

**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 - Others**

Pharmacological therapy

Amiodarone / Dofetilide

Experimental Studies

Paper	Amiodarone trials meta-analysis investigators (1997) Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials
Description	Meta-analysis
N=	Subjects=6553 (1452 HF), RCTs = 13 (5 HF) Age =61%, Male =83%, LV ejection fraction =31%
Intervention	Amiodarone at 200mg - 400mg/day as maintenance dose, Vs placebo or no-antiarrhythmic drug for 6 months to 3 years Post MI or HF patients all LV ejection fraction <45% where stated
Outcomes	Primary endpoints considered are mortality and Arrhythmic / sudden death, with sub-group analysis of various cardiac and clinical status parameters. Adverse effects are also assessed in separate log rank test. Original follow up varied from 0.4 –2.5 yrs
Results	<ul style="list-style-type: none"> • For all cause mortality the OR with amiodarone was 0.87 (95% CI 0.78 – 0.99) (p=0.03) but heterogeneity just significant (p=0.058) so by Der Simonian and Laird random effects model OR was 0.85 (0.71 – 1.02) (p=0.081) • In terms of mortality from arrhythmias and sudden death there were clear benefits with amiodarone OR of 0.69 (0.55 – 0.87) (p=0.0016) by fixed effect model with no heterogeneity. • There was no significant difference noted in the pooled effect of amiodarone compared to control on 'other cardiac / cardiovascular event' (p=0.821), 'other death' (p=0.398) • The effect of amiodarone on mortality rates in the trials with a HF population alone was significant with an OR of 0.83 (0.70 – 0.99) however this was not significantly different from the effects seen in post MI patients • There was a significant increase in the incidence of hypotension in patients enrolled in amiodarone arms of trials Vs controls OR 7.3 (p=0.00005) and no heterogeneity, with increased risks of hypertension (p=0.087); lung infiltrates (p=0.0003), bradycardia (p=0.0003), and liver dysfunction (p=0.0072) were all significantly more common • Mortality rates in the HF trials were three times that of the post MI trials although the effectiveness of amiodarone was largely similar
Comments	Sensitivity analysis studied discrepancies for control measures and many baseline characteristics. 4 of the 15 RCTs with no blinding Incomplete blinding of primary studies may have led to increased effects from these trials being fed into the pooled result Only 22% of patients considered in this analysis are HF so any effects must be treated with caution in extrapolation
Reference	107

Studies included	Cairns (1997), Julian (1997), Elizari (1996), Ceremuzynski (1992), Navarro-Lopez (1993), Burkart (1990), Hockings (1987), Cairns (1991), Singh (1995), Doval (1994), Garguichevich (1995), Nicklas (1991), Hamer (1989)
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Paper	Piepoli, M. (1998) Overview and meta-analysis of randomised trials of Amiodarone in chronic heart failure
Description	Meta-analysis
N=	n =4780 patients , 10 RCTs, with 8 detailing mortality events
Intervention	All interventions of amiodarone at 50mg to 300 mg/day as maintenance dose Vs control (not stated) in HF patients (including asymptomatic patients) or post MI with reduced LV ejection fraction or arrhythmias
Outcomes	Many mortality and cardiac event outcomes detailed in overview including incidence of Arrhythmias, change in LV ejection fraction, cardiac, and sudden death. However M/A limited to all cause mortality and side effects measured from 12 weeks to 6 years.
Results	<ul style="list-style-type: none"> • Pooled (fixed effect) effect of amiodarone on mortality showed OR 0.79 (95% CI 0.68 - 0.92) (p=0.003) but heterogeneity observed, so random effect model used and OR of 0.75 • Side effects as measured by proportion of patients with side effects showed significantly increased risk with amiodarone pooled OR 2.22 (95% CI 1.83 - 2.68) with adjustment to random effects model, with no heterogeneity
Comments	Original study populations ranged from 30 to 1500 patients No significant changes on mortality were seen in any individual trials Differences between results seen in original trials may have been due to age, sex, and severity of disease. There appears to be greater relative risk reduction in patients with more depressed clinical condition
Reference	108
Studies included	Cairns (1997), Julian (1997), Burkart (1990), Singh (1995), Doval (1994), Garguichevich (1995), Nicklas (1991), Hamer (1989), CASCADE (1993), Mahmarian (1994)

Paper	Torp-Pedersen, C., Moller, M., Bloch-Thomsen, P. E., Kober, L., Sandoe, E., Egstrup, K., Agner, E., Carlsen, J., Videbaek, J., Marchant, B., & Camm, A. J. 1999, "Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group.", <i>New England Journal of Medicine</i> , vol. 341, no. 12, pp. 857-865.
Description	Randomised Controlled Trial
N=	n=1518 dofetilide =762, placebo =756 Age =70yrs, Male =73%, Ischaemic heart disease =67%, NYHA class II =37%, Class III =53% Denmark.
Intervention	The intervention was initially 1mg/day of dofetilide to patients without atrial fibrillation and 500µg/day for those with atrial fibrillation, this was changed early in the study to 500µg/day for patients with creatinine clearance of 40-60 ml/min and 250µg/day to those clearing 20 –40 ml/min all Vs placebo with continuous treatment
Outcomes	Primary end point was all cause mortality, with other outcomes of various cardiac caused death, and morbidity in terms of arrhythmias, worsening HF and incidence of MI all to a mean of 18 months
Results	<ul style="list-style-type: none"> • The survival rates in the two arms were identical at 89% for on treatment analysis and for the whole duration there was no significant difference (p=0.54) • There was also no difference in survival among predefined subgroups including atrial fibrillation at baseline HR 1.01 (95% CI 0.75 – 1.36) • The dofetilide group saw a lower rate of hospitalisations for HF at 30% Vs 38% with a HR of 0.75 (0.63 – 0.89) (p<0.001) • There was no significant difference in the percentage of patients with an improvement in NYHA class. • At 12 months the rate of spontaneous cardioversion was higher in the dofetilide group 44% Vs 13% (p<0.001) • Of patients where were in sinus rhythm at baseline there were fewer patients in whom atrial fibrillation developed in the dofetilide group 2% Vs placebo group 7% (p<0.001)
Comments	Study results can be seen as relevant to the majority of HF patients except those with a history of drug induced arrhythmia, severely hyper / hypotensive, liver dysfunction, or acute myocarditis Hospitalisations for worsening HF were reduced in the intervention arm, but without any obvious explanation for this result other than the beneficial effect on atrial fibrillation Dofetilide does not effect survival adversely, and there appears to be good long term tolerability with the overall rate of adverse events and discontinuation of therapy showing no significantly different trends between study arms
Reference	111

Paper	Kober, L., Bloch, T., Moller, M., Torp-Pedersen, C., Carlsen, J., Sandoe, E., Egstrup, K., Agner, E., Videbaek, J., Marchant, B., Camm, A. J., & Danish, I. 2000, "Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial", <i>Lancet</i> , vol. 356, no. 9247, pp. 2052-2058.
Description	Randomised Controlled Trial
N=	n=1510 dofetilide =749, placebo =761 Age ~68.5yrs, Male =74%, Atrial fibrillation =7.5%, NYHA class II =54%, Class III =31% Denmark
Intervention	The intervention was initially 1mg/day of dofetilide to patients without atrial fibrillation and 500µg/day for those with atrial fibrillation, this was changed early in the study to 500µg/day for patients with creatinine clearance of 40-60 ml/min and 250µg/day to those clearing 20 –40 ml/min all Vs placebo for all study
Outcomes	Primary end point was all cause mortality, with other outcomes of various cardiac caused death, and morbidity in terms of arrhythmias, worsening HF and reinfarction; all to a mean of 18 months
Results	<ul style="list-style-type: none"> • All cause mortality did not vary significantly between the groups (p=0.226) • In the subgroup of patients also receiving a B blocker there was a borderline reduction in the risk of death when on dofetilide HR 0.69 (0.48 – 1.00) (p=0.05) • The study showed no significant reduction in the risk of cardiac death (p=0.101), arrhythmic death (p=0.139) or worsening HF (p=0.513) • Overall there were no differences in the incidence of adverse events, or frequency of study withdrawal between dofetilide and placebo. • Specific adverse events that occurred more often with dofetilide included torsade de pointes (7 Vs 0 cases), and QTc prolongation (19 Vs 3 cases) • Rates of ventricular tachycardia and fibrillation were similar between groups
Comments	No increase in the risk of death when dofetilide is adjusted to renal function and monitored in hospital for 3 days Less effect on hospitalisation fro HF than seen in parallel HF trial, probably due to population differences with fewer symptomatic patients included here, who were younger and were less likely to have atrial fibrillation at baseline Discovery of a positive trend towards mortality reduction in subgroup of patients with concomitant B Blocker therapy is encouraging, although primary trials will be needed in this area.
Reference	110

Paper	Doval, H. C., Nul, D. R., Grancelli, H. O., Perrone, S. V., Bortman, G. R., & Curiel, R. 1994, "Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA).", <i>Lancet</i> , vol. 344, pp. 493-498.
Description	Randomised controlled trial Argentina
N=	156
Intervention	An intervention with amiodarone at 300mg/day orally Vs no treatment as a continuous treatment
Outcomes	The main outcomes stated are all cause mortality, cardiopulmonary resuscitation, and symptomatic sustained ventricular tachycardia, as well as hospitalisation, and adverse affects to 2 years
Results	<ul style="list-style-type: none"> • A corrected risk reduction (accounting for the independent variables found for mortality) benefit of amiodarone on mortality was RR 0.69 (95% CI 0.52 – 0.91) (p=0.024) • Subgroup analysis showed that the effect of amiodarone was consistent in the various subgroups of sex, functional capacity (NYHA class) and presence or absence of NSVT on admission, with none of these groups demonstrating a different effect within the class.
Comments	The decrease in mortality and hospitalisation followed the same trend in all subgroups examined including the presence of NSVT The results cannot be generalised to patents showing less severe manifestations of HF or less impaired ventricular systolic functions Patients were randomised to treatment arms using computerised randomisation in blocks of ten stratified on site and presence of non-sustained ventricular tachycardia (NSVT)

Paper	Cleland, J. G. & Dargie, H. J. 1987, "Ventricular arrhythmias during exercise in patients with heart failure: the effect of amiodarone", <i>European Heart Journal</i> , vol. 8 Suppl D, pp. 65-69.
Description	Randomised Controlled Trial
N=	n=22, amiodarone =22 placebo =22 in cross over design Age =56 yrs, Male =86%, NYHA II =55%, NYHA III =45%, Ischaemic heart disease =64%, Dilated cardiomyopathy =36%
Intervention	After a loading dose amiodarone was given at 200mg/day for the course of the 3 months Vs placebo in HF patients NYHA class II-III
Outcomes	Exercise time and recovery ability were measured at crossover and end of the trial, with biochemical evaluation of plasma amiodarone levels, and clinical outcomes relating to discontinuation all at 3 months
Results	<ul style="list-style-type: none"> • There was no difference in the mean exercise performance observed, no patient deteriorated when on amiodarone • Post exercise (5 mins) heart rate was decreased dramatically with amiodarone where 84 BPM was recorded Vs 94 BPM on placebo (p<0.001) • There were dramatically fewer incidences of ventricular arrhythmias (both standard and complex) during exercise and in recovery (p values <0.001-0.01) • Clinical outcomes included three sudden deaths in the placebo group, whilst in the amiodarone group there were three withdrawals due to MI, worsening arrhythmias, and 2:1 heart block
Comments	Relevant to all HF patients with mild to moderate functional limitation regardless of aetiology Exercise induced ventricular arrhythmias were significantly reduced (often to no events) without impinging on patient exercise performance or symptoms When initiating amiodarone inpatients care should be taken to monitor for temporary exacerbation of arrhythmias
Reference	109

Pharmacological therapy**Anticoagulants*****Experimental Studies***

Paper	Lip, G. Y. & Gibbs, C. R. 2001, "Anticoagulation for heart failure in sinus rhythm", <i>Cochrane Database Syst.Rev</i> no. 4, p. CD003336.
Description	Systematic review
N=	4 RCTS (n=1221), 3 observational studies (n=366) and 4 post hoc trials (n=1000's) International
Intervention	All trials reviewed compare Warfarin, tromexan, or dicoumarol Vs placebo or no treatment
Outcomes	A range of outcomes across primary studies are reported, mostly with all cause mortality, sudden death, and stroke, at various outcome times (mostly long term)
Results	<ul style="list-style-type: none"> • Data from the 4 prospective controlled studies shown anticoagulation to be more efficacious than control for reducing all cause mortality OR 0.64 (95% CI 0.16 – 0.43), but only 24% of weight came from randomised trial • There was a non significant trend towards increased bleeding in patients on warfarin in the 2 trials that reported this outcome OR 1.52 (0.56 – 4.10) • From observational studies there were rates of thromboembolic events of 0% to 3.2% with 2 of the three papers finding significant benefit over control • From post hoc analysis of large trials, multivariate analysis showed warfarin to have a risk reduction in terms of sudden death of 32% compared to 25% for beta blockers, 24% for aspirin and 11% enalapril (SOLVD). Similarly data from CONSENSUS showed a 40% lower mortality. From V-HeFT there were 2.7 events of stroke / pulmonary embolism / peripheral embolism per 100 patient years on placebo compared to a rate of 2.9 events per 100 patient years on warfarin (V-HeFT 1). In the second V-HeFT trial the rates were 2.1 per 100 patients years without antithrombotic therapy compared to 4.9 events per 100 patients years with warfarin (p=0.01). In the SAVE trial there was a 81% reduction in the risk of stroke with warfarin compared to no treatment (RR 0.91 (0.13 – 0.27) but this was not compared to that found with aspirin 51% reduction • Overall a trend toward reduction in mortality and cardiovascular events with anticoagulants compared with control, but also a trend toward increased bleeding.
Comments	<p>Only able to include 1 modern and 3 older and smaller prospective trials, three observational trials and data from post hoc analysis of placebo arms of trials with allocation of agents in question at physicians will \searrow effects as active treatment likely to be given to more severely ill.</p> <p>It is likely that in post hoc analysis it is the patients who were at highest risk that were treated with warfarin</p> <p>It is possible that the effects of oral anticoagulation may differ according to the cause of heart failure</p> <p>The present data does not support the routine use of anticoagulants in patients with H Fin sinus rhythm.</p> <p>The ongoing trial by the Veterans administration (WATCH) may shed more light on the relative efficacy of warfarin and antiplatelet therapy</p>

