fu/ analyzed
Metra 2000	*Etiology* IDC(%): met=46(61.3); car=47(62.7) CAD(%): met=29(38.7); car=28(37.3) *NYHA class n(%)* II: met=23(30.7); car=23(30.7) III: met=44(58.7); car=46(61.3) IV: met=8(10.7); car=6(8)	NR/NR/150	Metra 2000	28 withdrawn/0 lost/122 analyzed

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse effects reported
Metra 2000	NYHA class (#pts at baseline/month 12) I: met=0/14, car=0/17 II: met=22/32, car=18/32 III: met=36/15, car=40/11 IV: met=3/1, car=3/1. *6-minute walk (mean change in ft at 12 mos): met = 416 to 479m =+63m or 206ft (vs +81) and car= 447 to 497m =+50m or 164ft (vs +63)* Minn LwHFQ mean score, baseline/12 months(change): met=39/32(-7); car=32/24(-8) Bicycle exercise testing duration; sec, mean at baseline/12 mo (change): met=593/649(+56); car=531/576(+45) *Death/urgent transplantation:* met=21; car=17	NR	*Most common AE's* met worsening heart failure=13(17.3%) dizziness=1(1.3%) hypotension=2(2.7%) symptomatic bradycardia=2(2.7%) car dizziness=11(14.7%) worsening heart failure=6(8.0%) symptomatic bradycardia=3(4.0%) hypotension=2(2.7%) Raynaud's phenomenon=1(1.3%)

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metra 2000	met=3; car=2

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Metra 2002 USA, Italy	RCT	Patients with chronic HF caused by an ischemic or nonischemic cardiomyopathy who had NYHA function II-IV symptoms, a LVEF </=35% by radionuclide ventriculography, and ongoing treatment with furosemide and an ACEI	Patients with an acute ischemic event or a coronary revascularization procedure within 3 months; a history of alcohol abuse; primary valve disease or congenital heart disease; frequent ventricular premature beats and/or runs of ventricular tachycardia; contraindications to beta-blocker therapy; concomitant treatment with other beta-blockers, α-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Metra 2002 USA, Italy	Weight <75 kg/Weight >/= 75 kg Metoprolol tartrate (met): 100/200 mg daily (n=17) Carvedilol (car): 50/100 mg daily (n=17) x 9-12 months	Furosemide ACE inhibitor	NYHA functional classification x 9-12 months	Mean age: met=60; car=56 Gender(%male): met=17.6; car=23.5 Race NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Author Year Country	Number withdrawn/ lost to fu/ analyzed
Metra 2002 USA, Italy	*Etiology* IDC n(%): met=11(64.7); car=11(64.7) CAD n(%): met=6(35.3); car=6(35.3) *NYHA functional class* II n(%): met=5(29.4); car=3(17.6) III n(%): met=12(70.6); car=13(76.5) IV n(%): met=0; car=1(5.9)	NR/NR/34	Metra 2000 USA, Italy	29 analyzed

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse effects reported
Metra 2002 USA, Italy	*Per protocol analysis met n=14; car n=15* *NYHA class, n at end of study(%)* I: met=3(21.4); car=4(26.7) II: met=10(71.4); car=7(46.7) III: met=1(7.1); car=3(20.0) IV: met=0; car=1(6.7)	NR	NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metra 2002 USA, Italy	NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Poole-Wilson 2003/Cleland 2006/Torp-Pedersen 2005/Torp-Pedersen 2007 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	RCT	Men or women with symptomatic chronic heart failure (HYHA class II-IV); at least one cardiovascular admission during the previous 2 years; on stable heart failure treatment with ACE inhibitors for at least 4 weeks unless contraindicated; on treatment with diuretics (≥40 mg of frusemide or equivalent) for at least 2 weeks; LVEF </= 35% measured within the previous 3 months by echocardiography or radionuclide ventriculography	Recent change in treatment within 2 weeks before randomization; requirement for intravenous inotropic therapy; current treatment with non-dihydropyridine calcium channel blockers (diltiazem, verapamil); amiodarone (>200 mg per day); class-I antiarrhythmic drugs; unstable angina; myocardial infarction; coronary revascularisation or stroke within the previous 2 months; uncontrolled hypertension (SBP >170 mm Hg or DBP >105 mm Hg); hemodynamically significant valvular disease; symptomatic and sustained ventricular arrhythmias within the past 2 months note adequately treatment with antiarrhythmic drugs or implantation of an automatic defibrillator; pregnancy; women with childbrearing potential on inadequate contraception; known drug or alcohol misuse; poor compliance; any other serious systemic disease; contraindication to beta blockers

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Poole-Wilson 2003/Cleland 2006/Torp-Pedersen 2005/Torp-Pedersen 2007 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Carvedilol (car) 50 mg Metoprolol (met) 100 mg x 58 months (mean)	ACE inhibitor Diuretic Digitalis Angiotensin II inhibitor Other vasodilator	Follow-up visits at 4-month intervals	Mean age: 62 79.8% male 98.9% White

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Author Year Country	Number withdrawn/ lost to fu/ analyzed
Poole-Wilson 2003/Cleland 2006/Torp-Pedersen 2005/Torp-Pedersen 2007 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	*NYHA class:* II: 48.4% III: 47.8% IV: 3.8% Duration congestive heart failure: 42.4 months *Cause* Ischemic heart disease: 52.5% Hypertension: 17.7% Dilated cardiomyopathy: 43.9% Previous valve surgery: 2.5% Left ventricular ejection fraction (mean): 26%	NR/NR/3029 (car n=1511; met n=1518)	Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	964(31.8%) withdrawn(car=481; met=483)/5(0.03%) lost to fu/3029 analyzed

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse effects reported
Poole-Wilson 2003/Cleland 2006/Torp-Pedersen 2005/Torp-Pedersen 2007 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	All deaths car=512(34%) met=600(40%) Hazard ratio(95% CI): 0.83(0.74-0.93) NNT: 18 p=0.002 Cardiovascular deaths car=438(29%) met=534(35%) Hazard ratio(95% CI): 0.80(0.70-0.90) NNT=17 p=0.0004 Non-cardiovascular deaths: car=74(5%); met=66(4%) (NS) All deaths and all-cause admission: car=1116(74%); met=1160(76%) (NS) Sudden Death: car=218 (14.4%), met=261 (17.2%); HR 0.81, 95% CI 0.68-0.97, P=0.02 Circulatory failure: car=168 (11.1%), met=197 (13%); HR 0.83, 95% CI 0.67-1.02, P=0.07 Death from stroke: car=13 (0.9%), met= 38 (2.5%); HR 0.33, 95% CI 0.18-0.62, P=0.0006 Fatal or nonfatal MI: car=57 (3.8%), met=79 (5.2%); HR 0.70, 95% CI 0.50-0.99, P=0.04 Other outcomes: Well-being/morbidity/mortality (combined endpoint: death, days in hospital, well-being/symptoms and need for increased diuretic use) - total days of life lost over 4 yrs: car 939,534/2,206,060 (42.6%) vs met 1,000,147/2,216,280 (45.2%) Outcomes from Remme et al (2007) cardovascular events: car=584(38.6%); met=667 (43.9%); HR 0.85, 95% CI 0.76-0.95, P=.003 Unstable angina: car=56 (3.7%); met=77 (5%); HR .71, 95% CI 0.501-0.998 P=.049	All reports of adverse events were included irrespective of whether the investigators thought they had been caused by the treatment; adverse events that were fatal or life-threatening, required or extended admission, or resulted in persistent or significant disability or incapacity were labelled serious	Overall adverse event incidence: car=1420(94%); met=1457(96%) Bradycardia: car= 144 (10%), met= 135 (9%) Hypotension: car= 215 (14%), met= 160 (11%) Incidence of new onset diabetes-related adverse events: car=10.6% (122/1151), met=13% (149/1147) (HR 0.78, 95% CI 0.61 - 0.99, P = 0.039) New onset diabetes: car= 119, met=145 (HR 0.78; 95% CI 0.61-0.997; P = 0.048)

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Poole-Wilson 2003/Cleland 2006/Torp-Pedersen 2005/Torp-Pedersen 2007 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	NR

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Study Design Setting	Eligibility criteria	Exclusion criteria
Galatius 2004 Denmark Poor Quality	RCT	Patients who fulfilled all standard indications for BB treatment in patients with systolic CHF	Patients who had contraindications for BB treatment; and those who had been admitted, had attended an emergency room, or who had been treated in the heart failure clinic for acute decompensation within 2 weeks prior to randomization. Patients were excluded from data analysis if they died before two months of follow-up.
Lombardo 2006	RCT	Caucasion patients aged ≥ 35 years w/ CHF, LV ejection fraction ≤ 40%, NYHA class II-III, stable clinical condition during prior 4 weeks.	SBP <90mm Hg; DBP <60mm Hg; HR <50 bpm; cerebral vascular accidents w/in previous 6 months; heart or vascular surgery or MI w/in previous 3 months; serious valvular conditions that required surgery; atrioventricular conduction abnormalites; milignancies; serious liver, kidney, connective tissue, respiratory, or hematologic disease; history of allergy; intolerance to ACE inhibitors; unstable angina, DM; digitalis intolerance; BMI >30; excercise tolerance limited by other disorders; pregnancy.

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Galatius 2004 Denmark Poor Quality	Bisopolol started at 1.25 mg daily and titrated up (if tolerated) to 10mg/day Carvedilol started at 3.125 mg bid and titrated up (if tolerated) to 25 mg bid	Diruetics = 90.1% ACE Inhibitors or ARB = 90.0% Digoxin = 21.8% Spironolactone = 21.8%	BB tolerance (no BB treatment at discharge or study end) Timing: 2 month of follow-up and at discharge from the clinic	Mean Age=70.15 75.6% male Ethnicity NR
Lombardo 2006	Carvedilol (car) started at 3.125 twice daily and titrated (if tolerated) to 25 mg twice daily. Nebivolol (neb) started at 1.25 mg daily and titrated (if tolerated) to 5mg daily if SEP ramined > 110mm Hg and HR remained at >60 bpm. X 6 months	NR	NYHA functional class advers events Timing: periodically 6-minute walk test Timing: baseline and at 6 months	Car vs. Neb. Mean Age: 66; 68 Male: 54%; 62% Ethnicity: 100% Caucasion

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Author Year Country	Number withdrawn/ lost to fu/ analyzed
Galatius 2004 Denmark Poor Quality	NYHA class III-IV=19.9% Months of CHF=25.2 Ischemic heart disease=52.9% Heart rate, mean bpm=76.3 SBP, mmHg =139.0	NR/90/87	Galatius 2004 Denmark Poor Quality	0/3/87
Lombardo 2006	Car vs. Neb. NYHA function class 2.48; 2.31 BMI: 26; 28 SBP (mm Hg) 138; 141 DBP (mm Hg) 83; 85 HR (bpm) 83; 81 DM 8; 11	NR/70/70	Lombardo 2006 Italy	2/0/70

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Outcomes	Method of adverse effects assessment?	Adverse effects reported
Galatius 2004 Denmark Poor Quality	BB tolerance (no BB treatment at discharge or study end): car=19(40%), bis=16(39%); NS 40%(n=35) of the patients didn't tolerate BB treatment. The reasons are dizziness(41%), bradycardia/arrythmia(16%), worsening of claudication/Raybaud's phenomenon(16%), depression/sleep disturbances(9%), asthma(9%), nausea(3%), other(6%)	NR in methods	40%(n=35) of the patients didn't tolerate BB treatment. The reasons are dizziness(41%), bradycardia/arrythmia(16%), worsening of claudication/Raybaud's phenomenon(16%), depression/sleep disturbances(9%), asthma(9%), nausea(3%), other(6%)
Lombardo 2006	NYHA functional Class: Car (baseline/6 mo) 2.5/2.2 (-0.3)(P=.05) Neb (baseline/ 6 mo) 2.3/2.2 (-0.1) (NS) 6 minute walk test (m): Car (baseline/6 mo) 227/259 Neb (baseline/6 mo) 249/279 (NS)	NR	Most common AE's Car. vs. Neb. Any: 7 (20%); 9 (26%) Hypotension: 1 (3%); 1 (3%) asthenia/fatigue/dizziness: 6 (17%); 8 (23%) bradycardia/ECG pauses >2.5 sec: 3 (9%); 1 (3%) increase of furosemide dosage: 4 (11%); 3 (8.6%) worsening of dyspnea: 4 (11%); 3 (8.6%) hospitalization for HF: 4 (11%); 2 (6%) death: 1 (3%); 1 (3%) no statistically sig. differences.

Evidence Table 11. Head-to-head trials of beta blockers for heart failure

Author Year Country	Withdrawals due to adverse events (%, adverse n/enrolled n)
Galatius 2004 Denmark Poor Quality	0
Lombardo 2006	2.8% (2/70) car 1/35; neb 1/35

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Sanderson 1999 China	NR	NR	Yes	Good Mean age: >55 Gender: >%male	51
Kukin 1999	NR	NR	Yes	Good Mean age: >55 Gender: >%male	67
Metra 2000	NR	NR	Yes	Good Mean age: >55 Gender: >%male	150

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Sanderson 1999 China	Valvular heart disease as the etiology of LV dysfunction, active myocarditis, unstable angina, a documented history of sustained ventricular tachycardia or symptomatic nonsustained ventricular tachycardia or second- or third degree atrioventricular block; chronic obstructive lung diseases, asthma, long-term alcohol or drug abuse or chronic renal failure (serum creatine >200 mmol/liter), hepatic hematological, neurological or collagen vascular disease	Yes	Yes	Yes	Yes
Kukin 1999	Obstructive valvular disease, acute myocardial infarction within 6 weeks, or active angina	Yes	N/A - open study	N/A - open study	N/A - open study
Metra 2000	Unstable angina,acute myoardial infarction, or a coronary revascularization procedure within 3 months; history of alcohol abuse; primary valve disease; congenital heart disease; systolic blood pressure <90 mm Hg; concomitant disease that might adversely influence prognosis or impair exercise capacity; contraindications to b-blocker therapy; concomitant treatment with other b-blockers, a-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Sanderson 1999 China	Unclear	Unclear	Attrition reported; Others NR	NR	Fair
Kukin 1999	No	NR	Attrition reported; Others NR	None	Fair
Metra 2000	No	NR	Attrition reported; Others NR	None	Fair

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Funding	Control group standard of care	Length of follow-up
Sanderson 1999 China	NR	Yes	12 weeks
Kukin 1999	SKB	Yes	6 months
Metra 2000	CARIPLO funds University of Brescia	Yes	44 months

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Metra 2002 US, Italy	NR	NR	Yes	Fair Mean age >55 Gender: >%female	34
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Permuted blocks by center, but no information about how sequence was generated.	adequate	Yes	Mean age: 62 79.8% male 98.9% White	3029

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Metra 2002 US, Italy	Patients with an acute ischemic event or a coronary revascularization procedure within 3 months; a history of alcohol abuse; primary valve disease or congenital heart disease; frequent ventricular premature beats and/or runs of ventricular tachycardia; contraindications to beta-blocker therapy; concomitant treatment with other beta-blockers, a-antagonists, calcium antagonists or antiarrhythmic agents (except amiodarone)	Yes	Yes	Yes	Yes
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Recent change in treatment within 2 weeks before randomization; requirement for intravenous inotropic therapy; current treatment with non-dihydropyridine calcium channel blockers (diltiazem, verapamil); amiodarone (>200 mg per day); class-I antiarrhythmic drugs; unstable angina; myocardial infarction; coronary revascularisation or stroke within the previous 2 months; uncontrolled hypertension (SBP >170 mm Hg or DBP >105 mm Hg); hemodynamically significant valvular disease; symptomatic and sustained ventricular arrhythmias within the past 2 months note adequately treatment with antiarrhythmic drugs or implantation of an automatic defibrillator; pregnancy; women with childbrearing potential on inadequate contraception; known drug or alcohol misuse; poor compliance; any other serious systemic disease; contraindication to beta blockers	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Metra 2002 US, Italy	No	NR	Attrition reported; Others NR	None	Fair
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	Yes	NR	31.8% attrition; others NR	None	Fair

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Funding	Control group standard of care	Length of follow-up
Metra 2002 US, Italy	NR	Yes	9-12 months
Poole-Wilson 2003 Europe *Carvedilol Or Metoprolol European Trial (COMET)*	F Hoffman La Roche and GlaxoSmithKline; first author has served as a consultant to or received travel expenses, payment for speaking at meetings or funding for research from one or more of the major pharmaceutical companies	Yes	58 months

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Galatius 2004	Inadequate; clinical database sequential number	Inadequate; clinical database sequential number	No; patients in carvedilol group were of a potentially greater severity (more males, lower mean LVEF, higher % of pts with LVEF<25%)	Mean Age=70.15 75.6% male Ethnicity NR	87
Lombardo 2006 Italy	NR	No	Yes	Car vs. Neb. Mean Age: 66; 68 Male: 54%; 62% Ethnicity: 100% Caucasion Percentage male smaller than other studies.	70

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Galatius 2004	Patients who had contraindications for BB treatment; and those who had been admitted, had attended an emergency room, or who had been treated in the heart failure clinic for acute decompensation within 2 weeks prior to randomization. Patients were excluded from data analysis if they died before two months of follow-up.	Yes	No	No	No
Lombardo 2006 Italy	SBP <90mm Hg; DBP <60mm Hg; HR <50 bpm; cerebral vascular accidents w/in previous 6 months; heart or vascular surgery or MI w/in previous 3 months; serious valvular conditions that required surgery; atrioventricular conduction abnormalites; milignancies; serious liver, kidney, connective tissue, respiratory, or hematologic disease; history of allergy; intolerance to ACE inhibitors; unstable angina, DM; digitalis intolerance; BMI >30; excercise tolerance limited by other disorders; pregnancy.	Yes	No	No	No

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score
Galatius 2004	No; excluded 3 patients that died prior to completing 2 months of treatment	NR	Yes No No No	NR	Poor
Lombardo 2006 Italy	Yes	Yes	Yes No No No	NR	Fair

Evidence Table 12. Quality assessments of head-to-head trials of beta blockers for heart failure

Author Year Country	Funding	Control group standard of care	Length of follow-up
Galatius 2004	Danish Pharmacy Foundation, Merck Sharp & Dohme A/S (Denmark), Roche A/S (Denmark), and the Quality Assurance Council at Frederiksberg	Yes	10.1 months
Lombardo 2006 Italy	No sources	Yes	6 months

Evidence Table 13. Outcomes in head-to-head trials of beta blockers for heart failure

Trial	Interventions*	Sample size	Duration	Baseline EF	Mortality	Worsening heart failure
Sanderson 1999 *Fair*	Carvedilol Metoprolol	51	12 weeks	26%	NR	NR
Kukin 1999 *Fair*	Carvedilol Metoprolol	67	6 months	18-19%	NR	car=3/37(8.1%) met=5/30(16.7%)
Metra 2000a *Fair*	Carvedilol metoprolol	150	12 months	20-21%	NR	car=6/61(9.8%) met=13/61(21.3%)
Metra 2000b *Fair*	Carvedilol Metoprolol	34	9-12 months	19-17%	NR	2 patients died due to worsening HF (group assignment NR)
Poole Wilson 2003 Carvedilol or Metoprolol European Trial (COMET)	Carvedilol Metoprolol	3029	58 months (mean)	26%	*All deaths* car=512/1511(34%) met=600/1518(40%) NNT=18 *P*=0.002	NR

