Chronic heart failure: management of chronic heart failure in adults in primary and secondary care

A clinical guideline for the NHS in England and Wales

APPENDIX J: EVIDENCE TABLES

Section 7.2: Pharmacological treatment of heart failure due to LV systolic dysfunction - Angiotensin II Receptor Antagonists

Pharmacological therapy
Angiotensin II receptor antagonists

Experimental studies

Paper	Sharma, D., Buyse, M., Pitt, B., & Rucinska, E. J. 2000, "Meta-analysis of observed mortality data from all-controlled, double-blind, multiple-dose studies of losartan in heart failure. Losartan Heart Failure Mortality Meta-analysis Study Group", *American Journal of Cardiology*, vol. 85, no. 2, pp. 187-192.
Description	Systematic review
N=	n=1,894, total n=1,154 losartan subjects, trials=6 (100 to 700 in each) International trials
Intervention	Use of Losartan at between 2.5 mg/day to 50 mg/day after ACEi wash out period Population group: Age ˜60 yrs (>70 yrs in ELITE study), >50% had ischaemic heart disease aetiology, LV ejection fraction 23% - 31%.
Outcomes	Mortality until the last day of therapy in ELITE study, and up to 14 days post discontinuation of study in other 5 trials
Results	• Total deaths in losartan group 3.12% Vs 6.35% in control (p=0.004) • In all studies the OR of observed mortality with losartan was 0.50 (CI 0.32 – 0.81) (p=0.004) • No significant difference between Losartan and ACEis (from 3 trials) (p=0.069) • Very significant effect in trials where no patients had previously been exposed to ACEi OR 0.44 (p=0.003) but only two trials • Re analysis using Peto's modification also showed a significant mortality benefit.
Comments	None of the studies included had mortality as primary end point Caution should be used in extrapolating these results to other Angiotensin II receptor antagonists
Reference	102
Trials included	Losartan haemodynamic study group (1995), Sweet (1994), Lang (1994), Dickstein (1995), Pitt (1997) ELITE, Klinge (1997)

Paper	Jong, P., Demers, C., McKelvie, R. S., & Liu, P. P. 1906, "Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials.", *Journal of the American College of Cardiology*., vol. 39, no. 3, pp. 463-470.
Description	Systematic review
N=	17 RCTs are included n=12,469; ARBs=7,060 controls=5,409 (placebo or ACEi) Age =56 to 73yrs mean, Male =48% to 100%, mostly NYHA classes II and III, class IV = 2% to 15% Canadian review of international trials
Intervention	5 different ARB pharmacological therapies are considered, namely losartan, candestartan, Valsartan, irebesartan, and eprosartan, at a variety of doses and frequencies and for duration of from 4 weeks to 1.5 years
Outcomes	The outcomes reported on are all cause mortality, and hospitalisation with follow up ranging from 4 weeks to almost 2 years
Results	• Using a random effects model the pooled OR for 15 of the trials (2 trials with no events in either arm) of ARBs Vs all controls for mortality with ARBs was OR 0.96 (95% CI 0.75 to 1.23) a non significant difference between the groups with borderline heterogeneity between trials. This lack of significant difference held when only trials without back ground ACEi were pooled • When the combined therapy with ARBs and ACEi was compared to an ACEi alone control the risks of death were virtually identical in both groups • Overall there was no statistical difference in the rate of hospitalisation between patient streated with ARBs and all control groups with a combined event rates of 14% and 17% respectively giving a pooled OR of 0.86 (0.69 to 1.06) • In contrast combined therapy with ARB and ACEi reduced the odds of hospitalisation compared to standard ACEi therapy to OR 0.74 (0.64 to 0.86) using a fixed effect analysis with no significant heterogeneity reported • The use of a fixed effect model rather then a random effects model for the pooled treatment effect on mortality did not effect the (non)significance of this analysis, however when substituted in the analysis for hospitalisation a statistically significant benefit of ARB use was seen (heterogeneity not stated). Also when the pooling method of Peto was utilized rather than the DerSimonian and Laird method there was still no significant effect of ARBs Vs control on mortality, but a positive significant effect in reduced hospitalisation was noted. • Sensitivity analyses demonstrated no differences in effect with or without ACEi intolerant patients being pooled or with or without trials reporting follow up greater than 6 months