Studies included	Falk (1993) PROMISE, Loh (1997) SAVE, Dunkman (1993) V-HeFT II, Anderson (1950), Swedberg (1987) CONSENSUS, Fuster (1981), Griffith (1952), Harvey (1950), Kyrle (1985), Natterson (1993), Al-Khadra (1998) SOLVD
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Paper	Lip, G. Y. & Gibbs, C. R. 2001, "Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm", <i>Cochrane Database Syst.Rev</i> no. 4, p. CD003333.
Description	Systematic review
N=	n=1 RCT (n=279) and 4 cohort studies n~20% of original trialists on antiplatelet regime International
Intervention	All trials reviewed compare Aspirin Vs Warfarin or Vs placebo with no details of dosages as prescribed by patient physicians
Outcomes	A range of outcomes across primary studies are reported, mostly with all cause mortality, sudden death, and cardiovascular events, at various outcome times (mostly long term)
Results	<ul style="list-style-type: none"> • WATCH prospective randomised trial began 1999 with 4500 patients on Warfarin Vs anti platelet (either aspirin or Clopidogrel) with outcomes of all cause mortality, MI , Stroke, and Ischaemic events • Prospective RCT showed no difference in combined endpoint of death / MI / Stroke with 32% in aspirin group, 24% in warfarin group , and 27% in no therapy. Although there was excess hospitalisation in the aspirin group (p=0.05) due to exacerbation of HF • The V-HeF trials showed no significant differences in the incidence of thromboembolism between patients on anti platelets or no therapy • The SOLVD trial indicated a reduced incidence of sudden cardiac death RR Vs placebo 0.79 (95% CI 0.61 – 0.95), and reduced all cause mortality HR 0.82 (0.73 – 0.92) and combined with hospitalisation for HF a HR of 0.81 (0.74 – 0.89) from the placebo arm of the trial. However, this effect was substantially reduced in patients within the enalapril arm • The SAVE trial showed aspirin therapy to reduce the total incidence of stroke Vs placebo RR 0.44 (95% CI 0.29 – 0.65) • Although there was no direct comparison made between aspirin and warfarin the V-HeFT studies the data suggests that aspirin was superior to warfarin in preventing thromboembolisms. • In the SOLVD and SAVE trials no comparison was made between aspirin and warfarin but both reduced the risk of sudden cardiac death.
Comments	A thorough literature search including Medline, Embase and Dare, with cardiology abstract and reference list hand searched and authors contacted Only able to include post hoc retrospective cohort data from placebo arms of trials with allocation of agents in question at physicians will ↘ effects as active treatment likely to be given to more severely ill.
Reference	113
Studies included	Falk (1993) PROMISE, Loh (1997) SAVE, Dries (1997) SOLVD, Dunkman (1992) V-HeFT II, Barrie Massie (1999) WATCH.

Pharmacological therapy

Aspirin

Experimental Studies

Paper	Olson, K. L. 2001, "Combined aspirin/ACE inhibitor treatment for CHF.", <i>Annals of Pharmacotherapy</i> , vol. 35, no. 12, pp. 1653-1658
Description	Systematic review
N=	n=2 Post hoc RCTs, n=5 RCTs in haemodynamics, n=? overall patients all HF patients Canadian reviewer, of international trials
Intervention	The addition of Aspirin to ACEi therapy is compared to ACEi alone.
Outcomes	From the post hoc analysis of RCTs outcomes of mortality are evaluated, from prospective RCTs haemodynamic measurements are reported
Results	<ul style="list-style-type: none"> • The CONSENSUS II analysis showed that patients taking aspirin at baseline derived less benefit in terms of mortality with ACEi than those not on aspirin. The SOLVD study showed no differences in the composite end point of death or hospitalisation with HF between taking an antiplatelet agent or not. However, the hazard ratio for mortality on enalapril and antiplatelet was HR 1.10 (95% CI 0.93 – 1.30) compared to a significant HR 0.77 (0.67 – 0.87) on enalapril without antiplatelet. • The analysis of the prospective RCTs was inevitably only limited to the haemodynamic outcomes recorded in the original studies. Given that as the review suggests these may not directly relate to clinical endpoints, and that all but 1 of the 5 studies included fewer than 30 patients the results will not be discussed here.
Comments	There may be different effects between acute and chronic doses of ACEi There is no information on the minimal effective dose of aspirin that eliminates the concern for an interaction. Mortality outcomes reviewed from observational studies, and haemodynamic effects from RCTs, no analysis of adverse effects or of costs
Reference	117
Studies included	Van Wijngaarden (1994), Hall (1992), Guazzi (1997), Spaulding (1998), Katz (1999)

Paper	Takkouche, B., Etminan, M., Caamano, F., & Rochon, P. A. 2002, "Interaction between aspirin and ACE Inhibitors: resolving discrepancies using a meta-analysis.", <i>Drug Safety</i> , vol. 25, no. 5, pp. 373-378.
Description	Systematic review
N=	n=8 trials, n=121 760 patients All patients with coronary heart disease. Patient groups of all ages and diagnoses Spanish and Canadian reviewers, International studies
Intervention	A range of ACEi, including Enalapril, Captopril, Trandolapril, Zofenopril, and Lisinopril in combination with aspirin or not
Outcomes	All studies report outcome of mortality for between 4 weeks and 5 years
Results	<ul style="list-style-type: none"> • Overall pooled value of drug interaction gives a synergy index of $S=0.91$ (95% CI 0.80 – 1.03), with >1 indicating beneficial synergy, and >1 an antagonistic effect, therefore no significant overall effect. • The alternative pooled product term analysis from regression in initial studies shows OR 1.11 (95% CI 0.96- 1.28) ($p=0.15$) also showing no negative or positive interaction
Comments	Data from HOPE and SOLVD not included due to unavailability of data The antagonistic effect of the drug interaction is reported although the confidence intervals provided cross the level of no interaction effect
Reference	119
Studies included	Krumholz (2001), ISIS-4 (1995), Swedburg (1992) CONSENSUS II, GISSI-3 (1994), CCS-1 (1995), Ambrosioni (1995). Pfeffer (1992) SAVE, Kober (1995).

Paper	Leor, J., Reicher-Reiss, H., Goldbourt, U., Boyko, V., Gottlieb, S., Battler, A., & Behar, S. 1999, "Aspirin and mortality in patients treated with angiotensin-converting enzyme inhibitors: a cohort study of 11,575 patients with coronary artery disease.", <i>Journal of the American College of Cardiology</i> , vol. 33, no. 7, pp. 1920-1925.
Description	Cohort study
N=	n=1179 whole study, n=464, aspirin =221, no aspirin =243 Age =62yrs, Male =76%, NYHA class II =71%, classes III/IV =29%, all CAD Israel
Intervention	The concomitant use of aspirin with an ACEi or not was assessed
Outcomes	Outcome of all cause mortality was assessed to 5 years
Results	<ul style="list-style-type: none"> • For patients with CAD and HF there were 24% death in the aspirin group compared to 35% deaths in the ACEi alone group (p=0.007) • When adjusted for age, gender, diabetes and B blocker the RR for 5 years mortality with aspirin was 0.70 (95% CI 0.49 – 0.99)
Comments	<p>Dose of aspirin not controlled, but most common dose quoted as being 250mg</p> <p>May be different interaction components within patients with ischaemic heart disease, post MI, or HF</p> <p>Results do not rule out a haemodynamic negative interaction not mirrored in survival</p> <p>The safety of aspirin may be a dose-dependant phenomena, or limited to certain subgroups</p> <p>Method of exposure to aspirin was estimated from baseline evaluation, with a proxy estimation of 55% use of aspirin in the no aspirin cohort by the end of the 5 year follow up if uptake was similar to that in the active trial</p>

Paper	Lapane, K. L., Hume, A. L., Barbour, M. M., & Lipsitz, L. A. 2002, "Does aspirin attenuate the effect of angiotensin-converting enzyme inhibitors on health outcomes of very old patients with heart failure?", <i>Journal of the American Geriatrics Society.</i> , vol. 50, no. 7, pp. 1198-120
Description	Cohort study
N=	n=12,703, Aspirin =2,406, No aspirin =10,297 Age =50% 65yrs to 85 yrs and 50% 85yrs and above, Male =36%, mild functional impairment =15%, moderate functional impairment =49%, severe functional impairment =36% Ischaemic heart disease =37% USA
Intervention	The exposure to aspirin is compared to no aspirin in elderly HF patients taking an ACEi
Outcomes	Outcomes of mortality, morbidity, hospitalisation (and times to these end points) are evaluated along with changes in physical function to a maximum 1 year
Results	<ul style="list-style-type: none"> • There was no statistical association between use of aspirin and time of death RR 0.99 (95% CI 0.92 – 1.07), nor were there any significant associations with aspirin use and time to death or hospitalisation, or time to functional decline • There was no significant difference in time to death with or without aspirin in a subgroup of post stroke patients • Subgroup analyses indicated that there were no significant differences in the interaction effect in high or low dose ACEi users and in different type of ACEi
Comments	<p>In very old HF [patients living in long-term care facilities the use of aspirin with ACEi did not decrease 1 year survival, hospitalisation, or rate of functional decline.</p> <p>Findings were very similar across subgroups of different ACEi, different doses, or presence of IHD</p> <p>Mortality rate high in this study at 39% might have made interaction effect difficult to tease out</p> <p>A low frequency of aspirin use amongst the study population at 16%</p> <p>Unable to distinguish between systolic and diastolic HF</p> <p>Not able to evaluate the effect of duration of drug use on the outcomes studied</p> <p>The assessment of exposure was for one time point only at baseline and it is estimated that potentially 5% of patients who were initially not on aspirin may have begun therapy during the follow up period</p>
Reference	120

Non-experimental studies

Paper	Cleland, J. G. 2002, "Is aspirin "the weakest link" in cardiovascular prophylaxis? The surprising lack of evidence supporting the use of aspirin for cardiovascular disease.", <i>Progress in Cardiovascular Diseases</i> , vol. 44, no. 4, pp. 275-292.
Description	Review
N=	
Intervention	
Outcomes	
Results	<ul style="list-style-type: none"> • Meta analyses of anti-platelets highlight the fact that there is no long-term trial of aspirin showing a benefit on mortality compared to placebo, and only one with a high dose in post stroke patients shows survival benefit, and it is possible that publication bias may have been over looked • Three observational studies in populations with pre-existing HF have shown trends towards excess mortality with high dose aspirin (doses not stated) • The WASH study with HF patients taking ACEi and randomised to aspirin to no antithrombotic therapy or warfarin, demonstrated a significant increase in the risk of hospitalisation for heart failure with aspirin, and a trend towards excess mortality, but was too small to be conclusive • A retrospective analysis of the CAPRIE trial of patients with Ischaemic disease and cardiac surgery found Clopidogrel to have a much more beneficial effect on vascular death or events than with aspirin. • The SOLVD and HOPE trials of patients who were stabilised on medication before the initiation of and ACEi showed that there was a consistent reduction in the mortality benefit of ACEi when taken alongside aspirin. • There are conflicting findings in terms of positive or negative interactions of aspirin and ACEi from observational data sets, but without randomisation to either of these drugs there is a possibility that they will not be a reliable guide.
Comments	<p>n=125 references Review split into subsections detailing possible mechanisms for the effect of aspirin, the use of aspirin therapy after acute arterial vascular event, or without an acute arterial vascular event, and evidence for an interaction between aspirin and ACEi Existing meta-analyses widely discussed. Side effects of aspirin use, and brief cost evaluation given.</p>
Reference	118

Pharmacological therapy

Isosorbide/Hydralazine combination

Experimental Studies

Paper	Cohn, J. N., Archibald, D. G., Ziesche, S., Franciosa, J. A., Harston, W. E., Tristani, F. E., Dunkman, W. B., Jacobs, W., Francis, G. S., & Flohr, K. H. 1986, "Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study", <i>New England Journal of Medicine</i> , vol. 314, pp. 1547-1552.
Description	Randomised Controlled Trial
N=	n=642, prazosin =183, hydralazine – isosorbide dinitrate =186, placebo =273 Age =58yrs, Male =100%, LV ejection fraction =30%, Coronary artery disease =44% USA Multi-centre study
Intervention	Average doses in trial were prazosin at 18.6 mg/day, hydralazine 270mg and isosorbide dinitrate 136mg/day (HLZ group) Vs placebo in patients with cardio thoracic ratio >0.55, LV diastolic diameter >2.7cm per square m, or LV ejection fraction <45%
Outcomes	All cause mortality was primary endpoint and blood pressure and LV ejection fraction were monitored every 6 months to a mean 2.3 years
Results	<ul style="list-style-type: none"> • There was a reduction in mortality with HLZ Vs placebo p=0.046, although not quite significant after adjustment for multiple timepoint testing (p=0.05) • At 2 years the mortality was lower in the HLZ group compared with placebo RR 0.66 (95% CI 0.46 – 0.96) (p=0.028) • The trial did not provide sufficient data to compare mortality rates beyond 3 years. • The mortality reduction seen with HLZ was slightly higher in patients with coronary disease than those without although this difference was not significant (p=0.47) • There was no significant difference in the effect on blood pressure between any of the groups • Although LV ejection fraction was significantly improved with HLZ compared to baseline at 8 weeks and 1 year (p<0.001), it did not change in the placebo or prazosin arms
Comments	Findings of this study are relevant to most HF patients except recent MI valvular disease, myocardial disease There were two apparent imbalances in allocation to treatment with a larger cardio-thoracic ratio, and lower exercise tolerance in the prazosin group compared to the other two arms (p=0.03 and 0.05 respectively) Vasoconstriction may have an important role in the progression of the disease, the mortality it causes or both Not possible to differentiate the effects of hydralazine and isosorbic dinitrate 19% of one or both drugs were discontinued due to side effects, and only 55% of patients were taking the full dose of both drugs at 6 months
Reference	129