*All in addition to standard therapy that included ACEI and diuretic

Evidence Table 13. Outcomes in head-to-head trials of beta blockers for heart failure

Trial	NYHA Class	Exercise capacity	Change in EF following treatment
Sanderson 1999 *Fair*	# patients at NYHA class I/II/III/IV car baseline: 0/10/14/1 week 12: 1/14/5/0 met baseline: 0/7/19/1 week 12: 1/19/3/0	Improvement in 6-min walk(feet) car=72(6.4%); met=99(8.5%)(NS)	Mean EF at Week 12 (% improvement) car=35(+34.6%); met=31(+24%)
Kukin 1999 *Fair*	# patients at NYHA class I/II/III/IV car baseline: 0/5/22/3 month 6: 0/9/21/0 met baseline: 0/5/17/1 month 6: 1/11/11/0	Improvement in 6-min walk(feet) car=63(5.5%); met=81(6.6%)(NS)	Mean EF(% improvement) car=25(+31.6%); met=23(+27.8%)
Metra 2000a *Fair*	# patients at NYHA class I/II/III/IV car baseline: 0/18/40/3 month 12: 17/32/11/1 met baseline: 0/22/36/3 month 12: 14/32/15/0	Improvement in 6-min walk(m) car=50(11.2%); met=63(15.1%)	Mean EF(% improvement) car=31.2(52.9%); met=28.8(33.3%)(*P*=0.038)
Metra 2000b *Fair*	# patients at NYHA class I/II/III/IV car baseline: 0/3/11/1 end of study: 4/7/3/1 met baseline: 0/5/9/0 end of study: 3/10/1/0	NR	Mean EF at EOS (% improvement) car=27.9(64.1%); met=30.0(47.0%)
Poole Wilson 2003 Carvedilol or Metoprolol European Trial (COMET)	NR	NR	NR

*All in addition to standard therapy that included ACEI and diuretic

Evidence Table 13. Outcomes in head-to-head trials of beta blockers for heart failure

Trial	Quality of life
Sanderson 1999 *Fair*	Minnesota QOL mean reduction in symptom score (%) car=9.1(52.9%); met=8.3(63.3%)
Kukin 1999 *Fair*	Minnesota LWHFQ mean reduction in symptom score(% mean change in points) car=15(28.8%); met=15(29.4%)
Metra 2000a *Fair*	Minnesota LWHFQ mean reduction in symptom score(%) car=8(25%); met=7(17.9%)
Metra 2000b *Fair*	NR
Poole Wilson 2003 Carvedilol or Metoprolol European Trial (COMET)	NR

*All in addition to standard therapy that included ACEI and diuretic

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria
Head-to-head trials			
Katritsis 2003 *Fair quality*	RCT multicenter	Patients subjected to cardioversion of persistent AF (> 7 days)	Terminal illness, age > 80 years, left ventricular ejection fraction <30, concomitant treatment with class I or III antiarrhythmic drugs, amiodarone use within 3 months before randomization, previous treatment with bisoprolol or carvedilol, and contraindications to beta blockade, such as conduction disturbances, asthma, or severe chronic obstructive pulmonary artery disease

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Head-to-head trials				
Katritsis 2003 *Fair quality*	Bisoprolol 10 mg daily (or 5 mg daily if LVEF < 40%) carvedilol 50 mg daily (or 25 mg daily if LVEF M 40%) x 12 months	No restrictions, with exception of class I or III antiarrhythmic drugs	Clinic visits at months 1, 3, 6 and 12	Mean age=65.5 82% male Ethnicity NR

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Head-to-head trials				
Katritsis 2003 *Fair quality*	Heart rate=71.3 beats per minute Left atrial diameter=4.4 cm Systemic blood pressure > 140/90 mm Hg=60% Coronary artery disease=18.9% Lone atrial fibrillation=11.1% Other conditions (valve disease, hyperthyroidism, dilated cardiomyopathy)=21.1% Diabetes mellitus=14.4%	NR/102/90	8 (8.9%) withdrew/3 (3.3%) lost to fu/82 analyzed for efficacy	Bisoprolol (n=43) vs Carvedilol (n=39) Relapse into AF= 23 (53.4%) vs 17 (43.6%); *P*=NS Median time to relapse (days) 20 vs 14; *P*=NS

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-head trials			
Katritsis 2003	NR	NR	Withdrew due to side effects: 3 (6.4%) vs 2 (4.7%); *P*=NS

Fair quality

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria
Placebo-controlled trials Metoprolol vs placebo			
Kuhlkamp 2000 Germany	RCT multicenter	Patients at 71 centers with persistent atrial fibrillation of 3 days to 1 year. Must be converted to sinus rhythm. Sufficient anticoagulation for 1+ months strongly recommended to providers.	Use of Class 1 or 3 antiarrhythmic drug, beta-blockers or calcium channel blockers; chronic treatment with amiodarone within 6 months; contraindications to beta-adrenergic blocking agents; untreated thyroid dysfunction; paroxysmal atrial fibrillation or history of it; cardiac surgery in the previous two months

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Placebo-controlled trials Metoprolol vs placebo				
Kuhlkamp 2000 Germany	n = 403 metoprolol (met): start 100 mg/day vs. identical placebo (pla) x 6 months Maintain 100 mg/day: met = 122/197 (62%) pla = 131/197 (67%) To 200 mg/day: met = 33/197 (17%) pla = 50/197 (25%) To 50 mg/day: met = 36/197 (18%) pla = 12/197 (6%)	Digoxin/digitoxin, ACE inhibitor, diuretics, nitrates, calcium-channel blockers of dihydropyridine type	Primary endpoint: relapse into atrial fibrillation or flutter. Mean followup time: met = 93 days pla = 73 days	Mean age 60.5 70% male Race: NR

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Placebo-controlled trials Metoprolol vs placebo				
Kuhlkamp 2000 Germany	Previous cardioversion: met = 18/197 (9%) pla = 22/197 (11%) Hypertension: met = 96/197 (49%) pla = 91/197 (46%) Coronary artery disease: met = 52/197 (26%) pla = 48/197 (24%) Heart failure: met = 51/197 (26%) pla = 49/197 (25%) Stroke/TIA: met = 15/197 (8%) pla = 12/197 (12%) Diabetes mellitus: met = 23/197 (12%) pla = 17/197 (9%) NYHA 1: met = 125/197 (64%) pla = 137/197 (70%) NYHA2: met = 64/197 (33%) pla = 54/197 (27%) NYHA3: met = 8/197 (4%) pla = 6/197 (3%)	Screened = NR Eligible = NR Enrolled = 403	Lost for efficacy data (no followup ECG) = 9/403 (2%) Lost for safety data = 4/403 (1%) Analyzed = 394/403 (98%) and 399/403 (99%)	Death: met = 3/200 (2%) pla = 0 Premature discontinuation due to relapse to atrial fibrillation/flutter: met = 96/197 (49%) pla = 118/197 (60%) Total relapse to atrial fibrillation: met = 87/197 (44%) pla = 118/197 (60%)

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo-controlled trials Metoprolol vs placebo			
Kuhlkamp 2000 Germany	NR	Dizziness/vertigo: met = 20/200 (10%) pla = 6/199 (3%) Bradycardia: met = 14/200 (7%) pla = 0 Cardiac failure: met = 3/200 (2%) pla = 0 Hypotension: met = 2/200 (1%) pla = 1/199 (1%)	Total: 26/394 (7%) Serious adverse events: met = 4/197 (2%) pla = 2/197(1%) Nonserious adverse events: met = 16/197 (8%) pla = 4/197(2%)

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria
Metoprolol vs placebo			
Khand 2003 UK *Fair quality*	RCT multicenter	Patients with persistent atrial fibrillation (> 1 month) and heart failure (appropriate symptoms of heart failure for more than two months and echocardiographic evidence of cardiac dysfunction [LVEF < 40% or preserved LV systolic function, together with LV hypertrophy, suggesting diastolic dysfunction in the absence of an alternative potential cause of symptoms]) who were receiving digoxin and diuretics	Heart rate at rest < 60 beats/min, systolic blood pressure < 90 mm Hg, sick sinus synddrome or complete heart block, current treatment with a beta-blocker or HR-lowering calcium channel antagonist or > 200 mg amiodarone, recent major cardiovascular event or procedures, asthma or reversible obstructive airways disease, serum creatinine > 250 µmol/l or significant hepatic disease, uncorrected significant valvular heart disease, or any life-threatening noncardiac disease

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Interventions (drug, regimen, duration)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Metoprolol vs placebo				
Khand 2003 UK *Fair quality*	Phase I Open digoxin +placebo Open digoxin+carvedilol 50 mg daily (or 100 mg daily for patients > 85 kg) x 4 months Phase II Digoxin Carvedilol 50 mg daily (or 100 mg daily for patients > 85 kg) x 6 months	ACE inhibitors Warfarin	1) LVEF 2) Ventricular rate control by 24-hour ambulatory ECG 3) Symptoms rated using patient self-administered, quantitative questionnaire designed to measure perception of the frequency and severity of symptoms (chest pain/discomfort, fatigue, and shortness of breath at rest, during walking at normal pace, and while climbing stairs and palpitations) and their functional capacity on 4-point scale (0=absent to 3=severe symptoms); responses were summed to produce a symptom score rangingn from 0 (no symptoms to 33 (worst symptoms) 4) Exercise tolerance by 6-minute corridor walk distance	Mean age=68.5 61.7% male Ethnicity NR

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes
Metoprolol vs placebo				
Khand 2003 UK *Fair quality*	IHD etiology=40.4% Mean duration of AF=131.5 weeks Mean previous cardioversion attempts=0.5 Mean resting heart rate of ECG=85.5 beats/minute Mean LVEF=24.1% Mean LVEDD=53.7 mm Mean LA size=48.4 mm NYHA class I=4.2% II=57.4% III=31.9% IV=6.4% Digoxin dose=0.245 mg Digoxin plasma concentration=1.54 mmol/l ACE inhibitors=70.2% Anticoagulated=80.8%	NR/NR/47	Phase I 6 (12.8%)/0/NR Phase II NR/NR/NR	Phase 1 (Combination vs Digoxin) LVEF: 30.6% vs 26%; *P*=0.048 Symptom score: 7 vs 8; *P*=0.039 6-min WD (ms): 394 vs 414; *P*=NS Mean 24-hour ventricular rate reduction: 65.2 vs 74.9 ; *P*≤0.0001 Phase II (carvedilol vs digoxin) LVEF: 21.6% vs 27.2%; *P*=NS Symptom score: 6 vs 8; *P*=NS 6-min WD (ms): 374 vs 403; *P*=NS Mean 24-hour ventricular rate reduction: 88.8 vs. 75.7; *P*=NS

Evidence Table 14. Randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Method of adverse effects assessment?	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Metoprolol vs placebo			
Khand 2003 UK *Fair quality*	NR	Deaths Phase I: 4.2% vs 4.3%; *P*=NS Phase II: 5% vs 4.8%; *P*=NS	Withdrawals due to adverse events Phase I: 3 (12.5%) vs 1 (4.3%); *P*=NS Phase II: 3 (15%) vs 1 (4.8%); *P*=NS Withdrawals due to worsening heart failure Phase I: 0 vs 0 Phase II: 3 (15%) vs 1 (4.8%); *P*=NS

Evidence Table 15. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Head-to-head trials					
Katritsis 2003	NR	NR	Yes	Selected for patients naïve to study drugs	102
Placebo-controlled trials					
Metoprolol vs placebo					
Kuhlkamp 2000	Adequate, computer generated	NR	Yes	No - selection for healthier population - mean age of sample = 60 years; mean age atrial fibrillation patients = 75 years	403

Evidence Table 15. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Head-to-head trials							
Katritsis 2003	Terminal illness, age > 80 years, left ventricular ejection fraction <30, concomitant treatment with class I or III antiarrhythmic drugs, amiodarone use within 3 months before randomization, previous treatment with bisoprolol or carvedilol, and contraindications to beta blockade, such as conduction disturbances, asthma, or severe chronic obstructive pulmonary artery disease	Yes	Yes	NR	NR	No	NR
Placebo-controlled trials							
Metoprolol vs placebo							
Kuhlkamp 2000	• Use of Class 1 or 3 antiarrhythmic drug, beta-blockers or calcium channel blockers; chronic treatment with amiodarone within 6 months. • Contraindications to beta-adrenergic blocking agents. • Untreated thyroid dysfunction • Paroxysmal atrial fibrillation or history of it • Cardiac surgery in the previous two months	Yes	NR	Yes	Yes	No	Yes

Evidence Table 15. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Head-to-head trials						
Katritsis 2003	Yes No No No	No No	Fair	NR	Yes	12 months
Placebo-controlled trials						
Metoprolol vs placebo						
Kuhlkamp 2000	Attrition=6.8%; others NR	No	Fair	AstraZeneca, Sweden	Yes	6 months

Evidence Table 15. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Random assignment	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Metoprolol vs placebo					
Khand 2003 UK	NR	NR	Yes	Mean age=68.5 61.7% male Ethnicity NR	47

Evidence Table 15. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups
Metoprolol vs placebo							
Khand 2003 UK	Heart rate at rest < 60 beats/min, systolic blood pressure < 90 mm Hg, sick sinus syndrome or complete heart block, current treatment with a beta-blocker or HR-lowering calcium channel antagonist or > 200 mg amiodarone, recent major cardiovascular event or procedures, asthma or reversible obstructive airways disease, serum creatinine > 250 µmol/l or significant hepatic disease, uncorrected significant valvular heart disease, or any life-threatening noncardiac disease	Yes	Yes	Yes	Yes	Yes	NR

Evidence Table 15. Quality assessments of randomized controlled trials of beta blockers for arrhythmia

Author Year Country	Reporting of attrition, crossovers, adherence, and contamination	Differential loss to follow-up or overall high loss to follow-up	Score (good/ fair/ poor)	Funding	Control group standard of care	Length of follow-up
Metoprolol vs placebo						
Khand 2003 UK	Yes No No No	No No	Fair	Roche Pharmaceuticals	Yes	Phase I=4 months; Phase II=6 months

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Fair quality **Atenolol**				
Forssman 1982 Sweden *Fair quality* RCT Crossover	History of migraine (Ad Hoc Committee)	NR	Atenolol (ate) 100 mg daily Placebo (pla) x 90 days; then crossover	Common analgesics and ergotamine

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Fair quality **Atenolol**				
Forssman 1982 Sweden	*Patient forms:* 1) number; 2) intensity (3-point scale); 3) duration of attacks; 4) incapacity for work; 5) medication	Mean age=40 80% female Race NR	NR	NR/NR/24 enrolled
Fair quality RCT Crossover	*Integrated headache:* score considering combined effect of intensity and duration Follow-up visits were made after 14, 56, 154, and 254 days			

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Fair quality			
Atenolol			
Forssman 1982 Sweden *Fair quality* RCT Crossover	4(16.7%) withdrawn/0 lost to fu/ 20 analyzed	Integrated headache Mean values/day: ate=2.38; pla=4.58 Relative mean value/day(ate:pla mean/% difference): (-2.2)/(-48%) Relative value per patient/day(# pts/%): ate>pla=19/95%; pla>/=ate=1/5% Number of attacks Mean values/day: ate=0.17; pla=0.23 Relative mean value/day(ate:pla mean/% difference): (-0.06)/(-26.1%) Relative value per patient/day(# pts/%): ate>pla=15/75%; pla>/=ate=5/25% Headache intensity Comparison of effect per patient(# pts/%): ate>pla=17/18(94.4%) Ergotamine intake Comparison of change in intake per patient(# pts w/significant reduction/%): ate>pla=14/14(100%) Common analgesic intake Comparison of change in intake per patient: data NR; no difference indicated per patient between periods	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Fair quality			
Atenolol			
Forssman 1982 Sweden	Dizziness of orthostatic type(# pts): ate=6; pla=1 Diffuse tiredness: ate=2; pla=0	ate=1 pla=0	
Fair quality RCT Crossover	Mood alterations: ate=1; pla=0		

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Bisoprolol				
van de Ven 1997 The Netherlands Fair quality RCT	Either sex, 18 to 75 years old; suffering from migraine with or without aura; had a migraine history of at least two years' duration; developed at least three documented migraine attacks during the 28-day run-in period	Current use of drugs for the prevention of migrain; treatment with cardiovascular drugs; usual contrindications for beta blocker use or hypersensitivity to these agents	Bisoprolol (bis) 5 mg OR 10 mg daily Placebo (pla) x 16 weeks	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Bisoprolol				
van de Ven 1997 The Netherlands Fair quality RCT	Patient diary assessed at 4-wk intervals	Mean age: bis 5 mg=38.3; bis 10 mg=38.9; pla=38.9 % female: bis 5 mg=78.4%; bis 10 mg=83.1%; pla=83.1% Race NR	Family history of migraine(# patients/%): bis 5 mg=28/37.8%; bis 10 mg=27/35.1%; pla=26/34.7% Age at onset(yrs): bis 5 mg=18.1; bis 10 mg=20.1; pla=22.7 Migraine with aura(# patients/%): bis 5 mg=17/22.9%; bis 10 mg=22/28.6%; pla=12/16% Migraine without aura(# patients/%): bis 5 mg=57(77%); bis 10 mg=55/71.4%; pla=63/84%	NR/NR/226 randomized

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Bisoprolol			
van de Ven 1997 The Netherlands Fair quality RCT	31(13.7%) withdrawn/lost to fu NR/analyzed NR	Migraine frequency(4-week mean/% reduction): bis 5 mg=2.6/39%; bis 10 mg=2.6(39%); pla=3.2/22% Attack duration(mean hours/% reduction): bis 5 mg=9.5/(-53.9%); bis 10 mg=14.3/(-44.6%); pla=13.2/(-43.6%)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Bisoprolol			
van de Ven 1997 The Netherlands Fair quality RCT	Adverse event incidence(# patients/%): bis 5 mg=26/35%; bis 10 mg=33/43%; pla=25/33% Most frequent adverse events(# patients/%): Fatigue: bis 5 mg=7/9.4%; bis 10 mg=9/11.7%; pla=7/9.3% Dizziness: bis 5 mg=6/8.1%; bis 10 mg=5/6.5%; pla=4/5.3%	Adverse event withdrawals(# patients/%): bis 5 mg=4/74(5.4%); bis 10 mg=7/77(9.1%); pla=4/75(5.3%)	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Metoprolol				
Andersson 1983 Denmark *Fair quality* RCT	Outpatients of both sexes, with an age over 16 and below 65 years diagnosed to have classical or non-classical migraine (World Federation of Neurology Research Group on Migraine and Headache) of a duration of at least 2 years	Other types of vascular headaches, chronic daily headache not separable from migraine; contraindication for beta blockers; other severe vascular diseases; oral contraceptives and pregnancy	Metoprolol durules (met-d) 200 mg daily Placebo (pla) x 12 weeks	Acute migraine medication allowed (e.g., ergotamine and analgesics)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Metoprolol				
Andersson 1983 Denmark *Fair quality* RCT	*Patient diary card:* 1) frequency; 2) Intensity (1=annoying, but patient not disabled; 2=patient partly disabled (affecting his/her ability to work); 3=patient disabled(unable to work or in bed); 3) consumption of acute migraine-relieving medicine	Mean age: pla=37.3; met-d=42.4 %female: pla=94.6%; met-d=73.5% Race NR	Classical migraine(#pts/%): pla=8/21.6%; met-d=9/26.5% Non-classical migraine(#pts/%): pla=29/78.4%; met-d=25/73.5% % heredity: pla=65; met-d=65 Mean migraine duration(years): pla=14.6; met-d=22.6 % earlier prophylactic treatment: pla=32; met=38 % earlier acute treatment: pla=76; met=74	NR/75 eligible/71 randomized

