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 - Diuretics

Pharmacological therapy
Diuretics

Experimental Studies

Paper	Faris, R., Flather, M., Purcell, H., Henein, M., Poole-Wilson, P., & Coats, A. 2002, "Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials", *International Journal of Cardiology*., vol. 82, no. 2, pp. 149-158.
Description	Systematic review
N=	N=18 RCTs included, with 8 reporting on studies of diuretic Vs placebo (n=545) and 10 comparing diuretics to active controls (n=280) Age =59yrs, Male =39%, NYHA class I =27%, class II =40%, class III =29%, with a few patients inclass IV, LV ejection fraction =46% UK review of international trials
Intervention	Interventions considered include furosemide (most common) amiloride, pertanide, and furosemide –hydrochlorothiazide, and Frumil at a range of doses and for a variety of durations. The RALES study was excluded from primary analysis owing to the active intervention being spironolactone not considered a conventional diuretic. This study is reviewed elsewhere (ID 958 (Pitt B))
Outcomes	Outcome measures reported include mortality, withdrawal and worsening HF (definition not given) , and exercise capacity (definition not given) all measured to various time durations.
Results	• In terms of effect of diuretics on mortality 3 trials (n=221) showed a death rate of 2.7% in the diuretic group compared to 10.9% in the placebo group demonstrating a significant pooled OR of 0.25 (95 % CI 0.07 to 0.84) (p=0.03). The confidence intervals for this effect are very wide and the number of events in the intervention group extremely low. Although no heterogeneity found the statistical test for this will be underpowered to detect this given the low number of trials. • From the 4 placebo controlled trials that compared between diuretics and placebo for worsening heart failure (n=448) there was a significant benefit in favour of diuretics OR 0.31 (0.15 to 0.62) (p=0.001) however there was significant heterogeneity in the results of the original trials and 2 trials with no events in the intervention arm. • Other analysis of active control trials showed significant benefit or diuretics over a range of therapies including ACEi, Digoxin, Ibopamine, and prenltorol in both worsening heart failure and exercise capacity

Comments	18 RCTs, 8 RCTs with placebo control, n=545. A brief description of the statistical methodology used to pool data using odds ratios by the Fixed effect method. But no details of duplicate selection or data extraction No details of formal trial quality assessment although all included trials are randomised and details pertaining to blinding and study design tabulated Given the variability in the intervention and dosage, the length of follow up, and the patient characteristics within original trials the benefit of combining the trials for quantitative analysis for controls against active agents is certainly likely to be small and comparisons of diuretics to placebo control questionable The small number of studies for each analysis makes evaluation of heterogeneity difficult with limited power for the Chi squared test which ↗ the confidence of effect size being standard across all pooled trials The inclusion of crossover trials in meta-analysis that is designed to compare in dependant groups will ↘ effect size found if there was insufficient washout within original trials leading to intervention contamination Patients were selected for original trials on the basis of symptoms, clinical and radiological findings and ventricular or haemodynamic function Authors state that data are insufficient by current standards to provide a formal evidence base to recommend diuretics in HF on the basis of an impact on mortality, however they will continue to be used in routine management for symptomatic relief Original trials were small with inadequate power to demonstrate clearly the effectiveness of diuretics in terms of morbidity and mortality. Wide variability in the study duration, concomitant medicine, and outcome measures used. There is heterogeneity in the mechanism of action of loop diuretics and thiazides, and the doses used in trials varied.
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Studies included	Burr (1977), Myers (1982) Sherman (1986), De Jong (1994), Walma (1997), Mathur (1984), Cheitlin (1991), Barr (1995), Boccanelli (1986), Richardson (1987), Parker (1993) Ibopamine Study Group, Andrews (1997), Cowley (1986), Haerer (1989), Ibopamine Working Group (1989), Dalhstrom (1986), Sievert (1989), Nordrehaug (1992)