Comments	A thorough description of methodology with inclusion of trials by consensus, and data extraction and quality assessment undertaken in duplicate. All analysis was based on intention to treat principle using pooled odds ratios. Both Fixed effects and random effects models were used, a conservative score for the Chi squared test of heterogeneity was set at p=0.1. Primary analysis was done with ARBs compared to grouped controls of placebo or ACEi, and subsequent analysis was undertaken for comparisons of ARBs Vs placebo, ARBs Vs ACEi, and ARBs & ACEi Vs ACEi alone. Other alternative analyses were undertaken using different pooling methods The inclusion of 12 of the 17 pooled trials with baseline ACEi therapy would tend to ↘ effect size seen The confounding factor of concomitant ACEi therapy, previous intolerance to ACEi and length of follow up were all assessed in sensitivity analysis Only 1 trial explicitly reported randomisation details but all but 2 trials were multi-centre design. 5 trials did not report on blinding and 2 trials did not give details of withdrawals A clear cut superiority of ARBs compared to mixed controls to reduce mortality or hospitalisation cannot be seen from this data ARBs may not exert a similar class effect so pooling may hide differences. Some benefits of ARBs may not be detected in the early stages of treatment so effects could have been missed in shorter term trials, although this was not proved in sensitivity analysis Only 2 of the included tirals were powered to detect a mortality effect of ARBs as a primary outcome. In patients for whom ACEi are not tolerated ARBs may be a reasonable substitute
Reference	100
Studies included	Sharma (2000), Pitt (2000), Cohn (2001), Crozier (1995), Murdoch (2001), Hamroff (1999), Bart (1999), Riegger (1999), Tonkon (2000), Baruch (1999), Weber (1997), Dickstein (1995), Pitt (1997), Lang (1997), Mazayev (1998), McKelvie

Paper	Cohn, J. N. & Tognoni, G. 2001, "A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure", *N Engl J Med*, vol. 345, no. 23, pp. 1667-1675.
Description	Randomised controlled trial
N=	N=5010 (treatment =2511, control =2499) HF patients International (16 countries)
Intervention	Oral Valsartan at 320mg Vs placebo in addition to optimum therapy was given as a continuous therapy
Outcomes	Primary endpoint was all cause mortality, also with a endpoint of mortality or morbidity (cardiac arrest / hospitalisation / inotropic support). Other outcomes were hospitalisation and changes in NYHA class and QOL, as well as side effects to a mean 23 months
Results	• Mortality was similar in the two treatment groups, with 262 cardiac deaths Vs 258, and 118 HF deaths Vs 125 in the valsartan and placebo groups respectively • Analysis of the composite endpoint of mortality and morbidity showed a significant benefit with valsartan RR of reaching endpoint 0.87 (97.5% CI 0.77 – 0.97) (p=0.009) • Ejection fraction was raised more in the valsartan group than with placebo 4.0% Vs 3.2% (p=0.001), and NYHA class was significantly improved also (23.1% Vs 20.7% improving and 10.1% Vs 12.8% worsening) (p<0.001) • QOL was seen to be improved with valsartan with little change amongst these patients compared to a decline on placebo, as evaluated by the Minnesota living with heart failure questionnaire (p=0.005) • There was significantly more discontinuation due to adverse events with valsartan than placebo at 9.9% Vs 7.2% (p<0.001) The most common events being dizziness 1.6% (p<0.001 Vs placebo), hypotension 1.3%, and renal impairment 1.1% (p<0.001 Vs placebo).
Comments	V large international trial Amongst study group 93% were on ACEi and 35% on B blocker The extensive blockade of multiple neuro-hormonal systems in HF patients could be deleterious Subgroup analysis of 344 black patients showed no significant benefit in terms of the composite mortality and morbidity endpoint RR 1.11 (95% CI 0.77 – 1.61) Also Mortality was significantly reduced in 226 patients who were on neither ACEi or B blocker RR 0.58 (p=0.012) but there was an adverse effect on mortality in 1610 patients who were taking both these drugs RR 1.41 (p=0.009)
Reference	103