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Metoprolol			
Andersson 1983 Denmark *Fair quality* RCT	Withdrawn: 4/75(5.3%) prior to randomization; 9/71(12.7%) after randomization/lost to fu NR/71 analyzed	Per protocol assessment (pla n=35; met-d n=30) *Attack frequency/4 wks(mean/% change):* pla=(-0.53)/(-10.3%); met-d=(-1.3)/(-29.5%) *Migraine days/4 wks(mean/% change): pla=(-0.19)/(-2.4%); met-d=(-2.3)/(-28.8%)* *Sum of severity score(migraine days x intensity)/4 wks(mean/% change):* pla=0.18/1.1%; met-d=(-5.68)/(-32.2%) *Acute tablet consumption/4 wks(mean/% change):* pla=(-0.49)/(-2.4%); met-d=(-8.85)/(-45.1%) *Subjective evaluation(# pts/%)* Marked/moderate: pla=6(18%); met-d=15(54%) Slight: pla=10(29%); met-d=7(25%) Unchanged/worse: pla=18(64%); met-d=6(21%)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Metoprolol			
Andersson 1983 Denmark	Incidence(# pts/%): met-d=16(53.3%); pla=10(28.6%)	Withdrawals(# pts/%): met-d=1(3.3%); pla=1(2.8%)	
Fair quality RCT	Most common adverse events(# complaints) at visit 4: Sleep disturbances: met-d=4; pla=4 Fatigue: met-d=3; pla=0 Gastrointestinal: met-d=2; pla=2 Bradycardia: met-d=2; pla=0 Paraesthesia: met-d=0; pla=1 Depression: met-d=1; pla=1 Others: met-d=0; pla=4		

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Kangasniemi 1987 Scandinavia *Fair quality* RCT	Outpatients aged 16-65 years, diagnosed as having classic migraine (NIH Ad Hoc Committee); 2-8 migraine attacks per month, of which at least 50% had to be accompanied by focal aura symptoms	Daily use of analgesics and/or total consumption exceeding 40 tablets/month; daily use of ergotamine and/or total consumption exceeding 16 mg/month; treatment with anti-depressive or neuroleptic drugs within the past 2 months; use of narcotic analgestics, chronic treatment with calcium antagonists, clonidine, other beta-blockers or NSAIDSs; change in oral contraceptive therapy 3 months before or during the study; contraindications for beta-blockers; insufficienty treated hypertension; transient ischaemic attacks; epilepsy; hypothyroidism and other severe psychiatric or somatic disease; and pregnancy	Metoprolol durules (met-d) 200 mg daily Placebo (pla) x 8 weeks, then crossover	Former acute migraine medication allowed (not specified)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Kangasniemi 1987 Scandinavia *Fair quality* RCT	*Diary card* measuring following variables: -Frequency of migraine attacks/interval headache -Time of onset and duration of migraine attack -Intensity of headache (1=mild; 2=moderate; 3=severe) - Symptoms before and during the headache phase - Global rating of the attack on a visual analogue scale (1-10) - Conumption of analgesics and ergotamine	n=74 Mean age=37.5 79.7% female Race NR	Family history: 54(73%) Attacks per month(mean): 4.3 Duration of migraine(mean years): 17.2 Duration/attack(mean hours): 12.6 Relationship migraine/menstrual cycle(# patients/%): 28/47% Previous prophylactic treatment(# patients/%): 5/6.8% Previous acute treatment(# patients/%): 65/87.8%	NR/NR/77 randomized

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Kangasniemi 1987 Scandinavia *Fair quality* RCT	3 withdrawn(1 due to narcotic abuse and 2 due to being "dark horses")/0 lost to fu/74 analyzed	Outcomes per 4 weeks (mean score/% change) Attack frequency: met=1.8/-52.6%; pla=2.5/-34.2% (*P*=0.0004) Days with migraine: met=1.9/-59.6%; pla=2.6/-44.7% (*P*=0.01) Days with interval headache: met=1.3/-27.8%; pla=1.6/-11.1% (NS) Sum of intensity score: met=3.6/-50.0%; pla=4.5/-37.5% (*P*=0.001) Sum of global ratings: met=8.6/-53.5%; pla=12.7/-31.4% (*P*=0.001) Mean intensity score per attack: met=1.86/-7.0%; pla=2/0.0% (*P*=0.002) Mean global rating per attack: met=3.8/-30.9%; pla=4.8/-12.7% (*P*=0.003) Mean duration per attack: met=6/-30.2%; pla=8/-7.0% (*P*=0.027) Consumption of analgesic tablets: met=1.9/-52.5%; pla=4.4/+10% (*P*<0.001) Consumption of analgesic tablets/attack: met=1/-16.1%; pla=2/+66.7% (*P*<0.001) Consumption of ergotamine tablets: met=1.5/-68.1%; pla=3/-36.2% (*P*=0.007)	Recorded at each visit using unspecified stardardized questionnaire on a 3-point scale (1=mild; 2=moderate; 3=severe)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Kangasniemi 1987 Scandinavia *Fair quality* RCT	Adverse effects incidence(% patients): met=36%; pla=18% Most frequent adverse effects(# complaints for weeks 1-4/5-8) Gastrointestinal: met=7/9; pla=1/2 Fatigue: met=6/7; pla=3/1 Cardiovascular: met=1/2; pla=0/3 Sleep disturbances: met=3/1; pla=0/0 Others: met=10/6; pla=7/8	NR	Classic migraine only

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Pindolol				
Ekbom 1971 Sweden *Fair quality* RCT	Aged 19-56, with classic or common migraine (Ad Hoc Committee, 1962) at a frequency of at least 4 attacks per 4-week period	Bronchial asthma, severe infectious diseases, diabetes mellitus, pregnancy, pathological ECG findings	Group 1: Pindolol (pin1) 7.5 mg daily *(n=7)* Group 2: Pindolol (pin2) 15 mg daily *(n=9)* Group 3: Placebo (pla) x 4 weeks *(n=10)*	Ergotamines
Sjaastad 1972 Norway *Fair quality* RCT Crossover	Aged 18-62 years, with classical and common migraine; attack frequency of >/= 2/month	NR	Pindolol (pin) 7.5-15 mg daily Placebo (pla) x 4 weeks, then crossover	Ergotamine preparations; salicylates; dextropropoxipheni chloride

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Pindolol				
Ekbom 1971 Sweden *Fair quality* RCT	*Patient record:* 1) frequency, 2) duration; 3) severity (graded on arbitrary 3-point scale); 4) consumption of ergotamine	Mean age=33.7 86.7% female Race NR	Classic migraine=4(13.3%) Common migraine=26(86.7%) Family history=26(86.7%) Unilateral headache pattern=26(86.7%) Associated symptoms: Nausea=28(93.3%) Vomiting=24(80%) Photophobia/ phonophobia=28(93.3%) Urina spastica=9(30%) Diarrhea=9(30%)	NR/NR/30 enrolled
Sjaastad 1972 Norway *Fair quality* RCT Crossover	*Special form:* 1) Severity on 3-point scale (Grade I=just discernible symptoms, not appreciably influencing working capaity; Grade II=pronounced symptoms not necessitating bedrest, but markedly influencing working capacity; Grade III=severe symptoms, necessitating bedrest; 2) Headache indices=headache days times severity of attacks	Mean age=35.8 78.6% female Race NR	Common headache=14(50%) Classic headache=14(50%)	NR/NR/28 enrolled

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Pindolol			
Ekbom 1971 Sweden *Fair quality* RCT	4(13.3%) withdrawn/lost to fu NR/26 analyzed	Headache frequency/4 wks(mean/% change from observation period): pin1=(-2)/(-13.3%); pin2=(-2)/(-18.2%); pla=(-2)/(20%) Headache index/4 wks(mean/% change from observation period): pin1=0; pin2=(-4)/(-20%); pla=(-4)/(-22.2%) Headache duration/4 wks(mean/% change from observation period): pin1=0; pin2=(-0.1)/(-1.4%); pla=(-0.7)/(-9.2%) Tablet consumption: data NR; paper indicates pin=pla	NR
Sjaastad 1972 Norway *Fair quality* RCT Crossover	4(14.2%) withdrawn/0 lost to fu/24 analyzed	*Reduction in headache indices(# pts/%)* pin "definitely" (>50% reduction in headache indices) better than pla=3(12.%) pin "slightly" better than pla=1(4.2%) pin=pla: 12(50%) pin worse than pla=8(33.3%) *Headache days(group total/4 wks):* pla=181; pin=194; increase of 13(7.2%) headache days on pin *Headache indices(group total/4 wks):* pla=318; pin=313; decrease of 5 points(1.6%) on pin	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Pindolol			
Ekbom 1971 Sweden *Fair quality* RCT	NR	Withdrawals: pin=4; pla=0 Withdrawals due to: Orthostatic hypotension=2 Increased headache=1 Dizziness/cystopyelitis=1	
Sjaastad 1972 Norway *Fair quality* RCT Crossover	Untoward effects noted: Initial lethargy: pin=3; pla=0 Dizziness/faintness: pin=6; pla=0 Chest discomfort: pin=1; pla=1	pin=3/28(10.7%) pla=0	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Propranolol				
Borgesen 1974 Denmark *Fair quality* RCT Crossover	Diagnosis of migraine (Ad Hoc Committee on Classification of Headache, 1962); suffered more than one attack per week; did not respond to known prophylactics	Cardiac disease; asthma or diabetes mellitus; physical or neurological abnormalities	Propranolol (pro) 120 mg daily Placebo (pla) x 12 weeks, then crossover	Symptomatic treatments allowed (e.g., salicylates, ergotamines and narcotics)
Dahlof 1987 Sweden *Fair quality* RCT Crossover	Aged 18-60 years; history of at least 2 years classical or common migraine (World Federation of Neurological Research Group on migraine and headache); 2-8 well-defined migraine attacks/month and fulfill at least 4 of the following criteria: 1) heredity; 2) pulsating headache; 3) prodromas and/or aura; 4) hemicrania; 5) phonophobia; 6) photophobia; 7) gastrointestinal disturbances	Previous treatment with a beta blocker	Propranolol (pro) 120 mg daily Placebo (pla) x one month followed by assessment during a 5-month treatment period; then crossover	Use of common acute medication allowed (unspecified)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Propranolol				
Borgesen 1974 Denmark *Fair quality* RCT Crossover	*Patient forms:* 1) severity on 3-point scale (severe=forcing patient to stay in bed; moderate=patient able to get up, but incapable of working; mild=patient uncomfortable, but able o work); 2) duration; 3) prodromal and accompanying symptoms; 4) medication used Patients seen at four weekly intervals to record 1) severity; 2) frequency; 3) working capacity; 4) subjective evaluation of the treatment	Mean age=37.6 83.3% female Race NR	Classical migraine (# pts/%): 15(50%) Common migraine (# pts/%): 15(50%)	NR/NR/45 entered
Dahlof 1987 Sweden *Fair quality* RCT Crossover	Diary cards: 1) frequency (method NR); 2) intensity (method NR); sent into investigator each month	Mean age NR 92.8% female Race NR	Classical migraine (# pts/%): 20/71.4% Common migraine (# pts/%): 8/28.5%	NR/NR/28 entered

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Propranolol			
Borgesen 1974 Denmark *Fair quality* RCT Crossover	15(33.3%) withdrawn/0 lost to fu/30 analyzed	Attack frequency in propranolol period relative to placebo period (# pts/%): >100%=9/30%; 100%=3/10%; 75-99%=1/3.3%; 50-75%=8/26.7%; 25-50%=2/6.7%; 1-25%=2/6.7%; 0%=5/16.7% Patient preference (# pts/%): pro=17/56.7%; pla=6/20%; no difference=7/23.3% Working capacity: data NR; pro>pla (P<0.05) Medication consumption: data NR; pro=pla	NR
Dahlof 1987 Sweden *Fair quality* RCT Crossover	0 withdrawn/0 lost to fu/28 analyzed	Migraine frequency(4-week mean): pro=3.2; pla=4.3 Integrated headache(mean): pro=7.6; pla=10.9 Tablets consumed(mean): pro=9; pla=15	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Propranolol			
Borgesen 1974 Denmark *Fair quality* RCT Crossover	Data NR; pro=pla for #/severity of complaints of fatigue drowsiness and diarrhea	pro=0 pla=2	
Dahlof 1987 Sweden *Fair quality* RCT Crossover	NR	NR	Looked at longlasting prophylactic effect following discontinuance

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diamond 1982 United States *Fair quality* RCT	Diagnosis of classical or common migraine(Ad Hoc Committee, 1962); a history of at least four attacks per month just prior to starting this trial	Patients with migraine associated with other types of headaches, migraine other than classic or common; known contraindications to propranolol	Propranolol (pro) 160 mg daily Placebo (pla) *Phase I(single blind): O*ne month of single-blind treatment, then crossover *Phase II(double-blind):* 6-14 months' with at least a single crossover, but with an option for two crossovers	Simple analgesics; narcotics; ergot compounds

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Diamond 1982 United States *Fair quality* RCT	*Patient daily records* Headache Unit Index (HUI): 'Total score of headache severity'(3-point scale: 1=mild/annoying; 2=moderate/interfering; 3=severe/incapacitating)/'total number of days observed' Relief Medication Unit Index (RMUI): 'Total score of relief medication units'(3-point scale: 1=simple analgesic; 2=narcotic; 3=ergot compound)/'Total number of days observed'	Age range of 21-64 78.7% female Race NR	NR	Phase I: NR/NR/245 admitted Phase II: All 148 patients that responded to propranolol from Phase I

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Diamond 1982 United States *Fair quality* RCT	*Phase I:* 41(16.7%) withdrawn/4(1.6%) lost to fu/204 analyzed *Phase II:* 48(32.4%) withdrawn/10(6.7%) lost to fu/100 analyzed	Phase I Mean HUI: pla=0.791; pro=0.562 (*P*<0.0001) Mean RMUI: pla=2.553; pro=1.728 (*P*<0.0001)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diamond 1982 United States *Fair quality* RCT	Frequency of most common adverse events(# patients/%) Dizziness: pro=16/6.5%; pla=3/1.2% Significant nausea: pro=23/9.4%; pla=9/3.7% Visual disturbances: pro=7/2.8%; pla=0 Diarrhea: pro=18/7.3%; pla=5/2.0% Epigastric distress: pro=17/6.9%; pla=1/0.4% Weight gain: 9/3.7%; pla=2/0.8% Weakness/fatigue: pro=32/13.1%; pla=8/3.3% Malaise/lethargy: pro=20/8.2%; pla=4/1.6% Insomnia: pro=17/6.9%; pla=2/0.8% Chest pain/heaviness: pro=8/3.3%; pla=0	Phases I & II combined: pla=3/245(1.2%); pro=14/245(5.7%)	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diener 1996 Germany *Fair quality* RCT	Between the age of 18 and 60 years; male or female; migraine with and/or without aura according to the IHS criteria; migraine history of at least 12 months' duration; a mean number of 2-10 migraine attacks per month within the last 3 months prior to the study	Pregnant or lactating women; psychiatric disorders; concomitant non-migraine headaches 3 times per month within the last three months; intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks peceding the trial; specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder); intake of drugs to treat migraine attacks > 12 days/month	Propranolol (pro) 120 mg daily Placebo (pla) Cyclandelate (cyc) 1200 mg daily	Acute migraine medication allowed (not specified)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Diener 1996 Germany *Fair quality* RCT	Headache diary	Mean age: pro=40; pla=39 % female: pro=76.9%; pla=74.5% Race NR	*pro n=78; pla n=55* Mean migraine history(years): pro=21; pla=19 Migraine with aura(#/% patients): pro=18/23.1%; pla=14/25.5% Migraine without aura(#/% patients): pro=59/75.6%; pla=41/74.5% Migraine with+without aura(#/% patients): pro=1(1.3%); pla=0	235/214/214

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Diener 1996 Germany *Fair quality* RCT	40 withdrawn/0 lost to fu/214 analyzed per ITT; 174 analyzed per protocol	*pro n=78; pla n=55* Migraine frequency(#/% patients with >/= 50% reduction of attacks): pro=33/42.3%; pla=17/30.9%(NS) Mean absolute reduction of migraine duration(hrs): pro=(-34.6); pla=(-13.7)(NS)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diener 1996 Germany *Fair quality* RCT	Overall adverse effects(#/% patients): pro=19/24.4%; pla=5/9.1% Types of adverse effects of propranolol: increased sweating, hypertension, sleep difficulty, depressed modd; drowsiness; gastric pain, respiratory difficulty, kidney pain Types of adverse effects of place NR	Overall withdrawals due to adverse events(#/% patients): pro=4/5.1%; pla=0	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Forssman 1976 Sweden *Fair quality* RCT Crossover	Diagnosis of migraine; age between 16 and 55 years; at least three attacks per month	Pregnancy or suspicion of pregnancy; indication of renal or heart disease, hypertension, diabetes or asthma; history of earlier treatment of migraine with propranolol	Propranolol (pro) 240 mg daily Placebo (pla) x 12 weeks, then crossover	Previously prescribed acute medication allowed (not specified); oral contraceptives
Kuritzky 1987 Israel *Fair quality* RCT Crossover	Patients aged 17-53, suffering from classical or common migraine for at least 2 years with at least 3 attacks per month	NR	Long acting propranolol (LA pro) 160 mg daily Placebo (pla)	Analgesics

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Forssman 1976 Sweden *Fair quality* RCT Crossover	*Printed record card:* 1) begin/end times; 2) intensity (slight, moderate or severe); 3) note about ability to work; 4) non-attack headaches; 5) amount of analgesics and preparations containing ergotamine or ergotamine derivatives *Integrated headache:* Indicates combined effect of duration and intensity; divided by number of days *Rating of therapeutic effect:* 'Good' = Reduction of attack frequency or of the number of days with headache by at least 50%; 'Appreciable' = reduction of up to 50%	Mean age=37.4 87.5% female Race NR	Classic migraine=5/32(15.6%) Common migraine=27/32(87.3%) Mean migraine duration(years): 18.9 Family history of migraine(# pts): 39/40(97.5%)	NR/NR/40 included
Kuritzky 1987 Israel *Fair quality* RCT Crossover	*Diary:* 1) Headache severity on 1-3 scale (unspecified); 2) duration (hours); 3) analgetics use	Mean age NR Gender NR Race NR	Classical migraine (# pts/%): 7/22.6% Common migraine (# pts/%): 24/77.4%	NR/NR/38 began