Paper	Cohn, J. N., Johnson, G., Ziesche, S., Cobb, F., Francis, G., Tristani, F., Smith, R., Dunkman, W. B., Loeb, H., & Wong, M. 1991, "A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure.", <i>New England Journal of Medicine</i> , vol. 325, pp. 303-310.
Description	Randomised Controlled Trial
N=	n=804, hydralazine – isosorbide dinitrate =401, enalapril =403 Age =16yrs, Male =100%, LV ejection fraction =0.29, CAD =53%, NYHA class II =51%, class III =43%, history of Hypertension =47%, Diabetes =20% 13 centres in USA
Intervention	20mg/day enalapril compared with 300mg hydralazine and 160mg isosorbide dinitrate /day (HLZ) as continuous therapy
Outcomes	Primary endpoint was mortality as a continuous variable and at 2 years, with other outcomes haemodynamic effects, ejection fraction, exercise tolerance, cardiothoracic ratio, hospitalisations, adherence to therapy and side effects assessed at 3, 6 months, then every 6 months for a mean 2.5 years
Results	<ul style="list-style-type: none"> • 2 year mortality was significantly lower with enalapril Vs HLZ mortality rates of 18% Vs 25% (p=0.016), but this was not significant over the whole study period (p=0.08) • There was no difference in the survival curves for the subgroup of patients who had taken part in the previous HLZ trial • There was no difference in the mortality due to worsening heart failure between the treatment groups • At 13 weeks the ejection fraction of patients on HLZ was significantly improved compared to enalapril (p=0.026) • At 2 years there was significantly increased exercise tolerance in the HLZ group compared with enalapril (p=0.02) • There was no significant differences in the effects of the two therapies on cardiothoracic ratio, adherence to regimen, or hospitalisations • There were excess incidence of headaches in the HLZ arm (73 Vs 54 events)
Comments	Results are widely applicable to the general HF population, given the demographic and severity characteristics of the study. Male only study makes comparison for females difficult Reduction in all cause mortality due to a significantly improved risk in terms of sudden death with enalapril Since enalapril and hydralazine – isosorbide dinitrate have independent beneficial effects there may be potential for dual therapy.
Reference	130

Paper	Fonarow, G. C., Chelimsky, F. C., Stevenson, L. W., Luu, M., Hamilton, M. A., Moriguchi, J. D., Tillisch, J. H., Walden, J. A., & Albanese, E. 1992, "Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C trial", <i>Journal of the American College of Cardiology</i> , vol. 19, pp. 842-850.
Description	Randomised Controlled Trial
N=	n=104, captopril =44, hydralazine =60 Age =52yrs, Male =85%, LV ejection fraction =0.20, Ischaemic origin of heart failure =57%. USA
Intervention	Captopril at mean 206 mg/day was compared to hydralazine 410 mg/day in patients with severe heart failure
Outcomes	Primary endpoint was mortality, with readmission for emergency transplant another outcome, tested to 12 months
Results	<ul style="list-style-type: none"> • With a mean outcome measurement of 8 months actuarial 1 year survival with captopril was 81% compared to 51% with hydralazine (p<0.05) • Hydralazine therapy was a independent predictor of mortality (p=0.05) along with elevated capillary wedge pressure, and low serum sodium
Comments	<p>The inclusion criteria for this study means that the findings can only be applied to severe heart failure patients</p> <p>Subgroup analysis of 77 patients in initial randomisation groups showed similar results</p> <p>Trial designed to determine whether the effect on mortality was independent of haemodynamic effects</p> <p>The hydralazine regimen did not itself have a negative effect on mortality with the range found being similar to other studies with vasodilators</p>
Reference	131

Paper	Ghose, J. C., Chakraborty, S., Mondal, M., & Bhandari, B. 1993, "Effect of vasodilator therapy on mortality in chronic congestive heart failure", <i>Journal of the Association of Physicians of India</i> , vol. 41, pp. 269-271.
Description	Randomised Controlled Trial
N=	n=153, captopril =52, hydralazine =50, placebo =51 Age =41 yrs, Male =78%, NYHA class III =13%, class IV =87% India
Intervention	100mg/day of captopril, was compared with 100mg hydralazine and 60mg isosorbide dinitrate / day, and a placebo control in NYHA class III-IV patients
Outcomes	Primary endpoints were mortality at 6 months and 1 year
Results	<ul style="list-style-type: none"> • Mortality at 1 year was 50% in the placebo group, 42% in the HLZ group, and 30% in the captopril group which relates to a reduction in mortality of 16% in the HLZ arm which was not significant and a 40% (RR 0.60) reduction in mortality on captopril (p<0.05) • The reduction of mortality from worsening heart failure risk with HLZ was 25% and 42% with captopril • There were no significant changes in NYHA class with either intervention • Hypotension and worsening renal function were the most common reported side effects with HLZ and captopril therapy
Comments	10% of placebo control, 14% of the HLZ group and, 10% of the captopril group were lost to follow up Relatively young and severe class of HF patients
Reference	132

Paper	Lin, M., Chiang, H. T., Chen, C. Y., & Chiang, B. N. 1991, "Comparison of enalapril and conventional vasodilator therapy in patients with chronic congestive heart failure", <i>Journal of the Formosan Medical Association</i> , vol. 90, pp. 452-459.
Description	Randomised Controlled Trial
N=	n=120, enalapril =60, hydralazine sorbinate =60 Age =68.5 yrs, Male =100%, Coronary Artery Disease =31% Taiwan
Intervention	Enalapril at 20mg twice daily compared with 200mg hydralazine and 80mg sorbatrate/day (HLZ) as a continuous therapy in patients with mild to severe HF
Outcomes	Clinical assessment of cardiac function and NYHA class, neurohormonal changes, biochemical changes, and outcomes of mortality and side effects, all at 1 month and 1 year.
Results	<ul style="list-style-type: none"> • Plasma renin activity was not significantly altered between the two study arms, although aldosterone level decreased significantly in the enalapril group 12ng/dl from 24ng/dl (p<0.005) while it rose significantly in the HLZ group 34ng/dl from 28ng/dl (p<0.005) • There was no significant difference in the effects of enalapril compared to HLZ on LV ejection fraction, or NYHA class • Enalapril produced a significant increase in creatinine clearance ratio 59ml from 49 ml (p<0.005) whereas the HLZ therapy saw no improvement • The incidence of headache occurred more frequently in the enalapril group than the HLZ group (p<0.05), otherwise there were no significant difference amongst adverse events in the study • There was no significant difference in the frequency of sudden death between the study groups
Comments	There may be differences in the aetiology of the patients included in this trial compared to UK patients due to ethnic differences The study groups had similar responses to vasodilators as defined by similar decreases in systolic and diastolic blood pressure, and LV ejection fraction HLZ therapy failed to improve renal function despite beneficial effects on cardiac performance
Reference	133

Paper	Rector, T. S., Johnson, G., Dunkman, W. B., Daniels, G., Farrell, L., Henrick, A., Smith, B., & Cohn, J. N. 1993, "Evaluation by patients with heart failure of the effects of enalapril compared with hydralazine plus isosorbide dinitrate on quality of life. V-HeFT II. The V-HeFT VA Cooperative Studies Group", <i>Circulation</i> , vol. 87, p. VI71-VI77.
Description	Randomised Controlled Trial
N=	n=804, Enalapril =403, Hydralazine – isosorbide dinitrate =401 Age =61 yrs, Male =100%, LV ejection fraction =29%, NYHA class I =6%, class II =51%, class III =43%, Coronary Artery Disease =53%
Intervention	20mg/day enalapril compared with 300mg hydralazine and 160mg isosorbide dinitrate /day (HLZ) as continuous therapy
Outcomes	Improvements in QOL of HF patients were examined by two self administered questionnaires. The first was the Heart Condition Assessment (HCA) questionnaire containing 11 items, and an early version of the Minnesota living with heart failure (LHF) questionnaire with 21 items, at 3, 6 months, 12 months and then annually to 4 years
Results	<ul style="list-style-type: none"> • There was a similar pattern of relative improvement over baseline scores for both intervention groups at 3 months followed by a slow deterioration of scores, though no significant differences between the treatment groups at any time point, on either scale. • There were also no differences in outcomes among subgroups of previous vasodilator use, quartiles of baseline HCA score, ejection fraction, peak oxygen consumption, and plasma norepinephrine concentrations • The changes in scores on the questionnaires were inconsistently related to peak oxygen consumption, ejection fraction, and plasma norepinephrine
Comments	Self assessment using questionnaires (details given in appendix) with good reproducibility with correlations of 0.88 and 0.87 for HCA and LHF effectively Additional analysis of the V-HeFT II study in terms of quality of life
Reference	135

Pharmacological therapies**Inotropic agents****Experimental studies**

Paper	Nony, P., Boissel, J. P., Lievre, M., Leizorovicz, A., Haugh, M. C., Fareh, S., & de, B. 1994, "Evaluation of the effect of phosphodiesterase inhibitors on mortality in chronic heart failure patients. A meta-analysis", <i>European Journal of Clinical Pharmacology</i> , vol. 46, no. 3, pp. 191-196.
Description	Systematic Review
N=	n=2808 13 RCTs from 17 originally selected French investigators of international studies
Intervention	PDIs Amrinone, Milrinone, vesnarinone (excluded following sensitivity analysis), indolian, and pimobendan. At between 2.5mg – 600mg day Vs placebo, with or without concomitant vasodilator, in HF patients NYHA class II-IV
Outcomes	Sole outcome measure of mortality at between 3 and 20 months
Results	<ul style="list-style-type: none"> • Total mortality risk of a PDI Vs placebo for all trials was found to be OR 1.17 (95% CI 0.94 – 1.46) (p=0.16) but with significant heterogeneity. • After sensitivity analysis removes vesnarinone trials (3) the increased mortality was statistically significant OR 1.41 (1.1 -1.8) (p<0.001) with no significant heterogeneity. • Within the non vesnarinone group the sub group analysis of concomitant vasodilator use or not showed little difference with both groups showing non significant increased risk (p=0.9) for both • An analysis of vesnarinone trials showed a significant reduction in the risk of mortality OR 0.3 (0.16 – 0.57) (p<0.001) and no heterogeneity, although only 3 trials were included here. • The use of other vasodilator therapy was not randomised in the primary trials • Lower doses or intermittent therapy when functional capacity becomes markedly declined of PDIs requires further investigation
Comments	Only applicable to patients with overt HF without valvular disease, myocarditis, hypertrophic cardiomyopathy, arrhythmias, angina, renal disease or hypertension. Wide range of outcome measurements combined and drug doses varied widely The proportions of patients with Ischaemic aetiology of HF may have varied between trials
Studies included	Massie (1985), Di Bianco (1987), Lardoux (1987), Uretsky (1990), Narahara (1991). Di Bianco (1994), Massie (1985)a, Dies (1989), OPC MRG (1990), Feldman (1991), Packer (1991), Assman (1991), Kubo (1992), Feldman (1993)

Paper	Thackray, S., Easthaugh, J., Freemantle, N., & Cleland, J. G. 2002, "The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure-a meta-regression analysis", <i>European Journal of Heart Failure.</i> , vol. 4, no. 4, pp. 515-529.
Description	Systematic review
N=	21 RCTS in al n=632, with 11 RCTS n=331 with inotropes compared to placebo Patient characteristics not stated UK review of international trials
Intervention	A range of inotropes both as continual or intermittent treatment, with some therapies titrated to produce a desired clinical standard including Dobutamine, Dopexamine, Toborinine, and Milrinone Vs placebo for a variety of treatment course lengths
Outcomes	The outcomes reported on are mortality, discontinuation of therapy, and effect of therapy on NYHA class. With a pooled incidence risk difference being employed to allow for different length of follow up in original studies
Results	<ul style="list-style-type: none"> • Overall there was no significant difference in mortality rates with inotropic therapy compared to placebo with a trend towards harm OR 1.50 (95% CI 0.51 to 3.92) with only 4 trials reporting events in both treatment and control groups • There was a trend towards fewer patients discontinuing treatment when on inotropic therapy than on placebo however this difference was not significant OR 0.52 (0.11 to 2.3) • An analysis of standard effect size across the 2 studies that reported on changes in patient functional status using NYHA scale showed a significant improvement in score of -0.75 (-1.42 to -0.08) (lower scores indicate less functional limitation). This analysis was undertaken using a fixed effect model as it was not possible to develop a full random effects model from 2 trials.
Comments	<p>A thorough search for studies including Medline Embase, and the Cochrane controlled trials register. Reference lists of selected studies were reviewed as were other reviews and bibliographies</p> <p>A good description of methodology with duplicate data extraction (although replicability not stated) and stratification of analysis for major variables such as severity of HF and reason fro treatment. Where cross over trials identified the results from the first period are used. Both fixed effect models and random effects models (where possible) were used to pool data. To avoid unjustifiably precise results from fixed effects models a full random effects approach was used based on Markov chain Monte Carlo integration techniques</p> <p>The outcomes of this study can only directly be related to patients with severe heart failure with acute decompensation</p> <p>Additional analysis of trials investigating the relative efficacy of various inotropic agents</p> <p>Measures of heterogeneity not indicated</p> <p>Fixed effects models should be treated with caution as they may under represent the variability in the results</p> <p>The efficacy of inotropic agents may depend on the underlying aetiology of HF</p> <p>B blockers will reduce the inotropic response to beta-agonists which may reduce potential benefit or harm from these agents and few of the patient cohort were on optimal pharmacotherapy.</p>
Reference	144
Studies included	Adamopoulos (1995), DICE (1997), Dies (1986), Elis (1998), Erlemeier (1992), Liang (1984), Gollub (1991), Asanoi (1995), Hoit (1994), Seino (1996), Anderson (1987)

