

**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 Converting Enzyme (ACE) Inhibitors**

Pharmacological therapy

ACE inhibitors

Experimental studies

Paper	Eccles, M., Freemantle, N., & Mason, J. 1998, "North of England evidence based development project: guideline for angiotensin converting enzyme inhibitors in primary care management of adults with symptomatic heart failure.", <i>BMJ</i> , vol. 316, no. 7141, pp. 1369-1375.
Description	Systematic review
N=	n=8457 RCTs n=39 for main study Patients with HF (but no specific cut off for LV ejection fraction given)
Intervention	Various ACEi for main analysis versus placebo for minimum 8 weeks Retrospective analysis on Enalapril Vs other ACEi
Outcomes	Outcomes of total mortality with intention to treat analysis in main study No follow up period stated
Results	<ul style="list-style-type: none"> • RR of mortality ACEi Vs Placebo of 0.83 (95% CI 0.76 – 0.90), heterogeneity test p=0.71 • ACEi are homogenous in effect as a drug class • The SOLVD trial (n=2569 patients, LV ejection fraction >35%) showed a significant reduction in mortality in Placebo group (RR 0.84), however the prevention study n=4228 showed no significant difference although a trend was present. • Stratified data from SOLVD on LV ejection fraction show more effect in lower LVEF patients.
Comments	<p>When analysis is grouped by normalized annual mortality across intervention and control groups in the study (dichotomised at +/- 15% mortality) then there is a great difference in the effect size of ACEi between studies with greater and lesser severities, with RR of 0.88 in low risk groups and 0.64 in high risk groups respectively.</p> <p>Quality of life study in SOLVD RCT showed no difference in QOL using 14 scales of physical functioning, emotional distress, social health, intimacy, life satisfaction, perceived health, productivity and dyspnoea, for asymptomatic patients but significantly significant improvements for dyspnoea and social functioning for symptomatic patients using ACEi.</p> <p>A meta analysis on exercise capacity RCTs =35 showed conflicting results, with differences in study size, follow-up duration, and exercise testing methods. 9 trials with 50+ patients and follow up 3-6 months showed improvements in treadmill capacity and symptoms. Again no differences were found in comparisons of different ACEis.</p> <p>A separate analysis of studies of Heart Failure and previous MI (n=6 000+) ACEi Vs placebo has significant benefits RR 0.80 (95% CI 0.74 – 0.88) for mortality</p>
Reference	71

Trials included	SOLVD treatment 1991, McGarry 1991, Magnani 1986, Bussman 1987, Catopril-Digoxin Multicenter Research group 1988, Captopril Multicenter Research group 1983, Barabino 1991, Keren 1992, Kleber 1992, CCMG 1995 (Captopril), De Bock 1994, Drexler 1989, Dossegger 1993, CCMG 1995 (Cilazapril), Nicholls 1984, CONSENSUS 1987, Enalapril CHF investigators 1987, Dickstein 1991, Rucinska 1991a, Rucinska 1991b, CASSIS 1995 (Enalapril), Fosinopril Heart Failure Study Group 1995, Zwehl 1990, Giles 1990, Gilbert 1993, Rucinska 1991c, Lechat 1993, Riegger 1990, Northridge 1991, Uprichard 1994a, Uprichard 1994b, Uprichard 1994c, Swedberg 1991, Maass 1991a, Gordon 1991, Maass 1991b, Maass 1991c, El Marie 1992, CASSIS 1995 (Spirapril)
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Paper	Lubsen, J., Chadha, D. R., Yotof, Y. T., & Swedberg, K. 1996, "Meta-analysis of morbidity and mortality in five exercise capacity trials evaluating ramipril in chronic congestive cardiac failure", <i>American Journal of Cardiology</i> , vol. 77, no. 14, pp. 1191-1196.
Description	Systematic review
N=	n=1095, RCTs: n=5 HF patients Age 18-80 years (no mean given). LV Ejection fraction <40% or <35% depending on trial. Europe, USA and South Africa.
Intervention	Ramipril at 1.25 – 20mg/day Vs Placebo
Outcomes	1) All deaths, 2) New hospitalisation 3) NYHA class (improved / unchanged / deteriorated), 4) Exercise capacity (exercise time as percentage of that at baseline) all at 12 to 24 weeks
Results	<ul style="list-style-type: none"> • Deaths 2.2% in ramipril and 3.8% in placebo groups OR 0.60 (CI 0.28 – 1.29) (p=0.13 NS) • Combined all cause mortality and hospitalisation OR 0.68 (CI 0.46 – 1.00) (p=0.05) Just significant • Correlation between treatment group and changes in NYHA functional class positive effect significant, but assessment of baseline and outcome not standardized • Small but significant effect on exercise time.
Comments	No description of selection or extraction procedure. Studies included did not have clinical outcomes assessed as focus of their design. One study (USA trial) was compared using incidence rate ratio rather than odds ratio (for short periods of follow up and low incidence rates this is comparable). Variance of natural logarithms used for analysis, and weighted by inverse of variance. No heterogeneity (p=0.45) but small number of trials Many outcomes studied, which were not stated primary endpoints.
Reference	72
Trials included	Not stated