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Forssman 1976 Sweden *Fair quality* RCT Crossover	8(20%) withdrawn/0 lost to fu/32 analyzed	Attack frequency of propranolol relative to placebo (# patients/%): Good effect(>/= 50% improvement)=11/34.4%; Appreciable effect(< 50 % improvement)=11/34.4%; No change/increase=10/31.3% Reduction of headache days of propranolol relative to placebo(# patients/%): Good effect(>/= 50%)=11/34.4%; Appreciable effect(< 50%)=10/31.3%; No change/increase=11/34.4% Integrated headache(mean/% change): pro=(-2.14)/(-41.6%); pla=(-0.37)/(-7.2%) Ergotamine consumption(change in average number/% of doses per patient per day): pro=(-0.17)/(-51.5%); pla=(-0.08)/(-24.2%) Analgesic consumption(change in average number/% of doses per patient per day): pro=(-0.16)/(-47.0%); pla=(-0.04)/(-11.8%)	NR
Kuritzky 1987 Israel *Fair quality* RCT Crossover	7(18.4%) withdrawn/0 lost to fu/31 analyzed	Number of migraine attacks (mean): LA-pro=3.23; pla=5.56 Attack severity (mean): LA-pro=15.66; pla=25.66 Attack duration (mean): data NR *(P*=0.002)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Forssman 1976 Sweden *Fair quality* RCT Crossover	*Most common side effects reported(# pts/%)* Increase in weight > 2 kg: pro=5(13.1%); pla=0 Insomnia: pro=5(13.1%); pla=1(2.6%) Tiredness: pro=4(10.5%); pla=3(7.9%) Uncharacteristic dizziness: pro=3(7.9%); pla=2(5.3%) Feeling of numbness/parasthesia: pro=2(5.3%); pla=1(2.6%) Nausea: pro=2(5.3%); pla=1(2.6%) Increased appetite: pro=1(2.6%); pla=0 Palpitations: pro=1(2.6%); pla=1(2.6%) Malaise: pro=0; pla=0	pro=2 pla=2	
Kuritzky 1987 Israel *Fair quality* RCT Crossover	Most common side effects: tiredness, insomnia and dizziness	NR	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Malvea 1973 United States *Fair quality* RCT Crossover	Age range of 25-57 with common migraine	Pregnancy, bronchial asthma, congestive heart failure, allergic rhinitis, diabetes mellitus and previous use of propranolol for headache	Propranolol (pro) <dose?> mg daily Placebo (pla) x <duration?>, then crossover	Analgesic, ergot and narcotic drugs
Mikkelsen 1986 Denmark *Fair quality* RCT Crossover	Aged between 18 and 65 years, with history of classic or common migraine (Ad Hoc Committee on Classification of Headache) with at least three migraine attacks per month which had been present for more than one year	Allergy to tolfenamic acid; serious heart, kidney, liver or psychiatric diseases, asthma, bronchitis, diabetes, active ulceration, pregnancy, or breast feeding; any administration of another prophylactic treatment for migraine within the month prior to the start of the study; use of tolfenamic acid within 6 months of study entry	Propranolol (pro) 120 mg daily Tolfenamic acid (tol) 300 mg daily Placebo (pla) x 12 weeks, then crossover	Other kinds of abortive treatment allowed but not specified

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Malvea 1973 United States *Fair quality* RCT Crossover	*Patient record* of: 1) headache frequency; 2) headache severity on 3-point scale (1=mild, annoying; 2=moderate or interfering; 3=severe or incapacitating; 3) use of analgesic and ergo drugs Reviewed at each 6-week period	Mean age NR 87.1% female Race NR	NR	NR/NR/31 enrolled
Mikkelsen 1986 Denmark *Fair quality* RCT Crossover	*Patient record sheet* 1) Number of attacks 2) Duration of attacks 3) Intensity of attacks (scale of 1-10) 4) Working capacity on 3-point scale (1=ability to work; 2=ability to be ambulant but not able to work; 3=bed confinement)	Mean age=38 Gender(% female)=83.9 % Race NR	Classic=10/31(32.2%) Common=21/31(67.7%)	NR/NR/39

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Malvea 1973 United States *Fair quality* RCT Crossover	1(3.2%) withdrawn/0 lost to fu/29 analyzed	Final preference(# patients/%): pro=16/55.2%; pla=8/27.6%; neither=5/17.2% Headache units/day(sum of means for group as a whole/% change): pro=(-6.8)/(-19.2%); pla=(-2.1)/(-8.3%) Symptomatic drug use/day(sum of means for group as a whole/% change): pro=(-27)/(-34.2%); pla=(-24)/(-30.4%)	NR
Mikkelsen 1986 Denmark *Fair quality* RCT Crossover	8(20.5%) withdrawn/0 lost to fu/31 analyzed	*Clinical data recorded over last 11 weeks of each treatment period:* Number of attacks(mean): pla=8.81; pro=6.65 Working capacity(Total attacks where patients were confined to bed): pla=5.48; pro=4.06(NS) Mean attack duration (hours) of attacks: pla=18.68; pro=14.26(NS) Pain intensity(on scale of 1-10): pla=6.97; pro=6.94(NS)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Malvea 1973 United States *Fair quality* RCT Crossover	Overall incidence: NR Side effects possibly related to the use of propranolol(# pts): Mild nausea: 5 Fatigue: 5 Numbness: 1 Heartburn: 1 Heaviness in leg/arm=1 Light-headedness=1 Vomiting=1 Tingling in leg/arm=1 Depressed=1	NR	
Mikkelsen 1986 Denmark *Fair quality* RCT Crossover	Overall adverse effects(# patients): pla=3; pro=3(NS) Adverse events recorded with: Placebo=slight neurological symptoms, hot flushes, diarrhea Propranolol=fatigue, polyuria, low back pain	NR	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Pita 1977 Spain *Fair quality* RCT Crossover	Migraine (Ad Hoc Committee) at a frequency of at least 3-4 attacks monthly and have a history of not responding to prophylactic therapy	Concomitant neurological or psychiatric disorders as well as diabetes mellitus, asthma or cardiac disease	Propranolol (pro) 160 mg daily Placebo (pla) x 2 months; then crossover	Symptomatic analgesic treatment (unspecified)
Pradalier 1989 *Fair - Poor* RCT	Suffering from migraine for at least two years with or without aura according to the criteria of the new International Headache Society classification	History of congestive heart failure or asthma; heart block; bradycardia (<50 beats/min); Raynaud phenomenon; hypertension; resistant to two previously well-followed prophylactic treatments	Placebo (pla) Long-acting propranolol (LA pro) 160 mg daily x 12 weeks	Usual medication

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Pita 1977 Spain *Fair quality* RCT Crossover	1) Frequency; 2) duration; 3) severity rated on 3-point scale (e.g., I=uncomfortable but able to work; II=patient unable to work but not needing bedrest; III=patient necessitating bedrest)	Mean age=32 77.8% female Race NR	Common(#/% patients): 5/9(55.6%) Classic(#/% patients): 4/9(44.4%)	NR/NR/9
Pradalier 1989 *Fair - Poor* RCT	Patient form documenting frequency and details of the headache (method NR)	Mean age: LA pro=37.1; pla=37.7 Gender(% female): LA pro=77.5%; pla=73.5% Race NR	Familial history of migraine: LA pro=65%; pla=52.9% Mean age at onset: LA pro=20.8; pla=19.1 Migraine frequency/week: LA pro=1.66; pla=1.40 Type of migraine Aura: LA pro=15%; pro=5.9% No Aura: LA pro=80%; pla=85.3% Aura+No Aura: LA pro=5%; pla=8.8% Severity of crisis(# pts. with severe crisis): LA pro=52.5%; pla=;47.0%	NR/NR/74 entered

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Pita 1977 Spain *Fair quality* RCT Crossover	1(11.1%) withdrawn/0 lost to fu/8 analyzed	Whole frequency/month: data NR; narrative indicates pro>pla Mean frequency/month: data NR; narrative indicates pro=pla Mean Grade(severity)/month: data NR; narrative indicated pro>pla for Grade III Preference(# patients): pro=7/8; pla=1/8	NR
Pradalier 1989 *Fair - Poor* RCT	33 withdrawn(19 prior to randomization)/9(16.3%) lost to fu/analyzed NR	Change in mean crises/month: LA pro= (-2.96/-48.4%); pla= (+0.41/+6.8%)	Volunteered information (e.g., "How did you tolerate the treatment?") and a standardized 17-item questionnaire

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Pita 1977 Spain *Fair quality* RCT Crossover	*NR*	NR	
Pradalier 1989 *Fair - Poor* RCT	Answers to adverse event questionnaire at Day 84 *(LA pro n=22; pla n=19)* Cold extremities: LA pro=0; pla=3(15.8%) Tiredness: LA pro=3(13.6%); pla=2(10.5%) Dyspnea: LA pro=3(13.6%); pla=1(5.3%) Dyspepsia: LA pro=1(4.5%); pla=0 Diarrhea: LA pro=1(4.5%); pla=0 Constipation: LA pro=2(9.1%); pla=2(10.5%) Insomnia: LA pro=2(9.1%); pla=2(10.5%) Depression: LA pro=0; pla=1(10.5%)	LA pro=0 pla=1(due to psoriasis)	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Rao 2000 India *Fair quality* RCT	Patients with two or more migraine attacks per week	NR	Placebo (pla) Cyproheptadine (cyp) 4 mg daily Propranolol (pro) 80 mg daily Cyproheptadine 4 mg daily+Propranolol 80 mg daily (cyp+pro)	NR
Wideroe 1974 Norway *Fair quality* RCT Crossover	Patients diagnosed with cassic or common migraine (Ad Hoc Committee, 1962) in whom the result of open treatment with propranolol 160 mg daily as part of a pilot study was rated as "excellent" (e.g., reduction of attack rate of more than 50%	NR	Propranolol (pro) 160 mg daily Placebo (pla) x 3 months, then crossover	Analgesic and antimigraine drugs

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Rao 2000 India *Fair quality* RCT	Migraine attack frequency, severity and duration rated by patient using 5-point scale 4=100%, "total" relief 3=75% relief 2=50% relief 1=25% relief 0=0% relief, no change	Mean age=28.6 67.2% female Race NR	NR	NR/NR/259 recruited
Wideroe 1974 Norway *Fair quality* RCT Crossover	*Patient record* of a) frequency; b) intensity; c) duration; d) change in premonitory symptoms; e) quality of the attack; f) degree of invalidity; g) consumption of analgesic/antimigraine drugs *Treatment rating by physician:* 1) excellent-a reduction in attack rate of more than 50%; 2) moderate-a reduction in attack rate of less than 50%; 3) no effect; 4) an increase in attack rate x monthly	Mean age=38 Gender(% female)=86.7 % Race NR	Classic=6/30(20%) Common=24/30(80%)	NR/NR/30

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Rao 2000 India *Fair quality* RCT	55 withdrawn/lost to fu NR/204 analyzed	*Frequency (mean response):* pla=1.77; pro=2.85 *Duration (mean response):* pla=1.77; pro=2.83 *Severity (mean response):* pla=1.64; pro=2.87	NR
Wideroe 1974 Norway *Fair quality* RCT Crossover	4 withdrawn/lost to fu NR/analyzed 26	Average rate of migraine attacks/month(mean/% change): pro=0.4(-86.7%); pla=1.7(-58.8%)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Rao 2000 India *Fair quality* RCT	Incidence(# patients): pla=1/69(1.4%); pro=11/62(17.7%)	NR	
Wideroe 1974 Norway *Fair quality* RCT Crossover	NR	NR	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Poor quality				
Propranolol				
Ahuja 1985 India *Poor quality* RCT Crossover	Suffering from migraine (Ad Hoc Committee on Headache) at a frequency of > 2 attacks per month in the previous 3 months	Intercurrent illness	Propranolol (pro) 120 mg daily Placebo (pla) x 8 weeks, then crossover	NR
Borgensen 1976 Denmark *Poor quality* RCT Crossover	(a) Diagnosis of migraine (Ad Hoc Committee on Headache, 1962) (b) > 1 migraine attack/week (c) Intractability with known prophylactics	Cardiac disease, asthma, diabetes mellitus, physical or neurological abnormalities	Propranolol (pro) 120 mg daily Placebo x three months, then crossover	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Poor quality				
Propranolol				
Ahuja 1985 India *Poor quality* RCT Crossover	*Severity:* rated on 3-point scale (3=severe; 2=moderate, incapacitating; 1=inconvenient, mild) *Severity index:* calculated by multiplying the number of attacks /8 weeks with severity points *Attack duration:* scored on 5-point scale (5=duration of attack exceeding pretreatment duration; 4=duration equal before and after treatment; 3=duration of attacks was 75 percent of pretreatment; 2=duration of attacks was 50 percent of pretreatment; 1=duration of attacks was 25 percent of pretreatment) *Duration index:* multiplying number of attacks/8 weeks with duration score	Age range of 17-55 46.1% female	NR	NR/NR/26 enrolled
Borgensen 1976 Denmark *Poor quality* RCT Crossover	NR	NR	Migraine Frequency(# patients): 2-5 attack/4 weeks=1	NR/NR/45 patients

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Poor quality			
Propranolol			
Ahuja 1985 India *Poor quality* RCT Crossover	NR/NR/NR	Attack frequency/8 weeks(mean): pro=8.58; pla=14.46 (*P*<0.05) Severity Index/8 weeks(mean): pro=20.69; pla=38.00 (*P*<0.05) Duration index/8 weeks(mean): pro=23.58; pla=52.19 (*P*<0.01)	NR
Borgensen 1976 Denmark *Poor quality* RCT Crossover	15(33.3%) withdrawn/lost to fu NR/30 analyzed	Attack frequency in pro period as percentage of that in pla period(number/% patients): > 100%=9/30% 100%=3/10% 75-99%=1/3.3% 50-75%=8/26.7% 25-50%=2/6.7% 1-25%=2/6.7% 0%=5/16.7%	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Poor quality			
Propranolol			
Ahuja 1985 India *Poor quality* RCT Crossover	data NR; no significant side effects of propranolol were observed during the trial period	NR	
Borgensen 1976 Denmark *Poor quality* RCT Crossover	NR	NR	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Diamond 1976 United States *Poor quality* RCT Crossover	Classic or common migraine	Asthma, cardiac disease, diabetes mellitus or any physical or neurologic abnormalities	Flexible dosing: Propranolol (pro) 80-160 mg daily Placebo (pla) x 4-8 weeks; then crossover x 8 weeks	Common analgesics, narcotics, ergot medications

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Diamond 1976 United States *Poor quality* RCT Crossover	*Severity* rated on 3-point scale (severe/3 headache units(HU)=incapacitation unable to perform their duties; moderate/2 HU=annoying headache with difficulties to carry out activities; mild/1 HU=bothersome headache which permit fulfillment of obligations with minimal or no difficulties) *Relief medication units(RMU):* ergotamine=3 RMU; narcotic=2 RMU; common analgesic=1 RMU *Headache Index(HI):* HU total/# days observed *Headache Index Ratio:* pla HI/pro H(1=no change; >1=better on pro; <1=better on pla) Relief medication index(RMI): total of RMU/# days observed *Relief medication index ratio(RMIR): pla RMI/pro RMI(1=no change; >1=better on pro; <1=better on pla)*	Average age=38.1 80.7% female Race NR	Common migraine: 57 pts.(91.9%) Classic migraine: 5 pts(8.1%)	NR/NR/83

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Diamond 1976 United States *Poor quality* RCT Crossover	21 pts(25.3%) withdrawn/lost to fu NR/62 analyzed	Responders (# pts preferred treatment): pro=34/62(54.8%); pla=17/62(27.4%) Corroboration of HIR/RMIR scores relative to treatment preference (# pts/%): pro=27/34(79.4%); pla=10/17(58.8%) Comparison of HIR:RMIR relative to treatment preference (pro responder=34; pla responder=17) Low ratio value (HIR/RMIR): pro resP=0.70/0.00; pla resP=0.37/0.00 Medium ratio value (HIR/RMIRO: pro resP=2.03/1.95; pla resP=0.75/0.75 High ratio value (HIR/RMIR): pro resP=14/?; pla=1.44/5.91	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Diamond 1976 United States *Poor quality* RCT Crossover	Incidence(# pts/%): pro=15/83(18.1%); pla=9/83(10.8%) Benign adverse reactions occurring on both pro and pla(data NR): nausea, light headedness, fatigue, difficulty catching breath, mild depression, heartburn Benign side effects on pro only(data NR): diarrhea, abdominal cramps, irritability, insomnia, sleepiness	pro=6/83(7.2%) pla=1/83(1.2%)	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Fuller 1990 London *Poor quality* RCT	Common or classical migraine as defined by the Ad Hoc Committee; migraine of one year's duration; with attacks occurring between once a week and once every four months; age between 16 and 65	Contraindications to propranolol or paracetamol; pre-existing migraine prophylaxis or beta-blocker therapy for other indications; non-migrainous headaches that are not clearly distinguishable from migraine	Propranolol 40 mg Placebo	Paracetamol
Johnson 1986 New Zealand RCT Crossover	Aged 22-80, with a history of least one migraine attack during the month preceding the trial; attacks associated with at least two of the following: 1) a strong family history, 2) nausea or vomiting, 3) some response to vasoconstrictors, 4) a classical prodrome	NR	Mefanamic acid (mef) 500 mg daily Propranolol (pro) 80 mg daily Placebo (pla) x 3 months; then crossover	Acute medication allowed (not specified)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Fuller 1990 London *Poor quality* RCT	Patient record cards	*n=14* *Median age=31* *78.6% female* *Race NR*	Common migraine=9/14(64.3%) Classical migraine=5/14(35.7%)	NR/NR/27 recruited
Johnson 1986 New Zealand RCT Crossover	*Patient charts:* 1) frequency; 2) duration; 3) severity (scale 1-10); 4) associated symptoms; 5) acute medication usage; 6) side effects; 7) disability scored on a 5-point scale (1=mild disability; 5=severe, confinement to bed in a darkened room) Patients assessed monthly	Per protocol analysis (n=17) Mean age=42 76.5% female Race NR	Per protocol analysis (n=17) Common migraine=11(64.7%) Classical migraine=6(35.3%)	NR/NR/29 enrolled