Paper	Cohn, J. N., Goldstein, S. O., Greenberg, B. H., Lorell, B. H., Bourge, R. C., Jaski, B. E., Gottlieb, S. O., McGrew, F., III, DeMets, D. L., & White, B. G. 1998, "A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators.", <i>New England Journal of Medicine</i> , vol. 339, pp. 1810-1816.
Description	Randomised Controlled Trial
N=	n= 3833, 30mg vesnarinone =1275, 60mg vesnarinone =1275, placebo =1283 Age =63yrs, Male =76%, Ischaemic origin =60%, LV ejection fraction =21% USA
Intervention	Intervention of either 30mg or 60 mg of vesnarinone per day (orally) Vs placebo in patients with severe HF but without valvular disease, reversible myocardial disease or implanted defibrillator
Outcomes	Outcomes of mortality and in composite with HF morbidity, and rate of hospitalisation and adverse events to a mean 268 days
Results	<ul style="list-style-type: none"> • Mortality was recorded in 19% of placebo group, 21% in the 30mg arm, and 13% in the 60 mg arm with time to event being significantly shorter in the 60mg arm than placebo (p=0.02) even after accounting for confounding factors, with a trend towards increased mortality in the 30mg group Vs placebo. The effect of 60mg vesnarinone on mortality was HR ~1.22 (95% CI 1.05 – 1.41) but not significant in subgroups of NYHA class IV and no-ischaemic disease • No significant difference was found in HF hospitalisation between the three groups • The time to combined end point of mortality of HF morbidity was also not significantly different between groups • Benefit of 60 mg vesnarinone on QOL determined by the living with heart failure questionnaire was clearly seen at 8 and 16 weeks with a decrease (improvement) in score of 7 points Vs 5 points on placebo (p<0.001) and 8 points Vs 6 points on placebo (p=0.003). No significant differences were found at week 26 or at any time for 30mg arm Vs placebo • Dose related adverse events were reported with vesnarinone in the incidence of diarrhoea (p<0.001) for 60mg Vs placebo and leukopenia
Comments	<p>The findings of this study can only be extrapolated to patients with the most severe HF (NYHA classes III-IV) and with LV ejection fraction <30%</p> <p>Alternative randomisation process used for patients awaiting heart transplant</p> <p>Little difference in HF morbidity between 30mg and 60 mg arms</p> <p>QOL only improved with 60mg vesnarinone but morbidity also significantly higher in this group</p> <p>Increased mortality due to greater number of sudden deaths</p> <p>Comparison to other studies show a near linear dose response of vesnarinone.</p>
Reference	141

Paper	Oliva, F., Latini, R., Politi, A., Staszewsky, L., Maggioni, A. P., Nicolis, E., & Mauri, F. 1999, "Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE multicenter trial.", <i>American Heart Journal</i> , vol. 138, no. 2 Pt 1, pp. 247-253.
Description	Randomised Controlled Trial
N=	n=38, dobutamine =19, placebo =19 Age =65.5yrs, Male =82%, Ischaemic origin =47%, NYHA III =45%, NYHA IV =55%, LV ejection fraction =22.5% Italy
Intervention	Infused dobutamine at 2.5 µg/kg/minute for 48 hours per week to 5µg/kg/minute at up to 72 hours in a week Vs a saline placebo in NYHA class III-IV patients
Outcomes	6 minute walk test, and heart catheterisation to 6 months and Hospitalisation and mortality to 6 months
Results	<ul style="list-style-type: none"> • Improvement were seen in cardiac index in dubutamine patients at first acute infusion but no significant heamodynamic effects at 8 weeks • There were 17 hospitalisations in the control group compared to 11 in the dobutamine arms respectively but diference was not statistically different • There were no significant changes in 6 minute walk test distances achieved between study arms • The time dependant analysis of cardiovascular death or hospitalisation for any cause showed great similarities between groups (p=0.91)
Comments	Only applicable to more severe cases of HF without atrial fibrillation, unstable angina or valvular heart disease Patients intolerant to dubutamine on initial assessment not included in trial, which limits the applicability of the trial. 2 patients (11%) stopped dobutamine arm due to tachycardia, but no sustained cases Dobutamine does not infer increased risk of cardiovascular death or worsening heart failure, however neither does it prolong the time free of hospitalisation.
Reference	138

Paper	Lubsen, J., Just, H., Hjalmarsson, A. C., La Framboise, D., Remme, W. J., Heinrich, N. J., Dumont, J. M., & Seed, P. 1996, "Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial", <i>Heart</i> , vol. 76, pp. 223-231.
Description	Randomised Controlled trial
N=	n=317 pimobendan 2.5mg/day (P 2.5) =106, pimobendan 5mg/day (P 5) =103, placebo =108 Age =65.5yrs, Male =80%, Ischaemic aetiology =69%, LV ejection fraction =27%, NYHA II =52%, III =48% European study
Intervention	Treatment with either 2.5mg/day or 5 mg/day of pimobendan Vs placebo for 24 weeks in patients with mild to sever HF and LV ejection fraction <45%
Outcomes	Primary endpoint was exercise time at 4 12 and 24 weeks, with clinical status measured at 24 weeks (NYHA class) and QOL assessed by Minnesota living with heart failure questionnaire at this time. Long term follow up included all cause mortality and hospitalisation for HF for a mean 11 months
Results	<ul style="list-style-type: none"> • Improvements to exercise time over placebo were 13, 27, 29 secs for (P 2.5) at each respective outcome assessment (p=0.03) and 19, 17, 28 secs for (P 5) (p=0.05) • Assessment of ranked exercise capacity showed no significant improvements with pimobendan • The Minnesota Living with Heart failure score was not significantly improved at any time point with either dosage compared with placebo • Medication was unblinded or levels reduced in more patients taking pimobendan than placebo (P 2.5) 34 cases, (P 5) 29 cases, Placebo 19 cases (p=0.04) • There were no significant differences in mortality with pimobendan and placebo during the 11 month follow up, and a multivariate regression for hazard ratio of pimobendan and death was found to be 1.5 (95% CI 0.9 - 2.5) for the (P 2.5) and 1.2 (0.7 - 2.1) for (P 5) groups respectively • Hospitalisation for HF during the 11 month outcome assessment was insignificantly increased with pimobendan
Comments	Analysis of change of NYHA class showed significant improvement but this was based at improvement at any one time point. No difference in exercise duration was found between the 2.5mg/day and 5mg/day arms There was a trend towards improved clinical condition in patients but also towards a higher mortality
Reference	142

Paper	Cuffe, M. S., Califf, R. M., Adams, K. F., Jr., Benza, R., Bourge, R., Colucci, W. S., Massie, B. M., O'Connor, C. M., Pina, I., Quigg, R., Silver, M. A., & Gheorghade, M. 2002, "Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial", <i>JAMA</i> , vol. 287, no. 12, pp. 1541-1547.
Description	Randomised Controlled Trial
N=	n=951, Milrinone =479, placebo =472 Age =65.5 yrs, Male =66%, LV ejection fraction =23.5% 78 centres in USA
Intervention	Milrinone at between 0.375 µg/kg/minute to 0.75 µg/kg/minute for between 48 and 72 hours was compared to placebo in HF patients also receiving an ACEi
Outcomes	Outcomes included days hospitalised for cardiovascular causes, in hospital mortality or morbidity, and clinical status by heart failure score at 60 days
Results	<ul style="list-style-type: none"> • The primary end point of days hospitalised for cardiovascular causes showed no differences in Milrinone treatment compared to placebo. • In hospital or 60 day mortality was not significantly different between study arms • There was only one time point (30 days) where heart failure score was decreased (improved) in Milrinone compared to placebo 67 points Vs 63 points (p=0.02) • Although there were no significant differences in treatment failure due to progression of HF there were more treatment failures in the milrinone group due to hypotension and atrial fibrillation (p=0.004 and p=0.001 respectively)
Comments	<p>Patients were matched for all demographic variables however there were differences in frequency of hospitalisations in the previous year with placebo group having fewer (p=0.04), also Milrinone arm more likely to be receiving a calcium blockers (p=0.03), and less likely to be using a diuretic (p=0.02)</p> <p>Relevant only to patients with moderate to severe heart failure, hospitalised with an acute exacerbation</p> <p>Does not include a population of HF patients with acute decompensation where inotropic therapy was thought essential</p> <p>Results do not support the use of Milrinone</p>
Reference	140

Paper	Lowes, B. D., Higginbotham, M., Petrovich, L., DeWood, M. A., Greenberg, M. A., Rahko, P. S., Dec, G. W., LeJemtel, T. H., Roden, R. L., Schleman, M. M., Robertson, A. D., Gorczynski, R. J., & Bristow, M. R. 2000, "Low-dose enoximone improves exercise capacity in chronic heart failure. Enoximone Study Group", <i>Journal of the American College of Cardiology</i> , vol. 36, no. 2, pp. 501-508.
Description	Randomised Controlled Trial
N=	n=105, enoximone 25mg X3 daily =33, enoximone 50mg X3 daily =37, placebo =35 Age =59yrs, Male =86%, LV ejection fraction =23% NYHA II-III USA
Intervention	Two intervention groups of enoximone at 75mg/day or 150mg/day Vs placebo in HF patients
Outcomes	Primary endpoint was exercise duration by treadmill testing (Naughton protocol) with measures of Symptoms and NYHA class, as well as adverse effects as secondary endpoints all to 12 weeks
Results	<ul style="list-style-type: none"> • Exercise duration on 150mg/day enoximone was significantly increased from baseline Vs placebo at weeks 4 and 12 (p<0.05) but not at week 8, with the 75mg/day group showing improvement at week 12 only (in time course analysis) • The last observation carried forward showed an increased benefit from enoximone at week 12 for both groups 115secs, and 117 secs improvement for 75mg and 150 mg /day respectively compared to 23secs with placebo (p=0.013 and p=0.003 respectively for the two intervention arms) • Patient and physician assessments of improvement showed no significant benefit of either enoximone intervention • There were no significant changes in NYHA class of patients between groups throughout the study • There was improvement in symptoms of dyspnoea in both enoximone groups Vs placebo for patients but only in patients with little or no dyspnoea at baseline, and only up to 8 weeks, although this was not related to increased diuretic use • Adverse events were reported at a nearly identical rate 1.71/patient in placebo arm, 1.67/patient in the 75mg arm, and 1.76/patient in 150mg arm
Comments	<p>Only 67% of enrolled subjects completed the study, similar proportions in each of three arms</p> <p>The results can be considered relevant to most HF patients with mild to moderate conditions, except those with valvular disease or atrial fibrillation</p> <p>One patient in enoximone 75mg/day classified as NYHA class I despite protocol stating class II-III patients only</p> <p>Multiple outcome measures and statistical analysis suggests data dredging with no null hypothesis stated</p> <p>No background ACEi therapy so clinical relevance difficult to assess</p> <p>Effects of exercise capacity improvements not consistent over all time periods</p>
Reference	139

Pharmacological therapy
Calcium channel blockers

Experimental Studies

Paper	Pahor, M., Psaty, B. M., Alderman, M. H., Applegate, W. B., Williamson, J. D., Cavazzini, C., & Furberg, C. D. 2000, "Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials.", <i>Lancet</i> , vol. 356, no. 9246, pp. 1949-1954.
Description	Systematic review
N=	n=27,743 (n =12,699 calcium antagonist, n =15,044 other antihypertensive) 9 RCTs (4 trials open labelled) Age ranged 54-76yrs amongst trials, Men 34-78%, 2 trials all diabetics, 4 trial some diabetics, 1 trial no diabetics, 2 trials not stated
Intervention	A range of calcium antagonists (including dihydropyridine) amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and also verapamil, diltiazem; at various doses as medium or long term therapy. Compared to other antihypertensives including diuretics, B-blockers, ACEi and clonidine, in hypertensive patients
Outcomes	Various clinical outcomes and All cause mortality, at 2 to 7 years depending on trial
Results	<ul style="list-style-type: none"> • OR of developing congestive heart failure with calcium antagonist 1.25 (95% CI 1.07 - 1.46) (p=0.005) • OR of any cardiovascular event with calcium antagonist 1.10 (1.02 – 1.18) (p=0.018) • No significant difference in chances of developing Stroke (p=0.1) and in all cause mortality (p=0.54) • Surprising findings given that the control of blood pressure was similar between the intervention and controls, but calcium antagonists may have pro-inflammatory and antifibrinolytic effects and they may promote sympathetic activation. However this analysis cannot provide proof that these drugs are harmful or whether other hypertensives have particular CHD and HF benefits.
Comments	Not strictly applicable as not clinically diagnosed HF population Calcium antagonists are inferior to other hypertensives in preventing MI and HF and that a surrogate marker of lowered blood pressure is not a consistent marker of efficacy in these conditions No outcome trials at the time with calcium antagonists as add-on therapy
Studies included	Tatti, P. (1998), Estachio, R.O. (1998), Casiglia, E. (1994), Brown, M.J. (2000), Borhani, N.O. (1996), National Intervention Cooperative study (1999), Hansson, L. (2000), Hansson, L. (1999), Rosei, E.A. (1997)