Paper	Neal, B., MacMahon, S., Chapman, N., & Blood, P. 2000, "Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. [see comments]", <i>Lancet</i> , vol. 356, no. 9246, pp. 1955-1964.
Description	Systematic review
N=	n=74 696 total (ACEi Vs placebo n=12 124, intervention = 6060) (ACEi Vs β block or diuretics n =16 161, intervention =8097) (ACEi Vs Calcium agonists n =4871, intervention 2440) Trials=17 (ACEi Vs placebo n=4) (ACEi Vs β block or diuretics n= 3) (ACEi Vs Calcium agonists n =2) Australian centred collaborative authors
Intervention	intervention with ACEi including Ramipril, Quinapril, Enalapril, Catopril, and, Lisinopril. Dosages not stated. Population group: Overall age ~62yrs, male =53% histories of CHD, cardiovascular disease, or High blood pressure
Outcomes	Incidence of Stroke, Coronary heart disease, Heart failure, Cardiovascular death, cardiovascular events , and total mortality, on first relevant outcome basis, average follow up ~4yrs
Results	<ul style="list-style-type: none"> • ACEi Vs placebo, no significant effect on heart failure RR 0.84 (95% CI 0.68 – 1.04) (p =0.11), over total mortality RR 0.84 (0.76 – 0.94) significantly improved. Both analyses showed no heterogeneity. • ACEi vs β block or diuretics, no significant differences in heart failure or total mortality, if anything small increased risk RR 1.03 (0.93 – 1.14) • ACEi vs Calcium agonists, marginal benefit in terms of heart failure RR 0.82 (0.67 – 1.00) , but not significant in total mortality. Again no heterogeneity between studies
Comments	Inclusion criteria given with date limitations. Data reviewed for completeness numbers in each arm tabulated and checked for consistency, with referral to other collaborators in case of scrutiny required. No assessment of quality. Although no clear evidence of reduction of risk in HF the 95% CI do not exclude possible benefits compared to placebo or Calcium antagonists High non adherence to protocol in the trials studied leads to reduced effect size when intention to treat analysis undertaken
Reference	69
Trials included	Not stated