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Fuller 1990 London *Poor quality* RCT	14 analyzed	Change in headache severity(2 hours post-dose): *1-3 point deterioration(# patients):* pro=1(7.1%); pla=4(28.6%) *No change(# patients):* pro=7(50%); pla=4(28.6%) *1-6 point improvement(# patients):* pro=6(42.8%); pla=6(42.8%) Patient analysis of response to treatment: *No effect:* pro=3(21.4%); pla=6(42.8%) *Poor:* pro=4(28.6%); pla=3(21.4%) *Fair:* pro=5(35.7%); pla=4(21.4%) Good: pro=2(14.3%); pla=1(7.1%) *Excellent: pro=0; pla=0*	NR
Johnson 1986 New Zealand RCT Crossover	12(41.4%) withdrawn/9(31%) lost to fu/17 analyzed	*Number of attacks/3 months(median/mean):* pro=11/13.8 pla=15/20 Median/% change(pro:pla): -4/-26.7% Mean/% change(pro:pla): -6.3/-31.3% *Total duration (hours) of attack(median/mean):* pro=75/115 pla=138/184 Median/% change(pro:pla): -63/-45.6% Mean/% change(pro:pla): -69/-37.5% *Average duration (hours) of attacks(median/mean):* pro=24/40 pla=26/40 Median/% change(pro:pla): -2/-7.7% Mean/% change(pro:pla): 0	Recorded by patients in charts

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Fuller 1990 London *Poor quality* RCT	*Propranolol(# patients):* Light-headedness=1 Stomach pains=1 Sleepiness=1 *Placebo(# patients):* Sleepiness=2 Nausea=2 Dizzness=1	NR	*Study of abortive treatment of migraine*
Johnson 1986 New Zealand RCT Crossover	Incidence: pro=2(8.7%); pla=1(4.2%) Adverse events on: pro=depression, gastrointestinal symptoms pla=dizziness	Withdrawals: pro=1 pla=1	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	18 to 65 years of age; meeting diagnostic criteria for migraine without aura as defined by the IHS; migraine frequency of 2-8 times/month, with a maximum of 15 headaches days per month, and a migraine history of greater than 1 year	Past trials of valproate or propranolol; failure of greater than 2 adequate trials of migraine prophylactic agents; severe medical or psychiatric illness; analgesic use of more than 15 days per month; presence of alcohol or drug abuse; use of no contraception by women of childbearing potential; unable to complete a headache diary or differentiate various headache types	Sustained release propranolol (SR pro) 180 mg daily Divalproex sodium (div) 1500 mg daily Placebo (pla)	Symptomatic medication allowed (unspecified)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	Patient diary Assessments performed at weeks 4, 8, 20, 24, and 36	Mean age NR 81.1% female Race NR		NR/NR/37

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	5(13.5%) withdrawn)/0 lost to fu/32 analyzed	Reduction in mean migraine *frequency*/4 weeks(#/% patients): pla=6/19%; pro=20/63% Reduction in mean migraine *days*/4 weeks(#/% patients): pla=7/22%; pro=22/69%	Documented on forms (not specified)

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Kaniecki 1997 United States *Poor quality* RCT Crossover Single blind	Adverse event profile for SR propranolol (# events): nausea=2 Fatigue=3 Dizziness=3 Weight gain=1 Depression=2 Increased headache=1 Impotence=1 Insomnia=1 Memory loss=1 Adverse event profile for placebo NR	Overall withdrawals due to adverse events=5(15.6%)	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Nadelmann 1986 *Poor quality* RCT Crossover	Fulfilled diagnostic criteria for classic and/or common migraine headaches (Ad Hoc Committee on the Classification of Headache); had at least four headaches per month during a one-month observation period	Migraine other than classic or common, or other headaches known to be associated with migraine, or if they had known contraindications to beta blockers	Propranolol (pro) 80-320 mg daily Placebo (pla) x 30 weeks (6-week dose-finding, 24-week double-blind)	Analgesics Tranquilizers Ergot Narcotics
Nair 1974 India *Poor quality* RCT Crossover	History typical of migraine; duration of headache of more than one year; attack rate exceeded 5 or more/month	NR	Propranolol (pro) 80 mg daily Placebo (pla)	*All patients used prochlorperazine 15 mgms daily throughout the duration of the study.* Use of metamizole and ergotamine tartrate also allowed as abortive treatment

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Nadelmann 1986 *Poor quality* RCT Crossover	Data recorded at two-week intervals Daily patient diaries *Headache Unit Index (HUI)* A mild headache=Annoying=1unit A moderate headache=Interfering=2 units A severe headche=Incapacitating=3 units for headaches lasting 2 days A very severe headache=Incapacitating=4 units/day for severe attacks lasting 2 or more days *Relief Medication Unit Index(RMUI)* Simple analgesic, tranquilizer=1 unit Narcotic=2 units Ergot compound=3 units	*Age(%)* 18: 1.6 20-29=37.1 30-39=30.6 40-49=24.2 50-59=4.8 60=1.6 *Gender(%)* Female=85.5 Male=14.5 *Race(%)* White=96.8 Black=3.2	*Diagnosis(%)* Common migraine=56.5 Classic/common migraine=43.5 Classic migraine=0 *History of migraine(% yrs duration)* 1-5=22.6 6-10=27.4 11-15=14.5 16-20=9.7 21-25=8.1 26+=17.7	NR/NR/67 registered
Nair 1974 India *Poor quality* RCT Crossover	*Patient charts(2):* 1) # of headaches suffered in one month; 2) # of tablets of metamizole and ergotamine tartrate consumed in one month	Mean age=27.2 50% female Race NR	NR	NR/NR/20

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Nadelmann 1986 *Poor quality* RCT Crossover	26 withdrawn/2 lost to fu/	**Sequence 1: contrast between mean change in placebo and propranolol treatment periods** **Sequence 2: contrast between mean change in propranolol and placebo treatment periods** **HUI** **Sequence 1: 0.33 (*P*=0.03)** **Sequence 2: (-0.18) (NS)** **RMUI** **Sequence 1: 0.66 (NS)** **Sequence 2: (-0.72) (NS)**	NR
Nair 1974 India *Poor quality* RCT Crossover	0 withdrawn/0 lost to fu/20 analyzed	Headache frequency(mean/month) pla=6.25 pro=3.15 Mean/% change(pro:pla): (-3.1)/(-49.6%)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Nadelmann 1986 *Poor quality* RCT Crossover	% Incidence Malaise: pro=14.1; pla=3.6 Fatigue: pro=40.6; pla=5.4 Lethargy: pro=26.6; pla=3.6 Bradycardia: pro=7.8; pla=0 Nausea: pro=15.6; pla=5.4 Diarrhea: pro=10.9; pla=1.8 Epigastric distress: pro=17.2; pla=3.6 Depressed moods: pro=7.8; pla=0 Vivid dreams: pro=10.9; pla=1.8	NR	
Nair 1974 India *Poor quality* RCT Crossover	NR	NR	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Palferman 1983 London *Poor quality* RCT Crossover	Outpatients with migraine, defined as episodic headache with other accepted disorders of cerebral function including visual disturbances and vomiting, and those with "non-migraine", defined as recurrent 'simple' or 'tension' headaches without the disorders of cerebral function	Patients under 16 or over 65 years; use of beta blockers contraindicated; patients with the possibility of other pathology, disclosed by history, examination or investigations, which might lead to headaches	Propranolol (pro) 120 mg daily Placebo (pla) x 8 weeks, then crossover	NR
Standes 1982 Norway *Poor quality* RCT Crossover	Outpatients of both sexes between the ages of 18 and 65 years with a history of between two and six common migraine attacks (Ad Hoc Committee) per month	Other types of headache (including classical migraine) and major head injuries; contraindications to beta-blocking agents; use of oral contraceptives; pregnant women; use of timolol or propranolol for other reasons than migraine	Propranolol (pro) 160 mg daily Timolol (tim) 20 mg daily Placebo (pla)	Ergotamine and analgesics

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Palferman 1983 London *Poor quality* RCT Crossover	Patient diary card Subjective daily syptoms graded 0-4 (0=no headache, 1=mild, 2=moderate, 3=severe, 4=worst possible) x 4 weekly intervals	**All patients (n=22)** **Mean age=37.8** **69.4% female** **Race NR** **Migraine patients only (n=10)** **Mean age=41.4** **80% female** **Race NR**	*All patients* Average symptom duration(yrs): 11.3 *Migraine patients only* Average symptom duration(yrs): 17.5	NR/NR/22 patients (10 migraine patients) enrolled
Standes 1982 Norway *Poor quality* RCT Crossover	*Patient record:* 1) incidence; 2) severity; 3) duration	Age range: Men=20-57; Women=22-57 80% female Race NR	NR	NR/NR/25 recruited

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Palferman 1983 London *Poor quality* RCT Crossover	14(38.8%) withdrawn/10(27.8%) lost to fu/22 analyzed	Average number of days with headache in 56 days: All patients (N=22): pla=26; pro=23 (NS) Migraine patients only (n=10): pla=24; pro=21 (NS) Average headache score All patients: pro=55; pla=47 (*P*=0.26) Migraine patients only: pro=52; pla=47 (NS)	NR
Standes 1982 Norway *Poor quality* RCT Crossover	7(28%) withdrawn/0 lost to fu/18 analyzed	Reduction in mean attacks/month(mean/% change): pro=(-3.43)/(51.6%); pla=(-2)/(-30.1%) Ergotamine use(change in % of attacks during which pain relieving tablets were taken): pro=(-18 percentage points); pla=(-13.4 percentage points) Other pain relief tablet use(change in % of attacks during which pain relieving tablets were taken): pro=(-29 percentage points); pla=(-35 percentage points) Reduction in frequency of attacks: Good(>/= 50% reduction): pro=13 pts./72.2%; pla=6 pts./33.3% Some(33.3-49% reduction): pro=0 pts.; pla=1 pt./5.5% No effect(0=33.2% reduction); pro=3 pts/16.7%; pla=8 pts./44.4% Negative effect(increased frequency): pro=2 pts/11.1%; pla=3 pts/16.7%	Patient report

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Palferman 1983 London *Poor quality* RCT Crossover	NR	NR	
Standes 1982 Norway *Poor quality* RCT Crossover	Incidence(# pts/%): pro=6/25(24%); pla=5/25(20%) Most common adverse events: Tiredness: pro=3/25(12%); pla=4/25(16%) Nausea: pro=1/25(4%); pla=1/25(4%) Sunburn feeling: pro=1/25(4%); pla=0 Depression: pro=1/25(4%); pla=0	2/25(8%) treatment NR	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	Outpatients of both sexes between ages of 18 and 65 years with a history of between 2 and 6 common migraine attacks per month (Ad Hoc Committee)	Other types of headache (including classical migraine) and major head injuries; contraindications to beta blockers; oral contraceptive use; heart rate < 54 after 3 min of rest and with supine DBP >/= 100 mmHg	Timolol (tim) 20 mg daily Propranolol (pro) 160 mg daily Placebo (pla)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	*Patient diary card:* 1) frequency; 2) duration; 3) severity of attacks; 4) number of responders (e.g., >/= 50% reduction in frequency of attacks compared to baseline; 5) frequency of attacks with associated symptoms; 6) frequency of attacks requiring medication; 7) headache index=frequency x severity x attack duration in hours; 8) second headache index: attack frequency x severity	Mean age=39.5 73.9% female Race NR	Clinical characteristics(mean) Duration of migraine(years): 20.9 Attack frequency/28 days: 5.7 Attack with nausea frequency/28 days: 2.6 Attack with ergotamine therapy frequency/28 days: 2.4 Attack with any therapy frequency/28 days: 5.1 Duration of attacks(hours): 9.8 Severity of attacks: 2.0	NR/NR/96

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	withdrawn=27(28.1%)/6(6.2%) lost to fu/80 analyzed	*Mean frequencies per 28 days/mean(%) change for propranolol relative to placebo* Frequency of attacks: pro=3.69; pla=4.84/-1.15(-23.8%) Frequqency of attacks with nausea: pro=1.37; pla=1.89/-0.52(-27.5%) Frequency of attacks with any therapy: pro=3.24; pla=4.20/-0.96(-22.8%) Severity of attacks: pro=1.83; pla=1.93/-0.10(-5.2%)(NS) Duration of attacks(hours): pro=7.38; pla=7.95/-0.57(-7.2%)(NS) Headache index2: pro=6.66; pla=9.03/-2.37(-35.6%) Headache index1: pro=50.3; pla=50.7/-19(-27.4%) Number of responders(# pts with 50% reduction in frequency): pro=48; pla=24/24(+50%)	Patient report

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Tfelt-Hansen 1984 Scandinavia *Poor quality* RCT Crossover	Incidence[# pts(%)]: pro=35(42.2%); pla=23(27.7%) Most commonly reported side effects: Fatigue/tiredness: pro=11(13%); pla=15(18%) Dizziness: pro=4(5%); pla=2(2%) Nausea: pro=5(6%); pla=2(2%) Sleep disturbances: pro=3(4%); pla=2(2%) Depression: pro=3(4%); pla=0 Abnormal dreaming: pro=0; pla=0	pro=6/89(6.7%) pla=2/90(2.2%)	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Weber 1972 United States *Poor quality* RCT Crossover	Met criteria for diagnosis of migraine and that were recognized as therapeutic management problems	Abnormal neurological examinations; disorders that could be aggravated by beta blockers (namely cariac disease, asthma, diabetes mellitus)	Propranolol (pro) 80 mg daily Placebo (pla)	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Weber 1972 United States *Poor quality* RCT Crossover	1) Frequency and 2) severity assessed at 4-week intervals Definitions of symptomatic responses Excellent: all or nearly all symptoms of migraine absent after first week of study Good: more than 50% reduction in frequency or severity of headaches Fair: minimal symptomatic improvement No effect: unspecified	Mean age=40.6 52% female Race NR	Classic: 13(68.4%) Common: 6(31.6%)	NR/NR/25

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Weber 1972 United States *Poor quality* RCT Crossover	withdrawn=6/25(24%)/lost to fu NR/analyzed 19	Symptomatic response(# pts/%) *First 3 months(pro n=8; pla n=11)* Good/Excellent: pro=5(63%); pla=0 Fair: pro=2(25%); pla=1(9.1%) No effect: pro=1(12.5%); pla=11(91%) *Second 3 months(pro n=11 who received placebo first; pla n=8 who received pro first)* Good/Excellent: pro=10(91%); pla=2(25%) Fair: pro=0; pla=0 No effect: pro=1(9.1%); pla=6(75%) *Irrespective of sequence* pro>pla(#/% pts): 15/79% pro=pla(#/% pts): 4/21%	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Weber 1972 United States *Poor quality* RCT Crossover	Abdominal cramps/diarrhea:1 patient	NR	

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Schellenberg 2008 head-to-head	Outpatients of both sexes between the ages of 18 and 65 years with confirmed migraine diagnosis with onset of migraine history <50 years of age, history of migraine <12 months, documented record of at least 2 migraines per month in previous 3 months, 2-6 migraine attacks in the 4 weeks prebaseline, adequate acute, symptomatic treatment of attacks, current contraception accepted if >3months adn unchanged during trial.	Prophylactic migraine treatments in previous 3 months, concomitant b-blocker, calcium antagonist, concomitant nondrug migraine treatment, use of symptomatic treatment for >10 days per month, change in current symptomatic treatment for migraine, history of hypersensitivity to metoprolol or nebivolol, history of substance abuse, pregnant or breast feeding, congestive HF, heart rate <50bpm, systolic blood pressure <100 bpm, peripheral arterial occlusive disease, uncontrolled DM, history of bronchospasm, clinically relevant abnormal laboratory values	Week 1: metoprolol (met) 47.5 mg; OR nebivolol (neb) 5 mg Week 2: met 95 mg OR neb 5 mg Weeks 3-16: met 142.5 mg OR neb 5 mg Week 17: met 95 mg OR neb 5 mg alternate days Week 18: met 47.5 mg OR neb 5 mg every two days	NR

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Schellenberg 2008 head-to-head	Primary endpoint: frequency of migrane attacks reported by patients during the last 4 weeks of the 14 week treatment. Secondary endpoints: time to therapeutic effect (evaluated 4-weekly), duration of attacks, intensity of headache, consumption of analgesics, evaluation of accompanying symptoms, migrane disability assessment, clinical global impression, patients global impression, quality of life, responder rates -- defined as a decrease of at least 50% in number of attacks from baseline to endpoint.	Mean age= 39 female 86% Race NR	Migraine disability assessment (MIDAS) mild impairment: 2 (6%) moderate impairment: 6 (20%) severe impairment: 22 (73%) Days with headache (per month prior 3 months) mean 18	Screened: 38 Eligible: 30 Enrolled: 30 met 14; neb 16

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Schellenberg 2008 head-to-head	2/NR/30	Preimary endpoint: Frequency of migraine attacks (mean): met 1.3; neb 1.6 Secondary endpoints: Onset of action (attacks during weeks 0-4) mean: met 1.9; neb 2.2 Responder rate at endpoint %: met 57%; neb 50% Duration of migrane attacks at endpoint (mean hours) met 26; neb 15 severity at endpoint (measured on 100-mm visual analogue scale) met 54; neb 50 Patients using pain medication at endpoint (%) met 77%; neb 67% Differences between the two groups was NS	AE reporting were completed during clinic visits.

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Schellenberg 2008 head-to-head	Number reported events: met 44; neb 32 number of treatment related events: met 13; neb 11 Patients reporting events: mild: met 1 (7%); neb 4 (25%) moderate: met 12 (86%); neb 6 (38%) severe: met 6 (43%); neb 2 (13%) patient withdrawl due to adverse events: met 1 (7%); neb 1 (6%) most common reported events: fatigue: met 11; neb 7 bradycardia: met 5; neb 1 hypotension: met 2; neb 1 supraventricular extrasystoles: met 2; neb 1	6.6% (2/30)	head-to-head trial need to move from placebo table

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)	Allowed other medications/ interventions
Siniatchkin 2007 Germany RCT parallel-group	Outpatients of both sexes between the ages of 18 and 60 years with migraine history of ≥ 12 months and a mean of 2-10 migraine attacks per month within last 3 months.	Pregnancy or lactaion; abuse of ergotamine, triptans or analgesics; any prophylactic treatment of migraine during 6 months preceeding the trial; neurological, psychiatric or internal disease during the treatment in the last year; all specific contradictions for b-blockers; concomitant non-migraine headaches more than 3 X per month w/in last 3 months; substance abuse; change in oral contraceptive use 3 months prior to the study.	Metoprolol (met) titrated by 50 mg weekly until the maximum dose of 200 mg. Placebo titrated by 50 mg weekly until the maximum dose of 200 mg X 3 months After 3 months met was decreased at 50 mg / week.	Usual abortive treatment allowed -- not specified. Patients were asked not to change their treatment during the study.