Paper	Boccanelli, A., Zachara, E., Liberatore, S. M., Carboni, G. P., & Prati, P. L. 1986, "Addition of captopril versus increasing diuretics in moderate but deteriorating heart failure: a double-blind comparative trial", *Postgraduate Medical Journal*, vol. 62, no. Suppl 1, pp. 184-187.
Description	Randomised Controlled Trial
N=	Subjects = 15 (captopril =7, frusemide =8) Age =57yrs, Male =53%, NYHA class II-III =100%, cardiomyopathy HF origin =80% Italy
Intervention	Interventions of captopril at 100mg/day or diuretic frusemide at 100mg/day were compared as a continuous treatment for 3 months
Outcomes	Various outcomes are assessed including functional status on NYHA scale, cardiac function, and blood serum parameters all at 1, 2 and 3 months
Results	• Mean exercise time changes from baseline were not significantly different between intervention groups. • LV fractional shortening was reduced more in patients in the diuretic arm by 6% Vs 3% increase ($p<0.05$). • Clinical and X ray responses were similar in both groups and this was mirrored in functional on frusemide showed a greater increase of maximal double product. • Diuretics give rise to reduced stroke volume and maintenance of cardiac output only depends on heart rate. • The reduction in end systolic wall stress was greater on captopril than on frusemide. • Captopril appears to be equally effective as the addition of additional diuretics in mild to moderate HF.
Comments	The outcomes of the study can be seen to be applicable to patients with moderate HF with a mix of aetiologies being included in the study.

Paper	Richardson, A., Bayliss, J., Scriven, A. J., Parameshwar, J., Poole-Wilson, P. A., & Sutton, G. C. 1987, "Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure", *Lancet*, vol. 2, no. 8561, pp. 709-711.
Description	Randomised Controlled Trial
N=	n=14 in crossover design Age =54yrs, Male =86%, Isschaemic HF origin =64% UK
Intervention	Treatment with captopril orally at 75mg/day or frumil (frusemide 40mg/day and amiloride 5mg/day) in cross over design with 8 week treatment schedules
Outcomes	Changes from baseline to exercise capacity and blood serum parameters were measured at 1, 4, and 8 weeks during treatment course
Results	• 4 patients withdrew while on captopril 2 with pulmonary oedema and 2 with breathlessness, and none when on Frumil. • Exercise duration did not change significantly from baseline on either intervention regime. • Plasma sodium, urea, and creatinine did not differ significantly on either treatment. • On captopril plasma rennin activity increased ($p=0.03$) and aldosterone fell ($p<0.001$) compared to when on Frumil. • Therapy with an ACEi combined with diuretic would seem logical as the ACEi would prevent the diuretic induced adverse metabolic effects while facilitating the renal effects • All patients were clinically stable for 3 months, however diuretic use may have been unnecessary in some of the population • The study provides evidence that ACEi therapy alone is not always sufficient for patients with mild HF
Comments	The results of this trial can only be related to patients with mild HF. The 4 patients who withdrew while on captopril cannot be differentiated from the rest of the study population on any clinical factor except a history of pulmonary oedema.

Paper	Cowley, A. J., Stainer, K., Wynne, R. D., Rowley, J. M., & Hampton, J. R. 1986, "Symptomatic assessment of patients with heart failure: double-blind comparison of increasing doses of diuretics and captopril in moderate heart failure", *Lancet*, vol. 2, no. 8510, pp. 770-772.
Description	Randomised Controlled Trial
N=	n=10 in cross over design Age =49-66 yrs, Male =100% UK
Intervention	The interventions of increased diuretics of up to 80mg/day was compared to the initiation of captopril at 150 mg/day for 4 weeks treatment
Outcomes	Improvements to baseline exercise performance was assessed along with perceived exertion during exercise on the Borg scale. Self paced walking tests at slow moderate and fast pace over 100m were evaluated, and visual analogue scoring of how fatigued patients had felt and generally how well they were feeling were all evaluated at the end of the 4 week treatment course. Many outcomes were patient reported or regulated and no tests of replicability were made. It is not clear how the outcomes seen would be translated to HF patients with less or more severe functional limitations.
Results	• In terms of exercise performance 8 out of 10 patients had a greater exercise tolerance on increased diuretics than on captopril ($p<0.05$) on exercise using the Borg scale showed no significant differences between the study arms. • The time taken to walk 100m at a self regulated slow pace was lower for patients taking increased diuretics 8 secs reduction than on captopril 5 secs reduction ($p<0.05$). • Visual analogue scores for treatment effect on breathlessness showed less effect of captopril than increased diuretics. • In this study both interventions improved the symptom limited exercise tolerance of patients although increased diuretics had a more favourable effect. • Neither treatment reduced the time to walk 100m at a moderate or fast rte indicating that the beneficial effect of treatment in HF patients is most evident at low work-rates.
Comments	The study can be seen to be widely applicable to most HF patients with moderate functional limitations. The interventions of increased diuretics of up to 80mg/day was compared to the initiation of captopril at 150 mg/day for 4 weeks treatment. It is unlikely that a single method can adequately assess many aspects of symptomatic change in response to treatment.
Reference	67