Paper	Flather, M. D., Yusuf, S., Kober, L., Pfeffer, M., Hall, A., Murray, G., Torp-Pedersen, C., Ball, S., Pogue, J., Moye, L., & Braunwald, E. 2000, "Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group.", <i>Lancet</i> , vol. 355, no. 9215, pp. 1575-1581.
Description	Systematic review
N=	n=12 763, RCTs = 5 Most MI patients with LVEF=40% (mean 29%) No data on NHYA class
Intervention	A range of ACEi at differing doses Vs Placebo for at least 6 months. Population of post MI patients with LV dysfunction with time since 1 st MI from 3 days to 1 month n=12 763, ACEi treatment arms =6 391
Outcomes	Mortality at 5 points to 4+ years follow up, reinfarction, or readmission for HF during follow up period, combinations of these, and incidence of stroke.
Results	<ul style="list-style-type: none"> • OR for death with ACEi Vs placebo = 0.80 (95% CI 0.74 – 0.87) (p<0.0001), event rate difference of 5.7%, NNT 15 patients for 30 months • OR for readmission for HF with ACEi Vs placebo = 0.67 (95% CI 0.61 – 0.74) (p<0.0001)
Comments	<p>Canadian based collaborative</p> <p>The definition of readmission for MI varied widely between the trials, but sensitivity analysis showed this made little difference to the overall conclusions</p> <p>The effect of ACEi were reviewed with stratified LVEF (<23% / 23-27% / 28-35% / >35%). For each strata a benefit of ACEi was observed, but the greatest potential benefits were seen in the lower stratum. This was not significant for outcomes of Mortality, HF readmission, or MI but was for a composite of these.</p> <p>Only benefits to mortality, and incidence of HF and MI studied, no harms in terms of side effects</p> <p>The beneficial effects on mortality were seen soon in during outcome monitoring, and increased during the course of treatment.</p> <p>Increase in symptomatic hypotension and renal dysfunction in patients in ACEi group but symptoms not life threatening and reversible with termination of therapy.</p>
Reference	70

Paper	Mancini, G. B. 2000, "Long-term use of angiotensin-converting enzyme inhibitors to modify endothelial dysfunction: a review of clinical investigations.", <i>Clinical & Investigative Medicine - Medecine Clinique et Experimentale</i> , vol. 23, no. 2, pp. 144-161.
Description	Systematic review
N=	n = 57, Trials=3 HF, NYHA =II/III
Intervention	Use of long term oral ACE inhibitor therapy (systemic or single dose excluded). For HF review treatment for 3 to 43 months (captopril / Enalapril / Perindopril / Ramipril)
Outcomes	Many different endpoints of endothelium assessment, biopsy, angiography, ultrasonography, plethysmography
Results	<ul style="list-style-type: none"> • 1 study negative, 1 study showed concordant trends in symptomology, resistance vessel endothelial function, and soluble adhesion molecule levels, in 8/13 patients, 1 study showed worsening of in vitro endothelium-dependant relaxation of the small resistance vessels in patients with ACE inhibitors. • Endothelial dysfunction in resistance vessels is not uniformly present in patients with HF • Benefits seen in hypotensive and diabetic sub groups. • Proxy outcome of Endothelial function not necessarily useful
Reference	73

Paper	Beller, B., Bulle, T., Bourge, R. C., Colfer, H., Fowles, R. E., Giles, T. D., Grover, J., Whipple, J. P., Fisher, M. B., & Jessup, M. 1995, "Lisinopril versus placebo in the treatment of heart failure: the Lisinopril Heart Failure Study Group", <i>Journal of Clinical Pharmacology</i> , vol. 35, pp. 673-680.
Description	Randomised controlled trial
N=	n = 193, (lisinopril intervention =130, placebo =63) Age =60 yrs, Male =75%, Coronary heart disease =44%, Cardiomyopathy = 41%. NYHA class II –IV USA
Intervention	Lisinopril at up to 20 mg / day for 12 weeks Vs placebo
Outcomes	Various outcomes of mortality, exercise capacity, clinical status, and QOL
Results	<ul style="list-style-type: none"> • For mortality no SD in effect (3.1% Vs 7.9) • Exercise capacity no SD (p=0.09 at 12 weeks) • More patients in lisinopril group better scores on global evaluation scales 65% Vs 36% were better (p<0.01), and ability to perform daily activities on 'Yale scale' was better (p<0.01) • Changes in ejection fraction were not significant • Effect in exercise time was found in subgroup of patients with LVEF<35% (p=0.02)
Comments	Benefit in QOL Some side effects of hypotension and renal impairment, but not serious adverse reactions Cannot extrapolate to other ACEi
Reference	74