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled
Siniatchkin 2007 Germany RCT parallel-group	Headache diary: days in which migraine occured, duration in hours, intensity (3 assessment times per day using visual analogue scale), dosage of all medications taken and side-effects.	Mean Age: met 36.7; placebo 37.3 female: met 20%; placebo 10% Race: NR	duration of disease in years: met 23.9; placebo 20.7 attack frequency days/ mo: met 5.2; placebo 4.0 attack duration (hours): met 18.6; placebo 17.3 intensity (scale 1-10): met 9.4; placebo 9.2 analgesics/triptans use (tablets/ months): met 6.4; placebo 7.3	Recruited: 20 ENRolled: 20

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Siniatchkin 2007 Germany RCT parallel-group	0/NR/20	Migraine days/month: Reported Z Scores met 2.8; pla 1.9 Attack intensity: met 3.9; pla .9 Duration of headache met 2.9; pla 1.1 *P*<0.05	patient diary

Evidence Table 16. Placebo controlled trials of beta blockers for migraine

Author Year Country Study Design	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)	Comments
Siniatchkin 2007 Germany RCT parallel-group	met: n=4 (40%): tiredness 2 (20%) dizziness 1 (10%) cardovascular 1 (10%) placebo: n=3 (30%) gastrointestinal distrubances 2 (20%) tiredness 1 (10%)	0 (0/20)	

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Nadelmann 1986	NR	NR	N/A-crossover	Fair higher female to male ratio	67 enrolled
Borgensen 1976 Denmark	**NR**	NR	N/A-crossover	Unknown; characteristics NR	45 selected
Fuller 1990 London	NR	NR	N/A-crossover	Good Median age=31 78.6% female	27 enrolled/14 analyzed
Rao 2000 India	Inferior; group allottment via latin square design	NR	NR	Good Mean age=28.6 67.2% female	259 recruited
Pradalier 1989	NR	NR	Yes	Good Mean age=37 75.7% female	74 enrolled
Wideroe 1974 Norway	NR	NR	N/A-crossover	Good Mean age=38 86.7% female	30 enrolled
Mikkelsen 1986 Denmark	NR	NR	N/A-crossover	Good Median age=38 83.9% female	39 enrolled

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Nadelmann 1986	Migraine other than classic or common, or other headaches known to be associated with migraine, or if they had known contraindications to beta blockers	Yes	NR	Yes	Yes
Borgensen 1976 Denmark	Cardiac disease, asthma, diabetes mellitus, physical or neurological abnormalities	Yes	NR	Yes	Yes
Fuller 1990 London	Contraindications to propranolol or paracetamol; pre-existing migraine prophylaxis or beta-blocker therapy for other indications; non-migrainous headaches that are not clearly distinguishable from migraine	Yes	Yes	Yes	Yes
Rao 2000 India	NR	Minimal	Yes	Yes	Yes
Pradalier 1989	History of congestive heart failure or asthma; heart block; bradycardia (<50 beats/min); Raynaud phenomenon; hypertension; resistant to two previously well-followed prophylactic treatments	Yes	Yes	Yes	Yes
Wideroe 1974 Norway	NR	Minimal	NR	Yes	Yes
Mikkelsen 1986 Denmark	Allergy to tolfenamic acid; serious heart, kidney, liver or psychiatric diseases, asthma, bronchitis, diabetes, active ulceration, pregnancy, or breast feeding; any administration of another prophylactic treatment for migraine within the month prior to the start of the study; use of tolfenamic acid within 6 months of study entry	Yes	Yes	Yes	Yes

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Nadelmann 1986	No	NR	Overall rate of attrition: 38.8% Others NR	No	Poor	NR; second author affiliated with Ayerst Laboratories
Borgensen 1976 Denmark	No	N/A	Attrition reported (33.3%); others NR	NR	Poor	NR
Fuller 1990 London	No	N/A	Attrition reported (48.1%); others NR	No	Poor	NR
Rao 2000 India	Yes	NR	Attrition reported (21.1%); others NR	No	Fair	NR
Pradalier 1989	Stated Yes, but unclear	NR	Attrition reported (44.6%); others NR	16.3% lost to fu	Fair-Poor	NR
Wideroe 1974 Norway	No	N/A	Attrition reported (13.3%); others NR	NR	Fair	Tablets/randomization provided by Imperial Chemical Industries Ltd.
Mikkelsen 1986 Denmark	No	N/A	Attrition reported(20.5%); others NR	No	Fair	GEA Ltd., Pharmaceutical Manufacturing Company

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Control group standard of care	Length of follow-up
Nadelmann 1986	Yes	34 weeks
Borgensen 1976 Denmark	Yes	6 months
Fuller 1990 London	Yes	4 attacks
Rao 2000 India	Yes	1 year
Pradalier 1989	Yes	12 weeks
Wideroe 1974 Norway	Yes	6 months
Mikkelsen 1986 Denmark	Yes	24 weeks

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Palferman 1983 London	NR	NR	N/A-crossover	Good Mean age=41.4 80% female	36 patients in total (16 with migraine)
Kaniecki 1997 United States	NR	NR	N/A-crossover	Unclear Mean age NR 81.1% female	37 recruited
Diener 1996 Germany	NR	NR	Yes	Good mean age=39 78.0% female	235 screened/214 randomized
van de Ven 1997 The Netherlands	NR	NR	Yes	Good mean age=38.7 82.3% female	226 randomized
Diamond 1982 United States	NR	NR	N/A-crossover	Unclear Mean age NR 78.7% female	245 admitted

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Palferman 1983 London	Under 16 or over 65 years; use of beta blockers contraindicated; possibility of other pathology, disclosed by history, examination or investigations, which might lead to headaches	Yes	NR	Yes	Yes
Kaniecki 1997 United States	Past trials of valproate or propranolol; failure of greater than 2 adequate trials of migraine prophylactic agents; severe medical or psychiatric illness; analgesic use of more than 15 days per month; presence of alcohol or drug abuse; use of no contraception by women of childbearing potential; unable to complete a headache diary or differentiate various headache types	Yes	no	NR	NR
Diener 1996 Germany	Pregnancy or lactation; psychiatric disorders; concomitant non-migraine headaches 3 times per month within the last three months; intake of centrally acting drugs or migraine prophylactic drugs during the 4 weeks peceding the trial; specific contraindication to beta-blocker (asthma, diabetes, clinically relevant hypotension, etc.) or cyclandelate (acute stroke, glaucoma, coagulation disorder); intake of drugs to treat migraine attacks > 12 days/month	Yes	Yes	Yes	Yes
van de Ven 1997 The Netherlands	Current use of drugs for the prevention of migrain; treatment with cardiovascular drugs; usual contrindications for beta blocker use or hypersensitivity to these agents	Yes	NR	Yes	Yes
Diamond 1982 United States	Migraine associated with other types of headaches, migraine other than classic or common; known contraindications to propranolol	Yes	Phase I single blind; Phase II double blind	Yes	Yes

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Palferman 1983 London	No	N/A	Attrition reported(38.8%); others NR	27.80%	Poor	ICI Pharmaceuticals
Kaniecki 1997 United States	No	N/A	Attrition reported(13.%)	No	Poor	Abbott Laboratories
Diener 1996 Germany	Yes	NR	Attrition(16.8%); others NR	No	Fair	NR
van de Ven 1997 The Netherlands	Use of ITT analysis is indicated; but unclear in way data is presented	NR	Attrition=31(13.7%); others NR	No	Fair	Merck
Diamond 1982 United States	No	N/A	Attrition: Phase I=16.7%; Phase II=32.4%; others NR	Phase I=4/1.6% Phase II=10/6.7%	Fair	Statistical evaluation provided by Ayerst Laboratories

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Control group standard of care	Length of follow-up
Palferman 1983 London	Yes	16 weeks
Kaniecki 1997 United States	Yes	36 weeks
Diener 1996 Germany	Yes	20 weeks
van de Ven 1997 The Netherlands	Yes	12 weeks
Diamond 1982 United States	Yes	6-12 months

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Kangasniemi 1987 Scandinavia	NR	NR	N/A-crossover	Good Mean age 37.5 79.7% female	77 randomized
Malvea 1973 United States	NR	NR	N/A-crossover	Fair Mean age NR 87.1% female	31 enrolled
Forssman 1976 Sweden	NR	NR	N/A-crossover	Good Mean age 37.4 87.5% female	40 included
Borgesen 1974 Denmark	NR	NR	N/A-crossover	Good Mean age 37.6 83.3% female	45 included
Ahuja 1985 India	NR	NR	N/A-crossover	Unclear; mean age NR 46.1% female	26 selected
Dahlof 1987 Sweden	NR	NR	N/A-crossover	Unclear mean age NR 92.8% female	28 entered
Kuritzky 1987 Israel	NR	NR	N/A-crossover	Unclear mean age NR gender NR	38 began

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Kangasniemi 1987 Scandinavia	Daily use of analgesics and/or total consumption exceeding 40 tablets/month; daily use of ergotamine and/or total consumption exceeding 16 mg/month; treatment with anti-depressive or neuroleptic drugs within the past 2 months; use of narcotic analgestics, chronic treatment with calcium antagonists, clonidine, other beta-blockers or NSAIDSs; change in oral contraceptive therapy 3 months before or during the study; contraindications for beta-blockers; insufficienty treated hypertension; transient ischaemic attacks; epilepsy; hypothyroidism and other severe psychiatric or somatic disease; and pregnancy	Yes	Yes	Yes	Yes
Malvea 1973 United States	Pregnancy, bronchial asthma, congestive heart failure, allergic rhinitis, diabetes mellitus and previous use of propranolol for headache	Minimal	NR	Yes	Yes
Forssman 1976 Sweden	Pregnancy or suspicion of pregnancy; indication of renal or heart disease, hypertension, diabetes or asthma; history of earlier treatment of migraine with propranolol	Yes	NR	Yes	Yes
Borgesen 1974 Denmark	Cardiac disease; asthma or diabetes mellitus; physical or neurological abnormalities	Yes	Yes	Yes	Yes
Ahuja 1985 India	Intercurrent illness	Yes	NR	Yes	Yes
Dahlof 1987 Sweden	NR	Yes	NR	Yes	Yes
Kuritzky 1987 Israel	NR	Yes	NR	Unclear	Unclear

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Kangasniemi 1987 Scandinavia	Unclear	N/A	Attrition=3/77(3.9%); others NR	None	Fair	NR
Malvea 1973 United States	No	N/A	Attrition=1(3.2%); others NR	None	Fair	Ayerst Laboratories
Forssman 1976 Sweden	No	N/A	Attrition=8(20%); others NR	None	Fair	NR
Borgesen 1974 Denmark	No	N/A	Attrition=15(33.3%); others NR	None	Fair	ICI-Pharma
Ahuja 1985 India	NR	N/A	NR	NR	Poor	Alkali and Chemical Corp. India Ltd. Provided tablets
Dahlof 1987 Sweden	Yes	N/A	Attrition=0; others NR	None	Fair	NR
Kuritzky 1987 Israel	No	N/A	Attrition=7(18.4%); others NR	None	Poor	NR

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Control group standard of care	Length of follow-up
Kangasniemi 1987 Scandinavia	Yes	16 weeks
Malvea 1973 United States	Yes	12 weeks
Forssman 1976 Sweden	Yes	34 weeks
Borgesen 1974 Denmark	Yes	24 weeks
Ahuja 1985 India	Yes	16 weeks
Dahlof 1987 Sweden	Yes	52 weeks
Kuritzky 1987 Israel	Yes	NR

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Standes 1982 Norway	NR	NR	N/A-crossover	Unclear mean age NR 80% female	25 entered
Forssman 1982 Sweden	NR	NR	N/A-crossover	Good mean age=40 80% female	24 included
Tfelt-Hansen 1984 Scandinavia	NR	NR	N/A-crossover	Good mean age=39.5 79.5% female	96 started
Weber 1972 United States	NR	NR	N/A-crossover	Fair mean age 40.6 68.4% female	25 enrolled
Diamond 1976 United States	NR	NR	N/A-crossover	Good mean age 38.1 80.7% female	83 enrolled
Sjaastad 1972 Norway	NR	NR	N/A-crossover	Good mean age 35.8 78.6% female	28 included
Ekbom 1971 Sweden	NR	NR	Yes	Fair mean age 33.7 86.7% female	30 included
Johnson 1986 New Zealand	NR	NR	N/A-crossover	Per protocol: Good mean age 42 76.5% female	29 started

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Standes 1982 Norway	Other types of headache (including classical migraine) and major head injuries; contraindications to beta-blocking agents; use of oral contraceptives; pregnant women; use of timolol or propranolol for other reasons than migraine	Yes	NR	Unclear	Unclear
Forssman 1982 Sweden	NR	Minimal	NR	Yes	Yes
Tfelt-Hansen 1984 Scandinavia	Other types of headache (including classical migraine) and major head injuries; contraindications to beta blockers; oral contraceptive use; heart rate < 54 after 3 min of rest and with supine DBP >/= 100 mmHg	Yes	NR	Yes	Yes
Weber 1972 United States	Abnormal neurological examinations; disorders that could be aggravated by beta blockers (namely cariac disease, asthma, diabetes mellitus)	Yes	NR	Yes	Yes
Diamond 1976 United States	Asthma, cardiac disease, diabetes mellitus or any physical or neurologic abnormalities	Minimal	NR	Yes	Yes
Sjaastad 1972 Norway	NR	Yes	NR	Yes	Yes
Ekbom 1971 Sweden	Bronchial asthma, severe infectious diseases, diabetes mellitus, pregnancy, pathological ECG findings	Yes	NR	Yes	Yes
Johnson 1986 New Zealand	NR	Yes	Yes	Yes	Yes

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Standes 1982 Norway	No	N/A	Attrition=7(28%); others NR	None	Poor	MSD (Norge) A/S
Forssman 1982 Sweden	No	N/A	Attrition=4(16.7%); others NR	None	Fair	ICI-Pharma Ltd.
Tfelt-Hansen 1984 Scandinavia	No	N/A	Attrition=27(28.1%); others NR	6(6.2%)	Poor	NR
Weber 1972 United States	No	N/A	Attrition: 6(24%); others NR	NR	Poor	Ayerst Laboratories
Diamond 1976 United States	No	N/A	Attrition: 21(25.3%)	NR	Poor	Ayerst Laboratories provided coded medications
Sjaastad 1972 Norway	No	N/A	Attrition=4(14.2%)	None	Fair	NR
Ekbom 1971 Sweden	No	NR	Attrition=4(13.3%); others NR	NR	Fair	NR
Johnson 1986 New Zealand	No	N/A	Attrition: 12(41.4%); others NR	9(31%)	Poor	Parke Davis Ltd.

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Control group standard of care	Length of follow-up
Standes 1982 Norway	Yes	40 weeks
Forssman 1982 Sweden	Yes	254 days
Tfelt-Hansen 1984 Scandinavia	Yes	40 weeks
Weber 1972 United States	Yes	6 months
Diamond 1976 United States	Yes	16 weeks
Sjaastad 1972 Norway	Yes	14 weeks
Ekbom 1971 Sweden	Yes	8 weeks
Johnson 1986 New Zealand	Yes	9 months

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population	Number recruited
Andersson 1983 Denmark	NR	NR	Yes	Per protocol: Good Mean age: pla=37.3; met-d=42.4 % female: pla=94.6%; met=73.5%	75 recruited
Schellenberg 2008 Germany	NR	NR	Yes	Good Mean age= 39 female 86%	38 screened 30 enrolled
Siniatchkin 2007 Germany RCT parellel-group	NR	NR	Yes	Mean Age: met 36.7; placebo 37.3 female: met 20%; placebo 10% Smaller female ratio than other studies	20 recruited

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded	Patient unaware of treatment
Andersson 1983 Denmark	Other types of vascular headaches, chronic daily headache not separable from migraine; contraindication for beta blockers; other severe vascular diseases; oral contraceptives and pregnancy	Yes	NR	Yes	Yes
Schellenberg 2008 Germany	Prophylactic migraine treatments in previous 3 months, concomitant b-blocker, calcium antagonist, concomitant nondrug migraine treatment, use of symptomatic treatment for >10 days per month, change in current symptomatic treatment for migraine, history of hypersensitivity to metoprolol or nebivolol, history of substance abuse, pregnant or breast feeding, congestive HF, heart rate <50bpm, systolic blood pressure <100 bpm, peripheral arterial occlusive disease, uncontrolled DM, history of bronchospasm, clinically relevant abnormal laboratory values	Yes	stated double blind, no detail given	stated double blind, no detail given	Yes
Siniatchkin 2007 Germany RCT parellel-group	Pregnancy or lactaion; abuse of ergotamine, triptans or analgesics; any prophylactic treatment of migraine during 6 months preceeding the trial; neurological, psychiatric or internal disease during the treatment in the last year; all specific contradictions for b-blockers; concomitant non-migraine headaches more than 3 X per month w/in last 3 months; substance abuse; change in oral contraceptive use 3 months prior to the study.	Yes	stated double blind, no detail given	stated double blind, no detail given	NR

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Score	Funding
Andersson 1983 Denmark	No	N/A	Attrition: 4/75(5.3%) prior to randomization; 9/71(12.7%) after randomization; others NR	NR	Fair	NR
Schellenberg 2008 Germany	Yes	Yes	No No Yes No	NR	Fair	Berlin-Chemie AG
Siniatchkin 2007 Germany RCT parellel-group	Yes	Yes	No No No No	NR	Fair	NR

Evidence Table 17. Quality assessments of placebo controlled trials of beta blockers for migraine

Author Year Country	Control group standard of care	Length of follow-up
Andersson 1983 Denmark	Yes	12 wks
Schellenberg 2008 Germany	Yes	30 weeks
Siniatchkin 2007 Germany RCT parellel-group	Yes	3 months

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Head-to-head trials				
Colombo, 1989 Italy *Fair quality*	RCT	Patients with cirrhosis that (i) bled from varices or acute gastric erosions, or the bleeding was defined as of "unknown origin," but no lesion besides varices was found by endoscopy done within 5 days, (ii) the bleeding stopped on conservative treatment (vasopressin, somatostatin and/or Sengstaken-Blakemore tube), (iii) no rebleeding requiring definitive treatment (endoscopic sclerotherapy or surgery) occurred before assignment, (iv) they had well-compensated cirrhosis (Child's A or B status); (v) they were less than 70 years of age; (vi) they had been given no previous treatments for portal hypertension (including beta blockers, endoscopic sclerotherapy or surgery), and (vii) they were hemodynamically stable	Patients for whom beta-blockade was contraindicated, who had active peptic ulcer, neoplastic disease and/or Child's C liver status	Propranolol (pro) 40-160 mg daily *(n=32)* Atenolol (ate) 100 mg daily *(n=32)* Placebo (pla) *(n=30)*

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Head-to-head trials				
Colombo, 1989 Italy *Fair quality*	Ranitinde, oral antacids, spironolactone, saluretics, lactulose, nonabsorbable antibiotics	GI hemorrhage and/or death Quality of life	*Mean age:* pla=54; ate=53; pro=52 *%male:* pla=76.7; ate=78.1; pro=87.5 Race NR	*Etiology(%)* Alcohol: pla=80; ate=81.3; pro=84.4 HBsAg: pla=6.7; ate=0; pro=9.4 Other: pla=13.3; ate=18.7; pro=6.3 *Child's class(%)* A: pla=46.7; ate=46.9; pro=43.8 B: pla=3.3; ate=53.1; pro=56.3 *Bleedings before index bleed(%)* 0: pla=20; ate=46.9; pro=31.2 1: pla=53.3; ate=34.4; pro=50 2 or more: pla=26.7; ate=18.8; pro=18.8 *Source of hemorrhage(%)* Varices: pla=70; ate=26; pro=90.6 Erosions: pla=23.3; ate=9.4; pro=6.2 Unknown: pla=6.7; ate=9.4; pro=3.1