Paper	Granger, C. B., Ertl, G., Kuch, J., Maggioni, A. P., McMurray, J., Rouleau, J. L., Stevenson, L. W., Swedberg, K., Young, J., Yusuf, S., Califf, R. M., Bart, B. A., Held, P., Michelson, E. L., Sellers, M. A., Ohlin, G., Sparapani, R., & Pfeffer, M. A. 2000, "Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors", *American Heart Journal*, vol. 139, no. 4, pp. 609-617
Description	Randomised controlled trial
N=	N=280, treatment =179, control =91 Age =66 yrs, Male =69%, Ischaemic origin =71%, LV ejection fraction =27% International
Intervention	Use of candesartan at doses up to target 16mg for 12 week period Vs placebo
Outcomes	Various clinical and QOL outcomes and percentage of completion for measure of tolerance
Results	• Difference in tolerability, 4.1% more discontinuation in candesartan arm than placebo (95% CI 4.8% fewer to 13% more) no SD • Other outcomes of mortality, clinical events, NYHA class, exercise capacity and QOL showed do difference • 64% attained target dose of 16mg • Completion of 12 week therapies in candesartan group was 82.7% (95% CI 77.1 – 88.2%). • Candesartan had higher tolerability in patients who were intolerant to ACEi due to specific reasons related to ACEi use 87.2% completion (p=0.02)
Comments	Mixed international study in 90 sites across 7 countries
Reference	101

Paper	Pitt, B., Poole-Wilson, P. A., Segal, R., Martinez, F. A., Dickstein, K., Camm, A. J., Konstam, M. A., Riegger, G., Klinger, G. H., Neaton, J., Sharma, D., & Thiyagarajan, B. 2000, "Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II.", Lancet, vol. 355, no. 9215, pp. 1582-1587.
Description	Randomised controlled study
N=	n = 3152 (losartan – 1578, captopril = 1576) Age = 71.t years, male = 69% International
Intervention	Losartan 50mg per day vs Captopril 50mg 3 times a day. Population group: 289 centres in 46 countries. Age = 71.t years, male = 69%
Outcomes	All cause mortality All cause admissions Mortality progressive Heart Failure Discontinuation
Results	• All cause mortality: Not significant (hazard ratio 1.13, 95% CI: 0.95 – 1.35) • All cause admissions: Not significant (1.04, 95%CI 0.78 – 1.08) • Mortality progressive Heart Failure: Not significant (0.88, 95%CI 0.59 – 1.30) • Fewer dropouts with losartan: 3% vs 8% (p = 0.001)
Comments	International study Losartan was better tolerated, including cough. Cannot extrapolate to other AII antagonists
Reference	104

Paper	Tonkon, M., Awan, N., Niazi, I., Hanley, P., Baruch, L., Wolf, R. A., & Block, A. J. 2000, "A study of the efficacy and safety of irbesartan in combination with conventional therapy, including ACE inhibitors, in heart failure. Irbesartan Heart Failure Group", *International Journal of Clinical Practice*, vol. 54, no. 1, pp. 11-14.
Description	Randomised controlled trial
N=	n=109, irbesartan =57, placebo =52 USA
Intervention	An intervention of 150mg/day irbesartan (orally) was given where tolerated Vs placebo to patients with Mild to moderate HF
Outcomes	Many outcomes were measured including changes to exercise performance, and clinical status at 6, 8 and 12 weeks, and LV ejection fraction, as well as blood serum levels and adverse events at week 12
Results	• In analysis of patients who completed the protocol the median exercise duration increased in the irbesartan arm by 64 sec, and increased by 41 sec with placebo, but no comparisons between groups is made • In terms of increases in LV ejection fraction over baseline there was a 4.4 unit improvement with Irbesartan compared with a 2.6 unit increase with placebo, giving a treatment difference of 1.7 units (95% CI –1.3 – 4.8) • A multiple endpoint of discontinuation, hospitalisation, use of supplemental diuretic or emergency room visit was reached by 12% of patients in the Irbesartan group and 21% in the placebo arm, but no comparisons made
Comments	First dose hypotension was not found to be common Not known if the same effects would be seen when ACEi were maximally titrated