Paper	Cohn, J. N., Ziesche, S., Smith, R., Anand, I., Dunkman, W. B., Loeb, H., Cintron, G., Boden, W., Baruch, L., Rochin, P., & Loss, L. 1997, "Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group", <i>Circulation</i> , vol. 96, pp. 856-863.
Description	Randomised Controlled Trial
N=	n=450, felodipine=224, placebo=226 Age =64yrs, NYHA class II =79%, class =21%, Coronary artery disease =55%, Hypertension =51%, Atrial fibrillation =25% USA
Intervention	10mg/day of oral felodipine ER Vs matching placebo in NYHA class II-III patients
Outcomes	Short term outcomes assessed at 12 weeks then 3 monthly included exercise performance (time maintained compared to baseline) Ejection fraction by radionuclide assessment, Quality of life by the Minnesota living with heart failure checklist, neurohormones PNE and ANP by assay, and long term outcomes of Hospitalisation, mortality, and adverse events.
Results	<ul style="list-style-type: none"> • Exercise capacity showed no improvement on felodipine in first 12 weeks but then tolerance began to fall in the placebo arm with a significant difference (p=0.01) at 27 months (from n=82 patients remaining) • LV ejection fraction was significantly improved in the felodipine arm at 3 months mean 2.1% increase Vs 0.1% decrease with placebo (p=0.001) although the difference was not significant at 12 months • NYHA class changes were no different between the groups, although QOL score had shown less deterioration at 27 months (p=0.038) this was the only time point where a statistically significant difference was noted • There were no significant differences in hospitalisation rates or time to hospitalisation between the study groups although a subgroup of patients NYHA III only showed a benefit of felodipine with a 40% rate compared to 58% with placebo (p=0.038) • The overall mortality rate was 14% in the felodipine arm and 13% with placebo RR 1.08 (95% CI 0.65 - 1.80) although the study was not designed with power to assess mortality • The only adverse event that was more common in the felodipine group than placebo was oedema (12% Vs 13% respectively (p=0.02)
Comments	Applicable to the majority of HF patients as study population from NYHA Classes II-III, however exclusion included hypertension, mitral regurgitation, severe angina and MI within 3 months A desirable haemodynamic effect was seen through lowered blood pressure suggesting potency as a vasodilator. Results do not support adding a dihydropyridine calcium antagonist to ACEi therapy routinely in HF patients, but may be safely used in such patients for another indication.
Reference	146

Paper	Liao, Y. H. 1998, "Interventional study of diltiazem in dilated cardiomyopathy: a report of multiple centre clinical trial in China. Chinese Cooperative Group of Diltiazem Intervention Trial in Dilated Cardiomyopathy. [see comments]", <i>International Journal of Cardiology</i> , vol. 64, pp. 25-30.
Description	Randomised Controlled Trial
N=	n=221, Diltiazem =114, Placebo =107. Age =47yrs, course of HF =4.5 yrs, NYHA class I =7% II=25% III=38% IV=30%, LV ejection fraction = 35.5% China.
Intervention	Intervention of diltiazem 60mg /day Vs placebo in HF patients with dilated cardiomyopathy as defined by WHO
Outcomes	Various cardiac parameters and changes in NYHA Class, hospitalisation, and mortality all to 6 months. Also an assessment of all noted side effects was made
Results	<ul style="list-style-type: none"> • Heart function was significantly improved for patients receiving diltiazem Vs placebo with Cardiac thoracic ration falling from 0.59 to 0.56 (p<0.05) and LV end diastolic diameter and ejection fraction improving by 4.28 mm and 6.52% respectively (both p<0.01) • Clinical improvements in patients on diltiazem were indicated by a significant improvement in NYHA class with 57% of patients recorded as class I at the end of the trial compared to only 28% in the placebo group (p<0.01) • Repeated hospitalisation was reduced by diltiazem with only 10.5% of patients admitted compared to 41.1% in the placebo group (p<0.01) • All cause mortality was reduced in the diltiazem arm with 3.5% deaths Vs 11.2% (p<0.05) however the numbers are very small 4 and 12 cases respectively and the follow up period relatively short. • Side effects reported were limited to spermocrystal and ejaculation pain in one patient and short term drug rash in another
Comments	<p>Can only be seen as significant to dilated cardiomyopathy patients.</p> <p>When assessed as a subgroup there were only significant improvements in heart function in patients with less severe dilated cardiomyopathy (LV end diastolic diameter =70mm.</p> <p>Young cohort makes results hard to transfer</p> <p>Action may be due to prevention of calcium overload and cytotoxic damage to myocardial cells</p> <p>Lower dose than other studies at 60 mg/day could be due to low blood pressure in these patients or ethnic differences</p>

Paper	O'Connor, C. M., Carson, P. E., Miller, A. B., Pressler, M. L., Belkin, R. N., Neuberger, G. W., Frid, D. J., Cropp, A. B., Anderson, S., Wertheimer, J. H., & DeMets, D. L. 1998, "Effect of amlodipine on mode of death among patients with advanced heart failure in the PRAISE trial. Prospective Randomized Amlodipine Survival Evaluation", <i>American Journal of Cardiology</i> , vol. 82, pp. 881-887.
Description	Randomised Controlled Trial
N=	Total n =1153 Ischaemic heart disease n =732, amlodipine =362, placebo =370 Non-ischaemic cardiomyopathy n =421, amlodipine =209, placebo =212 Age =65 yrs, Male =76%, LV ejection fraction =0.21, NYHA III =81% NYHA IV =19%. USA
Intervention	With mortality as defined as non-cardiovascular or cardiovascular (sub-grouped to sudden, pump failure, MI, other cardiac event, or unobserved) outcome assessed to 36 months (ave 14.5 months). Each mortality case was presented to a blinded assessment committee with a majority vote deciding cause of death.
Outcomes	With mortality as defined as non-cardiovascular or cardiovascular (sub-grouped to sudden, pump failure, MI, other cardiac event, or unobserved) outcome assessed to 36 months (ave 14.5 months)
Results	<ul style="list-style-type: none"> • In the overall study population there was 33% mortality in the amlodipine group compared to 38% in the placebo group, not significant difference (p=0.07) • For patients with Ischaemic HF neither the cause nor frequency of death varied significantly between the two treatment groups with hazard ratios of 1.02 (0.81 - 1.29) for all mortality and 1.13 (0.79 – 1.60) for pump failure death • For patients with non-ischaemic aetiology there were marked benefits with amlodipine deaths at 21% Vs placebo group 35% HR 0.54 (0.37 – 0.79), and pump failure deaths were less frequent at 6% Vs 11% HR 0.43 (0.21 - 0.87), both p =0.01. • Overall patients within the trial with an ischaemic origin of HF had a higher overall mortality (40%) than those with a non-ischaemic basis for HF (28%)
Comments	An additional analysis of the effects of amlodipine Vs placebo on the mode of death in a previously reported trial (PRAISE trial ref ID 1412). The ratio of sudden death to pump failure death may be related to committee adjudication on outcomes rather than assessment by a sole investigator Given the lack of effect of amlodipine in ischaemic patients and marked effect in non-ischaemic stratum it is unlikely that amlodipine exhibits a long term negative inotropic properties
Reference	145

Paper	Packer, M., O'Connor, C. M., Ghali, J. K., Pressler, M. L., Carson, P. E., Belkin, R. N., Miller, A. B., Neuberger, G. W., Frid, D., Wertheimer, J. H., Cropp, A. B., & DeMets, D. L. 1996, "Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group", <i>New England Journal of Medicine</i> , vol. 335, no. 15, pp. 1107-1114.
Description	Randomised Controlled Trial
N=	Total n =1153 Ischaemic heart disease n =732, amlodipine =362, placebo =370 Non-ischaemic cardiomyopathy n =421, amlodipine =209, placebo =212 Age =65 yrs, Male =76%, LV ejection fraction =0.21, NYHA III =81% NYHA IV =19%. USA
Intervention	Amlodipine at 8.8 mg day Versus placebo in severe (NYHA IIIb-IV) heart failure, sub-grouped by aetiology
Outcomes	Primary endpoint a composite of all cause mortality and cardiovascular morbidity. With mortality as secondary outcome assessed to 36 months
Results	<ul style="list-style-type: none"> • In the overall study population there were 39% mortality or morbidity in Amlodipine group compared to 42% in the placebo group • A hazard ratio of 0.91 (95% CI 0.76 – 1.10) (p=0.31) • The mortality rate was also not significantly lower • Patients with ischaemic heart disease showed no benefit with amlodipine compared to placebo in mortality or combined with morbidity. • Patients with non-ischaemic dilated cardiomyopathy showed an reduced risk of mortality or morbidity on amlodipine HR 0.69 (0.49 – 0.98) (p=0.04) • There was also in improved survival in the amlodipine arm with HR for mortality at 0.46 (0.37 – 0.79) (p<0.001)
Comments	<p>Overall compliance at 90% by pill counts</p> <p>Significant findings of a marked difference in the efficacy in non-ischaemic stratum compared to little benefit in ischaemic patients</p> <p>Adverse reactions of pulmonary and peripheral oedema were significantly more common, 27 Vs 18% and 15 Vs 10% respectively (p<0.05 for both)</p> <p>There were fewer patients with uncontrolled hypertension in the amlodipine arm than with placebo</p> <p>Although not a primary endpoint the incidence of worsening heart failure was similar for both groups (42% Amlodipine Vs 41% placebo) and hospitalisation rates for worsening heart failure showed no significant differences</p>
Reference	147

Paper	van der Vring, J. A., Bernink, P. J., van der Wall, E. E., van Velhuisen, D. J., Braun, S., & Kobrin, I. 1996, "Evaluating the safety of mibefradil, a selective T-type calcium antagonist, in patients with chronic congestive heart failure", <i>Clinical Therapeutics</i> , vol. 18, pp. 1191-1206.
Description	Randomised Controlled Trial
N=	n=45, placebo =15 for 5x8days, mibefradil =30 (5x n=6 for 8 days each) Age =65yrs, Male =82%, LV ejection fraction ~27%, all class II-III USA, Netherlands and Israel
Intervention	Mibefradil at 6.25 to 100mg /day in stepwise progression Vs placebo in heart failure patients with NYHA II-III
Outcomes	Various outcomes measured. Primary endpoint was safety with total number of adverse events and number of patients reporting adverse events, as well as Changes in clinical status by NYHA group and cardiovascular function parameters of Ejection fraction, blood pressure, and heart rate
Results	<ul style="list-style-type: none"> • Adverse events showed higher percentage in mibefradil treated groups 23.3% Vs placebo group 13.3%, but no dose related effect on adverse events. Including Angina (10%) Dizziness (7%) headache (7%) • NYHA class was improved to class I in 16.7% of treatment group Vs none in placebo group (although there were more patients in Group II in the intervention arm 83% Vs 67%) • No clinically relevant changes were found in LV ejection fraction • No clinically relevant changes were seen in blood pressure • Only meaningful decreases in heart rate were noted in patients ascribed to the 50mg and 100mg dose regimes with a -8 and -7 beats a minute mean decrease
Comments	A short term oral dosing trial shown not to worsen clinical or cardiac variables
Reference	148

Paper	Walsh, J. T., Andrews, R., Curtis, S., Evans, A., & Cowley, A. J. 1997, "Effects of amlodipine in patients with chronic heart failure", <i>American Heart Journal</i> , vol. 134, pp. 872-878.
Description	Randomised controlled Trial
N=	n=32, amlodipine =16, placebo =16. Age =64yrs, Male =94%, Symptoms for 2.3 yrs (2.2 SD) UK
Intervention	Amlodipine 10gm daily for 8 weeks
Outcomes	Various cardiovascular determinants assessed and exercise capacity documented by treadmill and corridor walk tests
Results	<ul style="list-style-type: none"> • There were no significant differences between study arms with respect to treadmill and corridor walk exercise test. • There were no significant changes to central or regional haemodynamic from baseline between the groups
Comments	No significant benefits of felodipine treatment but some trend to improved blood flow in calves Largely surrogate outcomes Amlodipine does not significantly affect cardiac index, or stroke volume at rest or during exercise Safety not assessed.
Reference	149

Nesiritide

Paper	Burger, A. J., Elkayam, U., Neibaur, M. T., Haught, H., Ghali, J., Horton, D. P., & Aronson, D. 2001, "Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy", <i>American Journal of Cardiology</i> , vol. 88, no. 1, pp. 35-39.
Description	Randomised Controlled Trial
N=	n=261, nesiritide at 0.015 µg/kg/min =103, nesiritide 0.030 µg/kg/min =100, dobutamine =58 Age =65yrs, Male =68%, White =69%, Ischaemic HF origin =56%, NYHA class I =<1%, class II =8%, class III =53%, class IV =38% USA
Intervention	Doses of either 0.015 µg/kg/min or 0.030 µg/kg/min were given intravenously as a continuous treatment compared with IV dobutamine in decompensated HF patients
Outcomes	Primary endpoints were spontaneous tachycardia either non sustained or sustained, ventricular fibrillation , with no discrete QRS complexes, and cardiac arrest to a maximum of 7 days with mortality reported to 21 days
Results	<ul style="list-style-type: none"> • Ventricular arrhythmias occurred more frequently in patients treated with dobutamine with 17% tachycardia in the low dose nesiritide group 8% in the high dose group and 22% with dobutamine (p=0.032) but no significant difference between the two nesiritide groups. A significant effect was recorded at both the acute phase of treatment (to 48 hrs) and with prolonged exposure to 7 days • Hypokalaemia was reported at identical frequencies across the three groups, hypermagnesia in 3% of the low dose nesiritide group, 1% of the high dose group and none of the dobutamine group. • Bradycardia was not significantly more often reported in any of the groups • There was significantly greater symptomatic hypotension with nesiritide than dobutamine (p=0.061) • There appears to be no significant difference in the incidence of mortality among study groups to 21 days
Comments	<p>Same trial as reference ID 1198 but with different outcomes reported</p> <p>The greater baseline frequency of previous VT in the nesiritide group may have lead to an underestimation of effect on protecting from arrhythmias</p> <p>The inhibitory effect of natriuretic peptides on sympathetic activity may mitigate the proarrhythmic effects of sympathetic and neurohormonal activation in patients with decompensated HF</p> <p>Nesiritide administered in doses up to three times higher than current recommended dose</p> <p>Twenty patients (10% from the nesiritide group required a second vasoactive drug, and 7 patients (12%) in the dobutamine group required a second inotrope</p>
Reference	151