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Head-to-head trials				
Colombo, 1989 Italy *Fair quality*	176 evaluated/ 94 eligible/ 94 enrolled	*Withdrawn:* pla=4(13%); ate=8(25%); pro=2(6%) *Lost to fu:* *pla=3(10%); ate=3(9.4%);* *pro=1(3.1%)* *Analyzed:* pla=30; ate=32; pro=32	*Fatal/nonfatal bleeding episodes at 1 year(% patients):* pla=51; ate=31; pro=24 *Total deaths:* pla=7(23%); ate=3(10%); pro=4(12%) *Deaths due to rebleeding:* pla=3(10%); ate=1(3.1%); pro=1(3.1%) *Deaths due to liver failure:* pla=2(6.7%); ate=1(3.1%); pro=2(6.2%) *Deaths due to unrelated causes:* pla=2(6.7%); ate=1(3.1%); pro=1(3.1%)	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Head-to-head trials		
Colombo, 1989 Italy *Fair quality*	NR	pla=0 ate=4(12.5%) pro=0

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Placebo-controlled trials				
Gatta, 1987 *Fair quality*	RCT	Biopsy-proven cirrhosis of different etiologies, who survived a vericeal bleeding, defined endoscopically (within 36 hours of bleed) as proven by criteria: 1) visualization of bleeding site; 20 visualization of a fibrin clot on a varix; 3) presence of varices in the absence of gastroduodenal lesions and of any assumption of drugs affecting gastric mucosa; within 15-40 days after bleeding	Child's C grade; massive ascites; renal failure persisting after compensating hemodynamic conditions (serum creatinine > 1.5 mg/dl); age < 18 or > 70 years; tumors; contraindications to beta-blocking agents (asthma, A-V block > 1 degree; heart failure; clinically evident diabetes)	Nadolol (nad) 40-160 mg daily (target heart rate reduction of 25%) Placebo (pla) x 145 weeks
Burroughs 1983 Hampstead, England *Fair quality*	RCT	Histologically confirmed cirrhosis; bleeding from a varix or varices; no bleeding for 48 hours	NR	Propranolol (pro) 80 to 800 mg daily with a goal of 25% heart rate reduction Placebo (pla) x 21 months Treatment initiated 48 hours after bleeding cessation

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Placebo-controlled trials				
Gatta, 1987 *Fair quality*	NR	Event endpoints of the study were considered 1) onset of side effects necessitating withdrawal of treatment; 2) occurrence of digestive hemorrhage from ruptured esophageal varices; 3) death x assessed monthly for first 3 months; then every three months	Mean age: 49 71% male Race NR	*Etiology* Alcoholic cirrhosis: 75% Cryptogenic cirrhosis: 12.5% Posthepatic cirrhosis: 12.5% *Child Class* A: 37.5% B: 62.5% Ascites: 25% >1 previous hemorrhage: 33.3% *Esophageal varices* 2: 29.2% 3: 41.7% 4: 29.2%
Burroughs 1983 Hampstead, England *Fair quality*	NR	Assessments at monthly intervals for first 3 months; then at three-month intervals	*Mean age: pro=51; pla=49* *Gender(% male): pro=46.1; pla=45.4* *Race NR*	*Causes of cirrhosis:* Alcoholism - Pro=35%; Pla=50% Chronic active hepatitis - Pro=27%; Pla=32% Cryptogenic - Pro=19%; Pla=14% Primary biliary cirrhosis - Pro=19%; Pla=4% *Pugh's grading:* A - Pro=65%; Pla=54% B - Pro=23%; Pla=36% C - Pro=11.5%; Pla=8% *Previous upper GI hemorrhage:* Pro=77%; Pla=77% *Transfusion (units) after index bleeding episode:* Pro=31%; Pla=41%

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Placebo-controlled trials				
Gatta, 1987 *Fair quality*	NR/54/24 nad (n=12) pla (n=12)	Lost to fu: 5/24(21%)	Per protocol analysis: Esophageal varices hemorrhage: nad=3(25%); pla=8(71%)(*P*<0.05) Death due to all causes: nad=1(8.3%); pla=3(27.3%)(NS)	NR
Burroughs 1983 Hampstead, England *Fair quality*	60 screened/48 eligible/48 enrolled	Withdrawn=4(8.3%)/0 lost to fu/48 analyzed	Rebleeding(# patients/%): pro=12/26(46.1%); pla=11/22(50%)(NS) Death due to variceal rebleeding(# patients/%): pro=4/26(15.4%); pla=2/22(9.1%) All-cause mortality(# patients/%): pro=4/26(15.4%); pla=5/22(22.7%)	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Placebo-controlled trials		
Gatta, 1987 *Fair quality*	NR	Withdrawals due to asthma: nad=1; pla=0
Burroughs 1983 Hampstead, England *Fair quality*	NR	Withdrawals: pro=4/26(15.4%); pla=0

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
El Tourabi 1994 Sudan *Fair quality*	RCT	Portal hypertension ***secondary to schistosomiasis***; age 18-65; past history of schistomiasis (demonstrated by ultrasound); esophageal varices; recent variceal hemorrhage	Evidence or history of heart failure; significant airway obstruction; heart block greater than first degree; insulin dependent diabetes mellitus; bradycardia; severe peripheral vaascular disease; pregnant or lactating; severe depression; MI within previous 3 months	Long-acting propranolol (LA pro) 160 mg daily Placebo (pla)

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
El Tourabi 1994 Sudan *Fair quality*	NR	Full clinical examinations at 3-month intervals Endoscopies performed at 12 and 24 months Primary endpoints: 1) time to first rebleed; 2) time to death	Mean age: LA pro=34.6; pla=37.1 % male: LA pro=80; pla=83 Race NR	*On admission, patients with:* Palmar erythema - Pro=2%; Pla=0 Gynaecomastia - Pro=2%; Pla=0 Spider naevi (bormore) - Pro=0; Pla=0 Jaundice - Pro=0; Pla=0 Peripheral edema - Pro=0; Pla=0 Clubbing - Pro=0; Pla=2.5% Loss of body hair - Pro=2%; Pla=2.5% Bruising - Pro=2%; Pla=0 Distended superficial abdominal veins - Pro=9.5%; Pla=15% Ascites - Pro=7%; Pla=15% Venous hump - Pro=2%; Pla=7.5% *Livers:* Studied - Pro=31%; Pla=15% Shrunken - Pro=24%; Pla=35% Not palpable - Pro=45%; Pla=50% Palpable - Pro=31%; Pla=15% *Spleens:* Studied - Pro=93%; Pla=97.5% Shrunken - Pro=0; Pla=2.5% Not palpable - Pro=5%; Pla=0 Palpable - Pro=95%; Pla=97.5%

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
El Tourabi 1994 Sudan *Fair quality*	*Propranolol:* n=42 *Placebo:* n= 40	33(40%) withdrawn due to "other" reasons/lost to fu=2(2.4%)/analyzed 82	LA pro n=42; pla n=40 Rebleeding(# patients/%): LA pro=1(2%); pla=8(20%)(*P*<0.02) Death(# patients/%): LA pro=3(7%); pla=7(17.5%)(*P*<0.02) Median time to rebleeding(# days): LA pro=539; pla=252	Occurrence of adverse effects were volunteered by patients and elicited at follow-up visits

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
El Tourabi 1994 Sudan *Fair quality*	Incidence(# patients/%): LA pro=14(33.3%); pla=12(30%) Most common adverse events(# pts/%) Abdominal swelling: LA pro=0; pla=1(2.5%) Blurred vision: LA pro=1(2%); pla=0 Coughing: LA pro=0; pla=1(2.5%) Diarrhea: LA pro=2(5%); pla=3(7.5%) Drowsiness: LA pro=1(2%); pla=1(2.5%) Dry mouth: LA pro=1(2%); pla=0 Epistaxis: LA pro=1(2%); pla=0 Fatigue: LA pro=0; pla=2(5%) Fever/hot sensation: LA pro=2(5%); pla=1(2.5%) Gastric discomfort: LA pro=1(2%); pla=(2.5%) Hematemesis: LA pro=2(5%); pla=2(5%) Heartburn: LA pro=2(5%); pla=1(2.5%) Hiccups: LA pro=1(2%); pla=0 Hypersomnia: LA pro=0; pla=1(2.5%) Indigestion: LA pro=0; pla=1(2.5%) Itching: LA pro=2(5%); pla=0 Melena: LA pro=0; pla=2(5%) Nervousness: LA pro=1(2%); pla=0 Pain in abdomen: LA pro=1(2%); pla=1(2.5%) Tinnitus: LA pro=1(2%); pla=0 Wheezing: LA pro=0; pla=1(2.5%)	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Jensen 1989 Denmark *Fair quality*	RCT	Liver disease; age <70; bleeding esophageal varices; no previous bleeding; absence of bleeding for 24 hours after sclerotherapy	Known contraindications to beta blockade	Propranolol slow release (pro SR) 160 mg daily Placebo (pla) x six months
Lebrec 1981a France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestenal bleeding due to ruptured esophageal or gastric varices; diameter of esophageal varices >5mm at x-ray exam; GI bleeding spontaneously stopped or did not relapse after cessation of esophageal tamponade; hepatic encephalopathy, ascites and jaundice absent or appeared only transiently after bleeding	NR	Propranolol (pro) 80-360 mg daily with goal of 25% heart rate reduction Placebo (pla) x 3 months Treatment initiated **10-15** days following bleeding cessation
Lebrec 1981b Lebrec 1984 France *Fair quality*	RCT	Histologically proven cirrhosis; gastrointestinal bleeding; source of hemorrhage was ruptured esophageal or gastric varices (as determined by endoscopy); volume of blood transfused within first 24 hours was 0.5 liter or more; jaundice was absent or mild; size of esophageal varices was large; gradient between the wedge and free hepatic venous pressures >10mm Hg; GI bleeding stopped and hemodynamic conditions were normal	Heart failure; asthma; chronic disease other than cirrhosis	Propranolol (pro) 40-360 mg daily with goal of 25% heart rate reduction Placebo (pla) Treatment initiated **2 weeks** following bleeding cessation

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Jensen 1989 Denmark *Fair quality*	NR	Endoscopy at monthly intervals	*Mean age: pro SR=46; pla=47* *Gender(% male): pro SR=100; pla=75* *Race NR*	*Liver disease:* Alcoholic cirrhosis - Pro=80%; Pla=87.5% Primary biliary cirrhosis - Pro=7%; Pla=0 Chronic active hepatitis - Pro=7%; Pla=6% Cryptogenic cirrhosis - Pro=7%; Pla=6% *Child's classification:* A - Pro=27%; Pla=25% B - Pro=47%; Pla=44% C - Pro=27%; Pla=31%
Lebrec 1981a France *Fair quality*	NR	NR	NR	*Type of cirrhosis(# patients/%):* Alcoholic=24/87.5% Hepatitis-B infection=1/4.2% Unknown=2/8.3%
Lebrec 1981b Lebrec 1984 France *Fair quality*	NR	Assessments at 2-month intervals through year 1; then at 4-month intervals through year 2	*Mean age:* pro=52.4; pla=49.9 *Gender(% male):* pro=81.6%; pla=72.2% Race NR	*Causes of cirrhosis:* Alcoholism - Pro=87%; Pla=89% Chronic Hepatitis B infection - Pro=8%; Pla= 5% Cryptogenic - Pro=5%; Pla=5% *Source of bleeding:* Ruptured varices - Pro=74%; Pla=78% Acute gastric erosions - Pro=26%; Pla=22% *Previous episodes of bleeding:* No - Pro=42%; Pla=36% Yes - Pro=58&; Pla=64%

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Jensen 1989 Denmark *Fair quality*	NR/NR/31 randomized	NR/NR/31 analyzed	Rebleeding(# patients/%): pro SR=3/15(20%); pla=12/16(75%)(*P*<0.05) Median treatments to achieve obliteration: pro SR=5; pla=5 Median time to obliteration(days): pro SR-163; pla=151	NR
Lebrec 1981a France *Fair quality*	NR/NR/24 admitted	NR/NR/24 analyzed	Rebleeding(# patients/%): pro=0; pla=5/12(41.7%)(*P*=0.037)	NR
Lebrec 1981b Lebrec 1984 France *Fair quality*	NR/NR/74 randomized	NR/lost to fu: pro=3/28(7.9%); pla=3/36(5.5%)/analyzed 74	*Rebleeding(# patients/%):* Year one: pro=1/38(2.6%); pla=16/36(44.4%)(*P*<0.0001) Year two: pro=6/38(15.8%); pla=23/36(63.9%) *Time to rebleeding(% patients free of rebleeding at years 1/2):* pro=87/79; pla=42/32(*P*<0.0001) *Death due to(# patients/%):* Liver failure/septicemia: pro=3/38(7.9%); pla=2/36(5.5%) Rebleeding: pro=0; pla=6/36(16.7%) Percentage of surviving patients at years 1/2: pro=94%/90%(NS); pla=84%/57%(*P*<0.02)	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Jensen 1989 Denmark *Fair quality*	Incidence(# patients/%): pro SR=4/15(26.7%); pla=3/16(18.7%) *Types of adverse events* Pro SR(# pts): Tiredness=2; diarrhea=2 Pla(# pts): Cold extremitis=1; skin rash=1	None
Lebrec 1981a France *Fair quality*	Undesirable side effect incidence: pro=0; pla=0	None
Lebrec 1981b Lebrec 1984 France *Fair quality*	*Incidence:* NR *Types of adverse events(# patients):* Pro: transient asthemia=8; feeling of well-being=10; transietly reduced sexual activity=2; heart failure development=1 Pla: nausea=1; dizziness=1; cutaneous rash=1	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Lo 1993 Taiwan *Fair quality*	RCT	***Cirrhosis***; complete obliteration of esophageal varices; esophageal variceal bleeding; received regular endoscopic injection sclerotherapy (EIS)	Visible esophagogastric varices; association with cancer growth; known contraindications to beta-blockade; beta blockers received prior to variceal obliteration	Propranolol (pro) 60-320 mg daily Placebo (pla)
Sheen 1989 Taiwan *Fair quality*	RCT	***Cirrhosis***; stabilized after after treatment for esophageal variceal hemorrhage	Previous treatment with endoscopic sclerotherapy; heart or lung disease; hepatocellular carcinoma	Propranolol (pro) 40 mg daily(mean dosage; range 30-60 mg) with goal of a 25% heart rate reduction Placebo (pla)

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Lo 1993 Taiwan *Fair quality*	NR	Study endpoints: 1) esophagogastic variceal rebleeding (defined as presence of hematemesis, melena and when more than two units of blood transfusion were required and the bleedign site was identified from esophagogastic varices by emergency endoscopy); 2) death	*Mean age:* pro=54.3; pla=51.2 *Gender(% male):* pro=88; pro=92	*Etiology of cirrhosis:* Alcoholic - Pro=11.5%; Pla=15% Post-hepatitic - Pro=81%; Pla=74% Cryptogenic - Pro=7%; Pla=7% *Pugh's grading:* A - Pro=69%; Pla=70% B - Pro=23%; Pla=26% C - Pro=7%; Pla=4%
Sheen 1989 Taiwan *Fair quality*	NR	Study endpoints: 1) Rebleeding from esophageal varices (proven by endoscopy); or 2) loss to follow-up Patients were seen every two months	*Mean age:* pro=43.6; pla=45.3 *Gender (% male):* pro=83; pla=88	*Cause of cirrhosis:* Alcoholic - Pro=33.3%; Pla=55.5% HBV - Pro=55.5%; Pla=33.3% Cryptogenic - Pro=22.2%;Pla=22.2% *Previous bleeding:* Pro=55%; Pla=53% *Encephalopathy:* Pro=0; Pla=0 *Ascites:* Pro=22%; Pla=28% *Pugh's grading:* A - Pro=78%; Pla=72% B - Pro=22%; Pla=28% C - Pro=0; Pla=0

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Lo 1993 Taiwan *Fair quality*	NR/NR/59 enrolled	6(10.2%) withdrawn/lost to fu: pro=1(3.3%); pla=2(6.9%)/53 analyzed	Esophagogastric variceal *recurrence*(# patients/%): pro=15/26(58%); pla=21/27(77%) Esophageal variceal *rebleeding*(# patients/%): pro=5/26(19.2%); pla=3/27(11.1%) Cardiac variceal rebleeding(# patients/%): pro=2/26(7.6%); pla=2/27(7.4%) Total rebleeding(esophageal+cardiac rebleeding)(# patients/%): pro=7/26(26.9%); pla=5/27(18.5%) *Death due to:* *(per protocol analysis: pro n=26; pla n=27)* Hepatic failure: pro=2/7.6%; pla=4/14.8% Variceal bleeding: pro=3/11.5%; pla=2/7.4% Hepatocellular carcinoma: 2/7.6%; pla=3/11.1% Cerebral hemorrhage: pro=1/3.8%; pla=0 All-cause mortality: pro=8/30.8%: pla=9/33.3%	NR
Sheen 1989 Taiwan *Fair quality*	230 screened/36 eligible/36 randomized (pro n=18; pla n=18)	NR/NR/18 analyzed	Rebleeding(# patients/%): pro=5/18(27.8%); pla=10/18(55.5%) Death due to rebleeding(# patients/%): pro=0; pla=2/18(11.1%) Freedom from rebleeding(% at 6, 12, 18 and 24 months): pro=94/87/68/57; pla=81/59/30/15	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Lo 1993 Taiwan *Fair quality*	*Propranolol(%)* Dizziness=28% Drowsiness=18% Chest tightness=11% *Placebo:* NR	*Propranolol(# patients/%):* 3/26(11.%) due to "intolerable general malaise *Placebo:* NR
Sheen 1989 Taiwan *Fair quality*	NR	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Study design Setting	Eligibility criteria	Exclusion criteria	Interventions (drug, regimen, duration)
Villeneuve 1986 Montreal, Canada *Fair quality*	RCT	Adult; within 72 hours of variceal hemorrhage (demonstrated by endoscopy)	Previous treatment with beta blockers or endoscopic sclerotherapy; absence of Placebo of hemorrhage for at least 6 hours before randomization, using a Sengstaken-Blakemore tube or vasopressin infusio if necessary; heart failure or aortic valve disease other than aortic sclerosis; asthma or chronic obstructive lung disease precluding the administration of beta blockers; cancer or other disease reducing life expectancy to <1 year	Propranolol (pro) initial dose of 80 mg daily wih a goal of plasma concentrations between 50-150 ng per ml Placebo (pla) Treatment initiated within 6-72 hours following bleeding cessation