Non-experimental studies

Paper	Braunschweig, F., Linde, C., Eriksson, M. J., Hofman-Bang, C., & Ryden, L. 2002, "Continuous haemodynamic monitoring during withdrawal of diuretics in patients with congestive heart failure", *Eur Heart J*, vol. 23, no. 1, pp. 59-69
Description	Case series
N=	
Intervention	
Outcomes	
Results	• All 4 patients followed up to day 21 • All cardiac function, haemodynamic, laboratory, QOL and physical functioning outcomes are tabulated for each weekly time-point • PATIENT 1 The patient began the study on Furosemide at 80mg/day, they did not complain of any increased symptoms during the drug withdrawal and reported an unchanged sense of well being. There were no clear clinical signs of cardiac decompensation and the 6 minute walking distance was unchanged during follow-up • PATIENT 2 As the patient was stable on only 30mg of extended release furosemide the drug was completely withdrawn on day 0, a relatively high QOL was reported at baseline (18 out of 105 with lower scores rating better). On day 7 of follow-up the patient reported increased exertion-related dyspnoea which was reflected by decreased walking distance. At the end of the study the same diuretic was re-instated and 35mg spironolactone added to therapy. • PATIENT 3 During the 2 weeks of withdrawal of 80gm furosemide this patient deteriorated from NYHA class II to class III and their ability to walk a distance in 6 minutes was shortened by 30m. This was mirrored by elevated BNP and echocardiographic signs of sever diastolic dysfunction. However, walking distance and NYHA class II was restored within a week when the same diuretic dose maintained at the end of the study and QOL improved to a better level than at baseline • PATIENT 4 The patient began on 60mg furosemide in the morning and 40mg at lunch, this was reduced by 40gmin the first week and totally in week 2. The patients reported significant worsening of dyspnoea after light exertion, QOL score deteriorated from 21 points to 26 points at day 14 and walking distance was shortened by 61m on day 7 and by 49m on day 14. At the end of the study 100mg of furosemide was re-instated in this patient and spironolactone added to therapy. • Diuretic withdrawal caused an acute response of volume overload in 3 of 4 patients studied. • A potential advantage of continuous haemodynamic monitoring is that alterations in the pressure are recognised before they are clinically relevant • In common outpatient management with often long intervals between visits, changes in body weight, physical status, and laboratory tests might not be so clear as assessed for this study • In future trials smaller changes in diuretic dose and longer observation periods could prove important

Comments	Aim of study to investigate the usefulness of an implantable haemodynamic monitor in adjusting diuretic medication 7 patients identified on diuretic therapy who were stable on medication and clinically for 3 months prior to study, 2 patients died and 1 was found to have refractory HF and was withdrawn. Diuretic were withdrawn over a 2 week period with dose halved on day 0, and completely withdrawn after day 7, and re-established on day 14, with all parameters recorded at day 0 then once a week for 3 weeks (ie 1 week after therapy re-initiated) Outcomes measured included cardiac function was evaluated with an implantable haemodynamic monitor device, blood samples taken, ECG recorded, Echocardiogram undertaken. At the same time intervals QOL was assessed using the Minnesota living with heart failure questionnaire, exercise capacity evaluated by the 6 minute walk test, and a complete physical examination used to determine NYHA class, it is these last 3 outcomes that are reported here. It is not reported how replicable were the outcome measures employed. Not clear if cases were concurrent or sequential, with the possibility of lessons learned during earlier cases impacting on treatment for later cases.
Reference	66