Paper	Young, J. B. 2002, "Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial", <i>Journal of the American Medical Association</i> no. 12, pp. 1531-1540.
Description	Randomised Controlled Trial
N=	n=489, for 3 hour double blind trial nitroglycerin =143, nesiritide = 204 , and placebo =142. For 48 hr open label trial nitroglycerin =216, nesiritide =273 Age =62yrs, Male =75%, NYHA class II =7%, class III =33% (?), class IV =42%, Ischaemic origin of HF =49% USA
Intervention	Either intravenous nitroglycerin at a level at physicians discretion, Vs intravenous nesiritide at 0.01 µg/kg/min for 211 patients and at up to 0.03 µg/kg/min for 62 patients
Outcomes	The primary end point was changes from baseline in pulmonary capillary wedge pressure (PCWP) at 3 hours, and patients evaluation of dyspnoea. Secondary outcomes included these same measures as well as global clinical status evaluation and safety profile to 24 hours. General adverse event were monitored to 14 days and mortality assessed to 6 months.
Results	<ul style="list-style-type: none"> • The reduction in PCWP was significantly greater in the nesiritide group than the nitroglycerin or placebo arms, at 3 hours the change from baseline was -5.8 mmHg, -3.8 mmHg, and -2.0 mmHg respectively, (p<0.001 for difference Vs placebo and p=0.03 for difference Vs nitroglycerin) • This difference was not explained by the higher proportion of patients in the nesiritide group who had the drug added to ongoing therapy with dobutamine or dopamine, with no significant difference seen when patients who were not on baseline dobutamine were analysed separately. • Nesiritide significantly reduced pulmonary vascular resistance at 3 hours compared to placebo but there was no significant difference compared to nitroglycerin • There were no differences in change to cardiac index among the 3 arm at 3 hrs. • Nesiritide was also associated with greater mean reduction in systolic and mean artery pressure than both nitroglycerin and placebo through to 3 hrs • The nesiritide group reported a significant improvement in dyspnoea score at 3 hrs compared to placebo (p=0.03), although the improvement was not significantly different to that seen with nitroglycerin • There were no significant differences between the study arms in changes to global clinical status scores • There were no significant differences in the rates of adverse events reported with 18% in the nesiritide group , 27% in the nitroglycerin arm and 14% on placebo. • There were no significant differences in the frequency of ischaemic events hypotension, or arrhythmias between the nesiritide and nitroglycerin group within the first 24 hours • There were no significant differences in the frequency of serious adverse event between the nesiritide and nitroglycerin arms up to 30 days <p>In terms of mortality to 6 months there were no significant differences between the two active agents</p>
Comments	The standard dose given of 0.01 µg/kg/minute was effective at improving haemodynamics and symptoms, but with less hypotension than has been reported with higher doses The trial suggests that nesiritide in addition to diuretics is a useful addition to initial therapy of hospitalised patients with acutely decompensated HF
Reference	152

Paper	Silver, M. A., Horton, D. P., Ghali, J. K., & Elkayam, U. 2002, "Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure", <i>Journal of the American College of Cardiology</i> , vol. 39, no. 5, pp. 798-803.
Description	Randomised Controlled Trial
N=	n=261, nesiritide at 0.015 µg/kg/min =103, nesiritide 0.030 µg/kg/min =100, dobutamine =58 Age =65yrs, Male =68%, White =69%, Ischaemic HF origin =56%, NYHA class I =<1%, class II =8%, class III =53%, class IV =38% USA
Intervention	Doses of either 0.015 µg/kg/min or 0.030 µg/kg/min were given intravenously as a continuous treatment compared with IV dobutamine in decompensated HF patients
Outcomes	Outcomes of duration of study drug to produce stabilisation, and overall hospital length of stay were recorded, and readmission (both all cause and HF cause) was monitored for 21 days, and finally 6 month mortality data was collected
Results	<ul style="list-style-type: none"> • Median duration of study drug was significantly shorter in the nesiritide groups than in patients taking dobutamine (by 25hrs in the 0.015 µg/kg/min group and by 39 hrs in the 0.030 µg/kg/min group (p<0.001 among all three test groups) • There was no significant difference in the overall length of stay among the study groups • There was a significant benefit with the lower dose nesiritide over dobutamine in the frequency of all cause readmission within 21 days with a 60% lower rate (p<0.005) although the significance did not hold for the higher dose nesiritide group, or for either group in terms of HF readmissions. • There was no significant difference in the rate of mortality at 6 months between nesiritide and dobutamine in a log rank analysis
Comments	Same trial as reference ID 876 but with different outcomes reported The dose of all therapies could be modified and a second parenteral vasoactive drug added or substituted for initial drug at the discretion of the attending physician, however nesiritide was discontinued if other vasodilator was added Nesiritide administered in doses up to three times higher than current recommended dose. No clear demonstration of added benefit of higher rather than lower dose nesiritide
Reference	150

Levosimendan

Paper	Follath, F., Cleland, J. G., Just, H., Papp, J. G., Scholz, H., Peuhkurinen, K., Harjola, V. P., Mitrovic, V., Abdalla, M., Sandell, E. P., & Lehtonen, L. 2002, "Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial", <i>Lancet</i> , vol. 360, no. 9328, pp. 196-202
Description	Randomised controlled trial
N=	n=203, levosimendan =103, dobutamine =100 Age =59yrs, Male =77%, Ischaemic origin of HF =47.5%, PCWP =24.5 mm Hg Europe
Intervention	An intervention of levosimendan given as an infusion of 24 µg/kg over 10 mins, followed by a continuous infusion of 0.1 µg/kg/min compared to a continuous infusion of 5 µg/kg/min of dobutamine (without loading dose) for a 24 hour period. If adequate response was not seen in 2 hours the infusion rate could be doubled
Outcomes	The primary endpoint was the proportion of patients who had a haemodynamic improvement at 24 hrs as defined by a 30% increase in cardiac output and a 25% decrease in pulmonary capillary wedge pressure. Also safety endpoints of adverse reactions and of blood and urine tests were assessed to 1 month. All cause mortality and hospitalisation were assessed at 31 days (blinded) and also retrospectively at 6 months
Results	<ul style="list-style-type: none"> • Performance at 24 hrs, HR 1.9 (95% CI 1.1 – 3.3) (p=0.022) with a similar effect in a per-protocol analysis. • A post hoc analysis for heterogeneity of effect size with or without concomitant B blocker use showed no significant effect on primary endpoint (p=0.46 for heterogeneity) • There were no significant differences between the groups in the improvement in symptoms of dyspnoea and fatigue. • Levosimendan appeared to have a beneficial effect over dobutamine in achieving a median score of more days alive and out of hospital in the first 180 days post infusion, with 157 days Vs 133 days (p=0.027) • Deaths within 31 days of infusion statistically fewer in the levosimendan group 8% compared to 17% on dobutamine HR 0.43 (0.18 – 1.00) (p=0.049), although this is a small event rate and a short period • Although there was a trend towards more frequent headache and migraine in the levosimendan group, this and the overall frequency of adverse events showed no statistically significant differences between the study arms.
Comments	The haemodynamic effects of levosimendan, unlike dobutamine were not attenuated by the concomitant use of B blockers Of patients in the levosimendan arm 93% are included in the analysis with full 24hr infusion, and 87% of the dobutamine arm completed the protocol, for those who did not receive the treatment or withdrew the lowest rank was assigned
Reference	154

Paper	Slawsky, M. T., Colucci, W. S., Gottlieb, S. S., Greenberg, B. H., Haeusslein, E., Hare, J., Hutchins, S., Leier, C. V., LeJemtel, T. H., Loh, E., Nicklas, J., Ogilby, D., Singh, B. N., & Smith, W. 2000, "Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators", <i>Circulation</i> , vol. 102, no. 18, pp. 2222-2227
Description	Randomised controlled trial
N=	n=146, Levosimendan =98, placebo =48 Age =57yrs, Male =82%, NYHA class III =66%, class IV =34%, LV ejection fraction =21% USA
Intervention	Levosimendan given as an bolus of a 6 µg/kg at hourly intervals with a continuous infusion of up to 0.4 µg/kg/min for 6 hours, was compared with a matching infused placebo
Outcomes	The primary endpoint was the proportion of patients with and increase in stroke volume or a decrease in PCWP of = 25% at 6 hours, with secondary endpoints were the change in these parameters from baseline and change in symptoms of dyspnoea or fatigue to the same time period
Results	<ul style="list-style-type: none"> • At 6 hours the stroke volume of the patients on levosimendan had increased by = 25% in 56% of patients compared to 4% of patients on placebo (p<0.001) • Levosimendan also produced a significant decrease in PCWP compared to placebo with 43% and 15% of patients respectively showing a = 25% decrease (p<0.001) • Dyspnoea was reported to have improved in 29% and worsened in 9% of patients given levosimendan compared to only 15% improvement and 17% worsening of those on placebo (p=0.037) as defined by patient reported symptoms. • There was no significant difference in the changes of symptoms of fatigue between the groups. • Adverse events were reported in 17% and 19% of the levosimendan and placebo groups respectively
Comments	Useful for short term treatment of patients with decompensated HF Stroke volume and pulmonary capillary wedge pressure were evaluated using a pulmonary artery catheter, symptoms of dyspnoea and fatigue were evaluated by the patient and the physician on a 6 point scale with no details of validation
Reference	155

Paper	Nieminen, M.S. et al (2000) Hemodynamics and Neurohumoral Effects of Continuous Infusion of Levosimendan in Patients With Congestive Heart Failure
Description	Randomised controlled trial
N=	n=151, Levosimendan 0.05 µg/kg/min =16, 0.1 µg/kg/min =23, 0.2 µg/kg/min =19, 0.4 µg/kg/min =23, 0.6 µg/kg/min =14, placebo =21, vehicle =15 Age ~62yrs, Male =87%, NYHA class III =97%, class IV =3%, LV ejection fraction =26% Europe
Intervention	Levosimendan was given as an infusion at a rate of either 0.05, 0.1, 0.2, 0.4, or 0.6 µg/kg/min after a loading dose 60 times this size given in 10 minutes, compared to a double blind placebo, and an open label vehicle or open label dobutamine
Outcomes	Various cardiac function and haemodynamic variables were measured over a period of 14 hours from the start of infusion, primary endpoints were a >15% increase in Stroke volume (SR), a >25% decrease in pulmonary capillary wedge pressure (PCWP) a rise in Blood pressure of >4 mmHg, a >40% increase in cardiac output (CO), a >50% decrease in PCWP requiring a reduction in the dose of study medication
Results	<ul style="list-style-type: none"> • As the vehicle showed no significant effect on any haemodynamic variables these patients were pooled with placebo in analysis • A clear dose response relationship was observed in response rates with all doses seeing significantly greater response rates than placebo (p=0.038 at lowest dose to p<0.005 for all other doses) • Levosimendan exerted a dose dependant effect of Cardiac output 0.4 to 1.6 L/min (depending on dose) change from baseline, Stroke volume -1.8 to 7.6 ml, and PCWP -3.8 to -7.1 mmHg (all p<0.001 for linear dose trend) • The decrease in PCWP tended to become larger with time. • There were some statistically significant changes in plasma atrial natriuretic peptide levels during the infusion of levosimendan but no significant effects in plasma epinephrine. • Overall 29% of patients treated with levosimendan experienced at least one adverse event during the study day compared with 20% of those who received a placebo • There were no clinically meaningful alterations in any laboratory safety parameters during the study day • Treatment response was significantly greater in patients with a baseline PCWP of more than 15mmHg than those with a lower baseline PCWP • There was no evidence that levosimendan exacerbated existing ischaemia.
Comments	The results of this study can only be of value to HF patients with Ischaemic origin of HF The study shows the optimum dosing regimen for levosimendan to be a bolus of 6-24 µg/kg delivered in 10 mins followed by infusion at 0.05 to 0.2 µg/kg/min
Reference	153

Others

Paper	Mulrow, C. D., Mulrow, J. P., Linn, W. D., Aguilar, C., & Ramirez, G. 1988, "Relative efficacy of vasodilator therapy in chronic congestive heart failure. Implications of randomized trials", <i>JAMA</i> , vol. 259, no. 23, pp. 3422-3426.
Description	Meta-analysis
N=	28 RCTs (3 with hydralazine) n=1976 for all trials For Hydralazine group the population was Age =61yrs, Male =73%, Ischaemic origin =60%, and all NYHA Class III-IV
Intervention	Individual trial data for each vasodilator class not stated
Outcomes	All cause mortality, and functional status are examined, with regression analysis including patient subgroup variables
Results	<ul style="list-style-type: none"> • Separate analysis of ACEi, Nitrates, Hydralazine, and A antagonists, with an overall pooled effect • The overall effect of hydralazine on mortality showed a non significant benefit, with the pooled OR compared to placebo of 0.94 (95% CI 0.35 – 2.56) • Hydralazine was the only agent that did not improve functional outcomes OR for improved function over placebo 2.18 (95% CI 0.94 – 4.89)
Comments	<ul style="list-style-type: none"> • The results pertaining to hydralazine therapy are only directly applicable to those of the HF population with moderate to severe functional limitation
Studies included	Papers included: Not explicitly stated.