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Villeneuve 1986 Montreal, Canada *Fair quality*		Assessments at monthly intervals for first 3 months; then at three-month intervals Primary endpoint=Variceal rebleeding (shown by endoscopy) Secondary endpoint=Survival	*Mean age:* pro=54; pla=58 *Gender(% male):* pro=57.1%; pla=75.7% Race NR	*Etiology of portal hypertension:* Alcoholic cirrhosis - Pro=74%; Pla=70% Posthepatitic cirrhosis - Pro=7%; Pla=8% Cryptogenic cirrhosis - Pro=9%; Pla=16% Biliary cirrhosis - Pro=7%; Pla=2% Portal vein thrombosis - Pro=2%; Pla=0 Idiopathic portal hypertension - Pro=0; Pla=2% *Pugh's grading:* A - Pro=9%; Pla=13.5% B - Pro=50%; Pla=57% C - Pro=43%; Pla=30% *Previous episodes of bleeding:* Pro=33%; Pla=30% *Alcohol consumtion (>60 gm daily) during month prior to admission:* Pro=43%; Pla=46% *Requied balloon tamponade for index bleed:* Pro=43%; Pla=43%

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment?
Villeneuve 1986 Montreal, Canada *Fair quality*	110 screened/79 eligible/79 enrolled	0 withdrawn/0 lost to fu/79 analyzed	Rebleeding(# patients/%): pro=32/42(76.2%); pla=30/37(81.2%) All cause mortality: pro=19/42(45.2%); pla=14/30(37.8%) *Mortality due to(# patients/%):* Rebleeding: pro=5/42(11.9%); pla=7/37(18.9%) Liver failure: pro=8/42(19.0%);pla=3/37(8.1%)	NR

Evidence Table 18. Randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Adverse effects reported	Withdrawals due to adverse events (%, adverse n/enrolled n)
Villeneuve 1986 Montreal, Canada *Fair quality*	NR	Withdrawals: pro=5/42(11.9%); pla=0 Propranolol AE withdrawals due to: Shortness of breath: 3 patients Cardiac failure: 1 patient Septic shock with hypotension: 1 patient

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population
Colombo 1989 Italy	Adequate. Block randomization. Series of triplet packages provided(ate; pro; pla); the contents of which varied at random.	Block number assignment corresponded to a particular package	Yes	Mean age=53 Gender=80.8% male
Gatta 1987	NR	NR	Yes	Mean age: 49 71% male
Burroughs 1983 Hampstead, England	Inferior method: sealed envelope	NR	Yes	Mean age: pro=51; pla=49 Gender(% male): pro=46.1; pla=45.4
El Tourabi 1994 Sudan	NR	NR	Yes	Mean age: LA pro=34.6; pla=37.1 % male: LA pro=80; pla=83 Race NR
Jensen 1989 Denmark	Adequate: Computer generated randomization schedule	NR	Yes	Mean age: pro SR=46; pla=47 Gender(% male): pro SR=100; pla=75 Race NR

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number recruited	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Colombo 1989 Italy	94	Patients for whom beta-blockade was contraindicated, who had active peptic ulcer, neoplastic disease and/or Child's C liver status	Yes	NR	Yes
Gatta 1987	24	Child's C grade; massive ascites; renal failure persisting after compensating hemodynamic conditions (serum creatinine > 1.5 mg/dl); age < 18 or > 70 years; tumors; contraindications to beta-blocking agents (asthma, A-V block > 1 degree; heart failure; clinically evident diabetes)	Yes	Yes	Yes
Burroughs 1983 Hampstead, England	48	NR	Yes	No; single-blind	Yes
El Tourabi 1994 Sudan	82	Evidence or history of heart failure; significant airway obstruction; heart block greater than first degree; insulin dependent diabetes mellitus; bradycardia; severe peripheral vaascular disease; pregnant or lactating; severe depression; MI within previous 3 months	Yes	NR	Yes
Jensen 1989 Denmark	31	Known contraindications to beta blockade	Yes	NR	Yes

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: deifferential/high	Score
Colombo 1989 Italy	Yes	Yes	NR	Attrition reported; others NR	Pla=3(10%) Ate=3(9.4%) Pro=1(3.1%)	Fair
Gatta 1987	Yes	No	NR	NR	Lost to fu: 5/24(21%)	Fair
Burroughs 1983 Hampstead, England	Yes	Yes	NR	NR	NR	Fair
El Tourabi 1994 Sudan	Yes	Yes	NR	Attrition=33(40%)	Lost to fu: LA pro=1(2.4%) pla=1(2.5%)	Fair
Jensen 1989 Denmark	Yes	Yes	NR	NR	NR	Fair

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Funding	Control group standard of care	Length of follow-up
Colombo 1989 Italy	Imperial Chemical Industries (Milan) supplied trial tablets	Yes	Mean=357 days
Gatta 1987	NR	Yes	Mean=145 weeks
Burroughs 1983 Hampstead, England	NR	Yes	21 months
El Tourabi 1994 Sudan	ICI Pharmaceuticals	Yes	2 years
Jensen 1989 Denmark	ICI Pharmaceuticals	Yes	6 months

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Randomization described?	Allocation concealed	Groups similar at baseline	Similarity to target population
Lebrec 1981a France	NR	NR	NR	NR
Lebrec 1981b Lebrec, 1984 France	NR	NR	Yes	*Mean age:* pro=52.4; pla=49.9 *Gender(% male):* pro=81.6%; pla=72.2%
Lo 1993 Taiwan	NR	NR	Yes	*Mean age:* pro=54.3; pla=51.2 *Gender(% male):* pro=88; pro=92
Sheen 1989 Taiwan	NR	NR	Yes	*Mean age:* pro=43.6; pla=45.3 *Gender (% male):* pro=83; pla=88
Villeneuve 1986 Montreal, Canada	Inferior method; sealed envelopes	NR	No; more patients in the pro group had severe Class C liver disease (43% vs 30%); less patients in the propranolol group were male (57.1% vs 75.7%)	*Mean age:* pro=54; pla=58 *Gender(% male):* pro=57.1%; pla=75.7%

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Number recruited	Exclusion criteria for recruitment	Eligibility criteria specified	Outcome assessors blinded	Care provider blinded
Lebrec 1981a France	24	NR	Yes	NR	Yes
Lebrec 1981b Lebrec, 1984 France	74	Heart failure; asthma; chronic disease other than cirrhosis	Yes	NR	Yes
Lo 1993 Taiwan	59	Visible esophagogastric varices; association with cancer growth; kNown contraindications to beta-blockade; beta blockers received prior to variceal obliteration	Yes	Yes	Yes
Sheen 1989 Taiwan	36	Previous treatment with endoscopic sclerotherapy; heart or lung disease; hepatocellular carciNoma	Yes	NR	Yes
Villeneuve 1986 Montreal, Canada	79	Previous treatment with beta blockers or endoscopic sclerotherapy; absence of Placebo of hemorrhage for at least 6 hours before randomization, using a Sengstaken-Blakemore tube or vasopressin infusio if necessary; heart failure or aortic valve disease other than aortic sclerosis; asthma or chronic obstructive lung disease precluding the administration of beta blockers; cancer or other disease reducing life expectancy to <1 year	Yes	No; single-blind	Yes

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Patient unaware of treatment	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: deifferential/high	Score
Lebrec 1981a France	Yes	Yes	NR	NR	NR	Fair
Lebrec 1981b Lebrec, 1984 France	Yes	Yes	NR	NR	Lost to fu: pro=3/38(7.9%) pla=2/36(5.5%)	Fair
Lo 1993 Taiwan	Yes	No	NR	Attrition=6(10.2%)	Lost to fu: pro=1(3.3%); pla=2(6.9%)	Fair
Sheen 1989 Taiwan	Yes	Yes	NR	NR	NR	Fair
Villeneuve 1986 Montreal, Canada	Yes	Yes	NR	Attrition reported(None); others NR	None	Fair

Evidence Table 19. Quality assessments of randomized controlled trials of beta blockers for bleeding esophageal varices

Author Year Country	Funding	Control group standard of care	Length of follow-up
Lebrec 1981a France	ICI Pharmaceuticals	Yes	3 months
Lebrec 1981b Lebrec, 1984 France	NR	Yes	24-38 months (mean=29 months)
Lo 1993 Taiwan	NR	Yes	Mean follow-up of 2 years and 4 months
Sheen 1989 Taiwan	Prosperous Foundation	Yes	Mean follow-up of 12.4 months
Villeneuve 1986 Montreal, Canada	Ayerst Laboratories	Yes	2 years

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Interventions	Sample size	Trial duration	Population characteristics	Quality
Foerster 1985	Atenolol (ate) 100 mg Pindolol SR (pin-SR) 20 mg	107	24 weeks	Mean age=41.4 65.4% male	Good • Designed specifically for AE assessment • Changes of >1 cm on VAS interpreted as AE
Fogari 1999	Atenolol (ate) 100 mg Bisprolol (bis) 10 mg Celiprolol (cel) 400 mg Propranolol (pro) 160 mg	152	18 months	100% male Mean age=52	Fair
Lithell 1987	Atenolol (ate) 50 mg Bisoprolol (bis1) 5 mg Bisoprolol (bis2) 10 mg	292	6 months	59.9% male Mean age=52.6	Fair
Walle 1994	Metoprolol CR 100 mg Atenolol 100 mg	58	6 weeks	43.3% male Mean age=58	Fair
Sundar 1991	atenolol: 100mg propranolol: 80mg	26	4 weeks	100% male Mean age=NR	Poor

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Results
Foerster 1985	Data for weeks 13-24(% patients)*:* *n: ate=53; pin=54* Sleep disturbance: ate=18; pin=44(*P*=0.01) Dreams: ate=16; pin=15 Fatigue: ate=28; pin=22 Raynaud's phenomenon: ate=14; pin=26 Muscle cramps: ate=12; pin=20 Sexual disturbance: ate=14; pin=8 GI disturbances: ate=21; pin=20
Fogari 1999	Overall AE incidence(# pts; %): pro=6/37(16.2%); ate=5/38(13.1%); bis=4/39(10.2%)
Lithell 1987	Withdrawals due to adverse events (# patients/%): ate=2/97(2.1%); bis1=4/97(4.1%); bis2=4/98(4.1%)
Walle 1994	Overall AEs: no differences (data NR) Serious AEs: meto vs ate = 0 vs 2 (3.3%) (bradycardia and syncope; both leading to withdrawal)
Sundar 1991	ate vs pro (%) headache: 0 vs 0 weakness: 10.5 vs 10.7 warmth: 2.6 vs 0 oedema: 0 vs 0 dyspnoea: 5.3 vs 0 constipation: 0 vs 0

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Interventions	Sample size	Trial duration	Population characteristics	Quality
Steiner 1990	Propranolol 80-240mg (mean=133.4mg per day) Atenolol 50-100mg (mean=56.4mg per day)	pro: 73 ate: 78	4 weeks	100% male Mean age=NR	Fair
Dahlof 1988	atenolol 50 mg metoprolol CR 100 mg	74	6 weeks	51(66%) male Mean age=54.4	Fair
Blumenthal 1988	atenolol 50-100mg propranolol: 40-80mg	26	2 weeks	100% male Mean age=42.5	Poor

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Results
Steiner 1990	pro(%) vs ate(%), all NS Bradycardia: 4(4.5) vs 9(10) Gastrointestinal distress: 9(10.1) vs 7(7.8) Dry mouth: 5(5.6) vs 4(4.4) Anxiety: 7(7.9) vs 2(2.2) Sleep disturbance: 4(4.5) vs 6(6.7) Libido decreased/impotence: 8(9): 5(5.6) Weakness/fatigue: 15(16.9) vs 8(8.9) Headache: 12(13.5) vs 9(10) Total: 57(64) vs 50(55.6) Withdrawals due to adverse events: pro: 5(6.85); ate: 0(0)
Dahlof 1988	Subjective symptoms- leg fatigue, constipation, diarrhoea, bradycardia, cold hands and feet, heavy breathing: NS Palpitation: meto> ate, *P*<0.05 Withdrawals due to adverse events: 2(2.6%)
Blumenthal 1988	sleep items: NS sexual functioning: NS energy: 4 (ate) and 4 (pro) reported being more tired in the morning, while 6 (pla) reported less fatigue.

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Interventions	Sample size	Trial duration	Population characteristics	Quality
Buhler 1986	Bisoprolol 10-20mg Atenolol 50-100 mg	104	8 weeks	82.7% male Mean age=53.8	Fair
Brixius 2007	Group A: nebivolol (neb) 5 mg daily X 12 weeks, once daily placebo x 2 weeks, metropolol succinate 95 mg daily x 12 weeks. Group B: metropolol succinate 95 mg daily x 12 weeks, once daily placebo x 2 weeks, nebivolol (neb) 5 mg daily X 12 weeks	48	28 weeks	mean age: group A 48.4; group B 47.2 Male: 100% Ethnicity: NR	Fair/ poor

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Results
Buhler 1986	Baseline:bis / baseline:ate (number), all NS headache- 20:7/ 19:9 tiredness- 17:20/ 17:13 Nervousness- 17:10/ 10:8 Sleep problems- 18:11/ 15:10 Cold extremities- 14:13/ 16:12 Sweating- 12:9/ 11:11 Tingling sensations- 12:6/ 9:5 Feeling of weakness- 11:6/ 5:7 Dizziness- 11:3/ 8:7 Joint pain- 9:9/ 6:8 Depressed mood- 12:11/ 9:5 Sex problems- 5:7/ 6:4 Withdrawals due to adverse events: bis (1): dizziness ate (5): diarrhea, skin rash, asthmatic bronchitis, vertigo, headache
Brixius 2007	No AE reported "No critical findings regarding safety issues occurred during the study. The results of safety analysis confirmed a good safety profile for both study drugs."

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Interventions	Sample size	Trial duration	Population characteristics	Quality
Yilmaz 2008	Nebivolol (neb) starting dose of 2.5 mg once daily titrated to achieve target DBP of <90 mmHg and SBP of <140 mmHg. Metoprolol succinate (extended release) starting dose of 25 mg once daily titrated to achieve target DBP of <90 mmHg and SBP of <140 mmHg. If after 2 weeks BP was normalized, amlodipine (5-10 mg daily) was added to treatment. Duration: x 6 weeks.	46	6 weeks	Baseline characteristics for patients who completed the study only. Mean age: 40.7 Male: 20/39 (51%) Ethnicity: NR	Fair

Evidence Table 20. Adverse events in head-to-head trials of beta blockers for hypertension

Trial	Results
Yilmaz 2008	No AE reported

Evidence Table 21. Safety of all head-to-head trials of beta blockers

Trial	Indication	Sample size	Duration	*P* value	*Selective beta blockers*					*Non-selective beta blockers*								
					ate	bis	met	bet	neb	ace	cart	carv	lab	nad	pen	pin	pro	tim
Overall adverse event incidence																		
Fogari 1999	Hypertension	152	18 mos	NS	13.1%	10.2%											16.2%	
Frishman 1979	Angina	40	8 wks	<0.0001												17.4%	94.4%	
van der Does 1999	Angina	368	3 mos	NS			30.0%					25.0%						
Narahara 1990	Angina	112	10 wks	NR				50.0%									42%	
								37.0%									45%	
Poole-Wilson 2003 COMET	Heart Failure	3029	58 mos	NS			96.0%					94.0%						
Tfelt-Hansen 1984	Migraine	96	40 wks	NS													42.0%	46.0%
Worz 1991	Migraine	78	12 wks	NS		29.5%	23.1%											
Kangasniemi 1984*	Migraine	35	8 wks	NS			57.1%										68.6%	
							45.7%										48.6%	
Olsson 1984*	Migraine	53	8 wks	NS			58.5%										58.5%	
							56.6%										58.5%	
Dahlof 1988	Hypertension	74	6 wks	NS	NR		NR											
Walle 1994	Hypertension	58	6 wks	NS	NR		NR											
Buhler 1986	Hypertension	104	8 wks	NS	NR	NR												
Steiner 1990	Hypertension	151	4 wks	NS	55.6%												64.0%	
Lombardo 2006	Heart [illegible]	70	6 mos	NS					26.0%			20.0%						
Schellenberg 2008	Migraine	30	30 wks	NR			93.0%		69.0%									
Bradycardia incidence																		
Metra 2000	Heart failure	122	44 mos	NS			2.7%					4.0%						
Dahlof 1988	Hypertension	74	6 wks	NS	NR		NR											
Walle 1994	Hypertension	58	6 wks	NR	3.3%		0.0%											
Poole-Wilson 2003	Heart Failure	3029	58 mos	NS			9.0%					10.0%						
Steiner 1990	Hypertension	151	4 wks	NS	10.0%												4.5%	
Lombardo 2006	Heart Failure	70	6 mos	NS					3.0%			9.0%						
Schellenberg 2008	Migraine	30	30 wks	NR			35.0%		6.0%									
Dizziness incidence																		
van der Does 1999	Angina	368	3 mos	NS			5.0%					4.8%						
Metra 2000	Heart failure	122	44 mos	0.0046			1.3%					14.7%						
Stensrud 1980	Migraine	28	6 wks	NS	0.0%												3.6%	
Tfelt-Hansen 1984	Migraine	96	40 wks	NS													5.0%	6.0%
Worz 1991	Migraine	78	12 wks	NS		10.2%	5.1%											
Buhler 1986	Hypertension	104	8 wks	NS	2.9%	6.7%												

Evidence Table 21. Safety of all head-to-head trials of beta blockers

Trial	Indication	Sample size	Duration	*P* value	*Selective beta blockers*					*Non-selective beta blockers*								
					ate	bis	met	bet	neb	ace	cart	carv	lab	nad	pen	pin	pro	tim
Hypotension incidence																		
Poole-Wilson 2003	Heart failure	3029	58 mos	NS			11.0%					14.0%						
Metra 2000	Heart failure	122	44 mos	NS			2.7%					2.7%						
Lombardo 2006	Heart failure	70	6 mos	NS					3.0%			3.0%						
Schellenberg 2008	Migraine	30	30 wks	NR			14.0%		6.0%									
Withdrawals due to adverse events																		
Lithell 1987	Hypertension	292	6 mos	NS	2.1%	4.1%												
Colombo 1989	Bleeding esophageal varices	94	357 days	NS	12.5%												0.0%	
Katritsis 2003	Atrial arrhythmias	90	12 mos	NS		6.4%						4.7%						
Tfelt-Hansen 1984	Migraine	96	40 wks	NS													5.6%	10.1%
Waagstein 2003	Heart failure	172	6 mos	NS			11.6%											
Worz 1991	Migraine	78	12 wks	NS		10.20%	6.40%											
Dahlof 1988	Hypertension	74	6 wks	NS	NR		NR											
Walle 1994	Hypertension	58	6 wks	NR	3.3%		0.0%											
Buhler 1986	Hypertension	104	8 wks	NS	0.9%	4.8%												
Steiner 1990	Hypertension	151	4 wks	NS	0.0%												6.9%	
Lombardo 2006	Heart [illegible]	70	6 mos	NS					3.0%			3.0%						
Schellenberg 2008	Migraine	30	30 wks	NR			7.1%		6.2%									

**Values represent rates from first and second months of treatment, separately*