Paper	DiBianco, R., Parker, J. O., Chakko, S., Tanser, P. H., Emmanuel, G., Singh, J. B., & Marlon, A. 1991, "Doxazosin for the treatment of chronic congestive heart failure: results of a randomized double-blind and placebo-controlled study", <i>American Heart Journal</i> , vol. 121, pp. 372-380.
Description	Randomised Controlled Trial
N=	n=73, doxazosin =36, placebo =37 Age =60yrs, Male =89%, LV ejection fraction =27%. Ischaemic heart disease =55% USA
Intervention	Doxazosin at a range of doses 16mg, 8mg, 4mg, 2mg, 1mg per day depending on maximum tolerated was compared with matching placebo for 12 weeks
Outcomes	A range of clinical and cardiac function outcomes, as well as QOL and adverse events are studied to 12 weeks
Results	<ul style="list-style-type: none"> • Clinical deterioration (progressive heart failure leading to hospitalisation, MI, or death) was recorded in 8 patients (22%) and none on doxazosin (p<0.004) • The investigators global evaluation of status showed less deterioration with doxazosin 3.2% compared with placebo 20.7% (p<0.05), although patient ratings showed no significance • There were no significant changes in the values of LV ejection fraction, cardiothoracic ratio, or treadmill tolerance time between the study arms • The distances patients recorded with pedometer recording were increased with doxazosin +1.8% while they decreased on placebo -0.5% (p<0.04) • Discontinuation of therapy due to side effects and laboratory changes in blood and urine analysis showed no significant differences between the groups
Comments	Doxazosin was well tolerated producing no major and few minor side effects

Paper	Dorszewski, A., Gohmann, E., Dorszewski, B., Werner, G. S., Kreuzer, H., & Figulla, H. R. 1997, "Vasodilation by urapidil in the treatment of chronic congestive heart failure in addition to angiotensin-converting enzyme inhibitors is not beneficial: results of a placebo-controlled, double-blind study", <i>Journal of Cardiac Failure</i> , vol. 3, pp. 91-96.
Description	Randomised Controlled Trial
N=	n=36, Urapidil =18, placebo =18 Age =55.5yrs, Male =92%, Coronary Artery Disease =31%, NYHA class III =89%, Class IV =11% Germany
Intervention	Urapidil at 60-120mg/day Vs matching placebo given after a run in for 12 weeks consecutively
Outcomes	Various outcomes are evaluated including changes to LV ejection fraction, QOL, and exercise endurance, and mortality monitored for safety only
Results	<ul style="list-style-type: none"> • From the first 36 patients entered the risk of mortality with urapidil as compared to placebo was OR 4.92 (95% CI 0.49 – 49.6) (p=NS) • There was no significant effect of urapidil on outcome compared with placebo in outcomes of blood pressure, haemodynamic parameters, and exercise function. • A marginal beneficial effect of urapidil was seen in QOL score on the Minnesota scale (adjusted 0 - 5) with a 0.5 point improvement compared to no change with placebo (p=0.02) although this benefit only brings patients inline with the placebo baseline value
Comments	Trial curtailed due to increased trend for mortality without beneficial cardiac outcomes The blockade of alpha receptors , in general is not of use in the chronic treatment of congestive heart failure

Paper	Hampton, J. R., van Veldhuisen, D. J., Kleber, F. X., Cowley, A. J., Ardia, A., Block, P., Cortina, A., Cserhalmi, L., Follath, F., Jensen, G., Kayanakis, J., Lie, K. I., Mancica, G., & Skene, A. M. 1997, "Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. ", <i>Lancet</i> , vol. 349, pp. 971-977.
Description	Randomised Controlled Trial
N=	n=1906, ibopamine =953, placebo =953 Age =65yrs, Male =80%, LV ejection fraction =26%, Ischaemic HF origin =59% 192 centres participated from 13 European countries
Intervention	300mg/day of ibopamine was given orally to NYHA class III-IV HF patients compared to placebo
Outcomes	Outcome assessments included limitation of activities using NYHA scale (with additional intervals), clinical assessment of symptoms, QOL scale, concomitant medication, hospitalisation, and mortality all to minimum 6 months, mean 355 days
Results	<ul style="list-style-type: none"> • During the study there was an increased risk of mortality in the ibopamine group 24.3% Vs 20.3% for placebo (p=0.017), with a RR of mortality 1.26 (95% CI 1.04 – 1.53) • There was no significant difference between the groups in cause of death, hospitalisation, patients nor physicians rating of symptoms, NYHA class, or QOL score • The only independent predictor of mortality in regression analysis was use of an antiarrhythmic drug at baseline
Comments	<p>Mortality rates were higher in patients withdrawn from treatment</p> <p>Nottingham scale was used for QOL outcomes but is not validated for HF patients</p> <p>In post hoc subgroup analysis patients in NYHA class III/IV or IV had a worse mortality rate than those in lower groups with ibopamine RR 1.49 (1.14 – 1.92)</p> <p>There is no known interaction between ibopamine and amiodarone or other antiarrhythmic agents, and is not itself thought to be proarrhythmic</p>
Reference	134

Paper	Massie, B. M., Berk, M. R., Brozena, S. C., Elkayam, U., Plehn, J. F., Kukin, M. L., Packer, M., Murphy, B. E., Neuberger, G. W., & Steingart, R. M. 1993, "Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Results of the flosequinan-ACE inhibitor trial (FACET)", <i>Circulation</i> , vol. 88, pp. 492-501.
Description	Randomised Controlled Trial
N=	n=322, 100mg/day flosequinan (F100) =110, 150 mg/day flosequinan (F150) =102, placebo =110 Age =58yrs, Male =71%, Ischaemic HF origin =41%, NYHA class II =53%, class III =44%, class IIV =3% USA
Intervention	The addition of either 100 or 150 mg/day of flosequinan to standard therapy was compared to addition of placebo for 16 weeks in HF patients with LV ejection fraction <35%
Outcomes	Various clinical, cardiac, and QOL outcomes, as well as exercise capacity were assessed every 4 weeks to 16 weeks
Results	<ul style="list-style-type: none"> • There was a significant increase in exercise capacity time in the F100 group +64 secs Vs +5 secs with placebo (p<0.05) but no difference with F150 group • Improvements in QOL on Minnesota scale were seen at nearly all time points for F100 intervention groups Vs placebo (p<0.05) • There was no significant improvements in the patient and physician assessment of improved status with flosequinan, nor was there an improvement in NYHA class • There was no significant advantage of either flosequinan regime in frequency of death or hospitalisation for HF. • Patient withdrawals from study due to adverse events was the same among the three treatment groups
Comments	33 participating centres in USA Flosequinan provides significant additional symptomatic benefit Unusually the higher 150mg/day dose did not have the same benefits as the 100mg/day regime A reduction of therapy to mitigate side effects was required in 30% of patients The benefit of flosequinan must be assessed on a case to case basis, with lower dosages considered.

Paper	Packer, M., Narahara, K. A., Elkayam, U., Sullivan, J. M., Pearle, D. L., Massie, B. M., & Creager, M. A. 1993, "Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. Principal Investigators of the REFLECT Study", <i>Journal of the American College of Cardiology</i> , vol. 22, pp. 65-72.
Description	Randomised Controlled Trial
N=	n=193, flosequinan =93, placebo =100 Age =58yrs, Male =87%, Ischaemic origin of HF =44%, LV ejection fraction =26% USA / Canada
Intervention	Flosequinan at 100mg per day was compared to placebo continuously for 3 months
Outcomes	Multiple outcomes included clinical assessment of HF symptoms, cardiac size and function, and blood analysis, and changes to exercise capacity from baseline, at every 2 and 4 weeks depending on test up to 3 months
Results	<ul style="list-style-type: none"> • At 12 weeks exercise tolerance had increased significantly with flosequinan 96 secs Vs 47secs increase with placebo (p=0.022) • 55% of patients who were receiving flosequinan but only 36% of those on placebo benefited from treatment in terms of clinical status at 3 months • There was no significant differences between groups in terms of changes in NYHA class, cardiothoracic ratio, and LV ejection fraction • The only significant change in blood analysis was a decrease in serum bilirium level in the flosequinan group (p=0.03) • The only adverse event that showed a significant difference between the study arms was headaches reported in 22% of flosequinan patients Vs 9% of placebo group (p=0.04)
Comments	The results are applicable to most HF patients except those with a primary valvular or pericardial disorder, or renal and hepatic disease Flosequinan was not associated with side effects of proarrhythmia, and fluid retention that have limited the use of similar drugs in HF Flosequinan is primarily a vasodilator but exerts positive inotropic effects An effective and well tolerated drug for the management of patients with symptomatic HF despite the use of digoxin and diuretics
Reference	136

Paper	Parker, J. O. 1993, "The effects of oral ibopamine in patients with mild heart failure--a double blind placebo controlled comparison to furosemide. The Ibopamine Study Group", <i>International Journal of Cardiology</i> , vol. 40, pp. 221-227.
Description	Randomised Controlled Trial
N=	n=130, Ibopamine =54, Furosemide =53, placebo =23 (for double blinded assessment after run in period) Age ~58yrs, Male =81%, NYHA class I =48%, class II =52% USA / Canada
Intervention	400mg/day ibopamine and 40mg furosemide are compared to matching placebo in an 8 week intervention
Outcomes	The primary endpoint was stated as being changes in maximum exercise time as tested by a modified Naughton protocol on treadmill. Secondary outcomes include symptom assessment, resting electrocardiogram, blood chemistry and haematology, as well as QOL assessment at various points to 8 weeks
Results	<ul style="list-style-type: none"> • At the end of the 8 week evaluation period both ipobamine and furosemide had been shown to significantly increase exercise over compared to placebo with a 1.3 min and 1.1 min increase over baseline compared to a 0.3 min increase with placebo (p=0.020, and 0.033 respectively) • There were no significant changes for either treatment compared with placebo in the severity of HF on NYHA scale, QOL on four indices, and biochemical parameters. • There were only 14 adverse events reported on placebo, compared with 42 on ipobamine and 27 on furoseminde, with headaches occurring most frequently.
Comments	Results of this study can only be seen to be relevant to patients with mild HF Ibopamine was well tolerated causing infrequent adverse clinical events There was no significant improvement (although a trend) in exercise capacity with ipobamine at 2 weeks
Reference	137

Paper	Waldo, A. L., Camm, A. J., DeRuyter, H., Friedman, P. L., MacNeil, D. J., Pauls, J. F., Pitt, B., Pratt, C. M., Schwartz, P. J., Veltri, E. P., Cagide, A., Elizari, M. V., Gimeno, G., Aroney, G., Aylward, P., Calvert, A., Campbell, T., Davis, M., Fletcher, P., & et, a. 1996, "Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction", <i>Lancet</i> , vol. 348, pp. 7-12.
Description	Randomised controlled trial
N=	n=3121, d-sotalol =1549, placebo =1572, before trial curtailed Age =60yrs, Male =86%, LV ejection fraction =31%, NYHA class II =72%, Class III =21% International study
Intervention	d-sotalol at up to 400mg/day if tolerated was given as continuous treatment compared to placebo in post MI patients with LV ejection fraction >40%
Outcomes	Primary outcome was all cause mortality, secondary analysis on cardiac mortality. Other outcomes were cardiovascular mortality, arrhythmic events and cardiovascular admission to mean 148 days
Results	<ul style="list-style-type: none"> • On termination of the trial the mortality rate was higher in the d-sotalol patients 5.0% than with placebo 3.1%, giving a relative risk of mortality 1.65 (95% CI 1.15 – 2.36) (p=0.006) • Similar risks were found in cardiac and arrhythmic assumed mortality RR 1.65 (1.14 – 2.39) and RR 1.77 (1.15 –2.74) respectively, both (p=0.008) • There was no significant difference in the rates of non-fatal cardiac events between the groups • All subgroups (Age, sex, time from MI, LV ejection fraction, and concomitant therapies) showed similar increased risk with d-sotalol, although the effect was more pronounced in higher LV ejection fraction stratum (31-40%) and in women (although few included in trial)
Comments	<p>The results of the study will only be relevant to patients with mild to moderate HF following a MI NYHA Class IV, and unstable angina patients excluded Concomitant treatment with diuretics, digoxin, B blocker, calcium channel blocker, or ACEi was allowed and subgroup analysis used to monitor this Lack of protective effect of d-sotalol possibly due to potential prolongation being lost when sympathetic activity increases These finding should not be extrapolated to other potassium channel blockers which have additional antiarrhythmic effects</p>
Reference	156

Paper	Califf, R. M., Adams, K. F., McKenna, W. J., Gheorghade, M., Uretsky, B. F., McNulty, S. E., Darius, H., Schulman, K., Zannad, F., Handberg, T. E., Harrell, F. E., Jr., Wheeler, W., Soler, S. J., & Swedberg, K. 1997, "A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST)", <i>American Heart Journal</i> , vol. 134, pp. 44-54.
Description	Randomised Controlled Trial
N=	n=471, epoprostenol =237, conventional treatment =234 Age =65yrs, Male =76%, Ischaemic origin of HF =67.5%, LV ejection fraction =17.5%, NYHA class III =41%, class IV =59% International
Intervention	Intervention with a median dose of 4ng/kg/min of epoprostenol by infusion Vs normal treatment as a continual therapy in patients with NYHA class III-IV HF and LV ejection fraction <30%.
Outcomes	Cardiac events and side effects were assessed at fortnightly then monthly visits, and 6 minute walk test and QOL tests assessed at these times and then 3 monthly.
Results	<ul style="list-style-type: none"> • No significant differences were seen in any of the end points other than death (exercise duration, dyspnoea score, QOL scores on 4 scales). • Survival curves for mortality at termination of trial showed a detrimental effect of epoprostenol at p=0.055) with event rates of 48% and 37% at 6 months noted. • Subgroup analysis identified patients with ischaemic cause of HF, those recruited outside North America, and those with better LV ejection fraction (>20%) to have a greater detrimental trend • Infusion with epoprostenol lead to increased mortality with no evidence of improved QOL.
Comments	The results are only applicable to the most severe HF population who have not responded to conventional treatment. Trial terminated due to excess mortality in epoprostenol arm. Less than 20% of patients in active arm had to withdraw due to adverse events, most commonly hypotension and nausea. As with other vasodilators short term QOL benefit might be achieved but at the price of increased mortality.
Reference	158

Paper	Sueta, C. A., Gheorghiade, M., Adams, K. F. J., Bourge, R. C., Murali, S., Uretsky, B. F., Pritzker, M. R., McGoon, M. D., Butman, S. M., Grossman, S. H., Crow, J. W., Shaffer, C. L., & Thorn, M. D. 1995, "Safety and efficacy of epoprostenol in patients with severe congestive heart failure", <i>American Journal of Cardiology</i> , vol. 75, pp. 34A-43A.
Description	Randomised Controlled Trial
N=	n=33, epoprostenol =16, standard therapy =17 Age =57yrs, Male =88%, Ischaemic origin of HF =61%, NYHA class III =36%, class IV =64% USA
Intervention	A mean dose of 7.7ng/kg/min was continuously infused through a permanent indwelling central venous catheter Vs normal therapy for 12 weeks.
Outcomes	Outcomes studied included changes to haemodynamic parameters, and exercise performance (96 minute walk test), as well as NYHA class, and LV ejection fraction all to 12 weeks. Also adverse events were recorded. Poor study design and high drop out rates makes all outcomes difficult to assess.
Results	<ul style="list-style-type: none"> • There was a significant improvement in the distance walked in 6 minutes amongst patients on epoprostenol compared to conventional treatment with a 72m improvement Vs 39m worsening (p=0.033) by carry forward technique. • There were no significant differences in LV ejection fraction, or NYHA class between the groups compared to baseline. • In terms of haemodynamics there were no significant differences in changes over baseline between the groups in heart rate, blood pressure, cardiac index, or pulmonary capillary wedge pressure. • Adverse reactions led to withdrawal of 3 patients in the epoprostenol arm due to hypotension and syncope (1) infectious episode (1) and hypotension complicated by angina and ventricular fibrillation (1). • While no patient withdrew from the standard therapy. • Other events of flushing (1) nausea and vomiting (3) diarrhoea (1) and headache (4) were resolved after reduction of epoprostenol therapy. • Possible that long-term therapy with epoprostenol could worsen neuro-hormonal activation.
Comments	The results of this study can only be related to patients with severe heart failure without aortic or mitral valve stenosis, restrictive cardiomyopathy, uncorrected thyroid disease, or active myocarditis. Therapy requires use of a complicated delivery system, although few patients struggled with this and there were no home based infections. Most patients had persistent symptoms despite conventional therapies. Increased cardiac output was not maintained during long term therapy. Ongoing long term events will be considered in FIRST trial.
Reference	157

Paper	Ceremuzynski, L., Gebalska, J., Wolk, R., & Makowska, E. 2000, "Hypomagnesemia in heart failure with ventricular arrhythmias. Beneficial effects of magnesium supplementation", <i>Journal of Internal Medicine</i> , vol. 247, no. 1, pp. 78-86.
Description	Randomised Controlled Trial
N=	n=36, Magnesium sulphate (MS) =24, placebo =12 LV ejection fraction =30%, NYHA class II =42%, class III =50%, class IV = 8% Poland
Intervention	An intervention with 8g magnesium dissolved in 250ml of 5% glucose, i.v. infused over 12 hours, Vs placebo of plain 250ml of 5% glucose in HF patients with persisting LV arrhythmias despite best care.
Outcomes	Biochemical measurements of serum magnesium levels and a 24 Holter reading were taken at 1 day, with ventricular ectopic beats (VEBs) averaged per hour, and non sustained ventricular tachycardia (nsVT) described as three or more consecutive VEBs with heart rate >100 BPM for less than 30 secs.
Results	<ul style="list-style-type: none"> • Appears to be superior to pharmacological antiarrhythmic interventions and devoid of side effects. • Potentially bodyweight and duration of disease and diuretic treatment need to be considered for optimum doses. • There were significant reductions in the incidence of VEBs, couplets of these and nsVT in the MS arm versus baseline (p=0.0001, 0.003, and 0.01 respectively, whilst there was no significant differences over baseline with placebo. • No comparison between groups is given. • Of patients who improved in terms of LV regularity in MS arm their serum magnesium increased from 0.71 mmol/l at baseline to 0.84 mmol/l (p=0.01)
Comments	Only patients in sinus rhythm that continue to display complex arrhythmias despite diuretic, ACEi and digoxin therapy, and magnesium sub-carbonate if serum levels were low can be seen to benefit from this therapy. Appears to be superior to pharmacological antiarrhythmic interventions and devoid of side effects.

Paper	Keith, M. E., Jeejeebhoy, K. N., Langer, A., Kurian, R., Barr, A., O'Kelly, B., & Sole, M. J. 2001, "A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure", <i>American Journal of Clinical Nutrition</i> , vol. 73, no. 2, pp. 219-224.
Description	Randomised Controlled Trial
N=	n=56, Vitamin E =26, placebo =30 Age =67 yrs, Male =78%, LV ejection fraction =23%, NYHA class III =86%, class IV =12% Canada
Intervention	Identical gel capsules with either 335.6mg of RRR- α tocopherol or placebo for a 12 week course.
Outcomes	Biochemical measurements of liver and kidney function were taken by blood samples, as was natriuretic peptide ANP, and plasma vitamin e levels, as well as human tumour necrosis factor also were evaluated. In addition breath samples were examined for pentane and ethane, and QOL assessed with the Minnesota living with heart failure questionnaire, all to 12 weeks. Mostly proxy outcomes.
Results	<ul style="list-style-type: none"> • Vitamin supplementation alone did not influence indexes of oxidative stress, surrogate markers of function and prognosis, or QOL. • There were no significant reduction in the markers of oxidative stress when on vitamin E compared with placebo, and concentrations of ANP neuro-hormonal and cytokine markers of prognosis were not changed with vitamin E. • There were no significant changes in QOL scores in either group with the treatment group improving from 35 to 36 points and the placebo group worsening from 40 to 41 points. • There were few significant adverse effect reported, with only some reports of an oily taste with vitamin E but this was not significant.
Comments	The results of the trial are likely to be generally applicable to most HF patients with moderate to severe HF (NYHA classes III-IV). HF patients with advanced disease may be beyond the point at which vitamin therapy may benefit
Reference	159

Paper	Miric, M., Miskovic, A., Vasiljevic, J. D., Keserovic, N., & Pesic, M. 1995, "Interferon and thymic hormones in the therapy of human myocarditis and idiopathic dilated cardiomyopathy", <i>European Heart Journal</i> , vol. 16, no. Suppl O, pp. 150-152.
Description	Randomised Controlled Trial
N=	n=40, IFN =14, thymomodulin =13, conventional treatment =13 Age =26.6, Male ~60%, NYHA class II =8%, class III =70%, class IV =22%. Serbia/Germany
Intervention	There were two intervention arms of purified leukocytic IFN- α at 3 million U per meter square of body surface area 3 times a week subcutaneously, or 10 mg Thymus-TFX thymomodulin 3 times a week intravenously, Vs normal care
Outcomes	A clinical evaluation, echocardiograph, chest X-ray and Holter monitoring were undertaken at 6 months, 1 year, and 2 years with rest and exercise ventriculography also undertaken at 2 years. Small numbers of patients in each arm and lack of blinding makes outcomes questionable. Mostly proxy outcomes.
Results	<ul style="list-style-type: none"> • At 6 months LV ejection fraction had improved in 77% of patients on IFN or thymomodulin and only 46% of patients on conventional treatment ($p < 0.001$), and this was further improved at 2 years. • Maximum exercise time at 2 years was 5.2 mins with IFN, 5 mins with thymomodulin and 3.3 mins with conventional treatment ($p < 0.01$ for active over control with corrected multiple test). • At 2 years 70% of the patients in the active treatment arms and 30% of the conventionally treated patients showed improvement in their functional class. • 12 of 14 patients (86%) in the IFN arm reported a flu-like syndrome a few hours after administration. • 4 of 13 patients (31%) treated with thymomodulin experienced a slight but reversible increase in body weight.
Comments	Only a small fraction of the HF population can be seen to be successfully treated with the intervention in question as only biopsy proven cases of idiopathic myocarditis and dilated cardiomyopathy were included, with familial cardiomyopathy and all forms of secondary myocarditis excluded 3 patients included were less than 15 years old.

Paper	Osterziel, K. J., Strohm, O., Schuler, J., Friedrich, M., Hanlein, D., Willenbrock, R., Anker, S. D., Poole-Wilson, P. A., Ranke, M. B., & Dietz, R. 1998, "Randomised, double-blind, placebo-controlled trial of human recombinant growth hormone in patients with chronic heart failure due to dilated cardiomyopathy", <i>Lancet</i> , vol. 351, pp. 1233-1237.
Description	Randomised Controlled Trial
N=	n=50, rhGH =25, placebo =25 Age =54yrs, Male =86%, LV ejection fraction =26%, NYHA class II =58%, class III =26% Germany
Intervention	A dose of 2 IU of rhGH was given by subcutaneous injection each day compared with placebo
Outcomes	A follow up of 96days mean was undertaken in blood pressure by automatic sphygmomanometer, cardiac dimensions by MRI, Clinical status by NYHA class assessment, exercise performance by walking test, and haemodynamic variables were all assessed. Side effects were also recorded. Wide range of outcomes studied with no a priori hypothesis suggest data dredging. The Age dependant activity of the intervention may have had a bearing on the limited positive outcomes.
Results	<ul style="list-style-type: none"> • Although treatment improved LV myocardial mass this didn't relate to a clinical benefit. • The short treatment and assessment times may not have allowed the benefits of rhGH therapy to come to fruition. • There were no significant differences in weight, NYHA class, or walking test differences between the study arms. • rhGH treatment did not significantly change any haemodynamic variables nor plasma concentrations of epinephrine or norepinephrine. • The rhGH group did see an increase in LV mass +25g Vs -2.1g on placebo (p<0.001), and there was a significant relationship of this with serum IGF-I by regression analysis (r=0.55, p=0.0001) • Adverse event rates appear to be similar in both arms with 1 patient in the rhGH arm reporting joint pain.
Comments	Only HF patients with dilated cardiomyopathy can be related to outcomes of this study.
Reference	160

Paper	Rizos, I. 2000, "Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration", <i>American Heart Journal</i> , vol. 139, no. 2 Pt 3, p. S120-S123.
Description	Randomised Controlled Trial
N=	n=80, L-carnitine =42, placebo / no treatment =38 Age =49yrs, Male =49%, LV ejection fraction =28%, NYHA class III =74%, class IV =26% Greece.
Intervention	Oral L-carnitine at 2g/day was compared to placebo for three months blind, then continuous open label therapy Vs no treatment.
Outcomes	Primary endpoint was all cause mortality at 3 years, with various haemodynamic measurements and exercise performance tested at 1, 3, 6, 12, 24 months, with only 3 month results reported here.
Results	<ul style="list-style-type: none"> • A mean follow up period of 33.7 months showed that there was a significant improvement in survival for patients on L-carnitine ($p < 0.04$) with 3 year mortality rates of 3% with L-carnitine and 18% with placebo / no treatment. • At 3 months there were statistically significant differences in terms of exercise performance with the Weber classification, maximal exercise time, and peak oxygen consumption, arterial and pulmonary blood pressure and cardiac output. • 3 (7%) of the patients on L-carnitine reported minor gastrointestinal problems but were not withdrawn
Comments	These results clearly can only be related to patients with dilated cardiomyopathy with moderate to severe HF.
Reference	161

Paper	The investigators of the study on propionyl-L-carnitine in chronic heart failure 1999, "Study on propionyl-L-carnitine in chronic heart failure", <i>European Heart Journal</i> , vol. 20, pp. 70-76
Description	Randomised Controlled Trial
N=	n=537, PLC =271, placebo =266 Age =60.5 yrs, Male =86%, LV ejection fraction =28%, NYHA class II =74%, class III =26% Europe
Intervention	An intervention of 2mg / day of propionyl-L-Cartinine (PLC) for 6 months (orally) Vs matching placebo
Outcomes	The primary end point was change in exercise time over baseline, and also QOL score and negative outcomes, as well as safety and adverse events all at interim times and at 6 months (data quoted).
Results	<ul style="list-style-type: none"> • There were no significant differences observed between treatment groups for maximum exercise duration 10 Vs 3 Secs increase (p=0.657). • There were no significant differences observed between groups for any of the other efficacy variables (QOL. 6 minute walk). • The occurrence of adverse events was similarly high in either group with at least one adverse event in 98% of the PLC arm and 97% of the placebo arm. • Post Hoc subgroup analysis based on LV ejection fraction showed those in >30% and =40% have a 40 secs increase on PLC compared to placebo (p=0.01) while the =30% group having only a 23 secs increase (p=0.06).
Comments	<p>The majority of HF patients can be seen to be relevant to the outcomes of the study, given the wide range of aetiologies included and the inclusion of mild to moderate HF patients.</p> <p>Secondary efficacy variables were assessed on completers only except for safety and adverse events.</p> <p>Last observation carry forward was used where possible otherwise the lowest value obtained from the whole study population was used.</p> <p>The expected improvement of peripheral muscle function and metabolism was tested by exercise duration as the simplest and most sensitive measure.</p> <p>The subgroup of LV ejection fraction =30% may have scored lower due to greater fatalities of hospitalisation leading to lower values in ITT.</p>

Paper	Skudicky, D., Bergemann, A., Sliwa, K., Candy, G., & Sareli, P. 1927, "Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study", <i>Circulation</i> , vol. 103, no. 8, pp. 1083-1088.
Description	Randomised Controlled Trial
N=	n= 39, pentoxifylline =20, placebo =19 Age =49Yrs, Male ~ 67%, LV ejection fraction =23.5%, NYHA class II =82%, class III =18%. South Africa
Intervention	A treatment with pentoxifylline at 1200 a day (oral) was tested for 6 months Vs placebo
Outcomes	Exercise performance, NYHA class, blood plasma assessment, and various LV dimension and cardiac function evaluations were made all at 6 months. Lack of precision with analysis of drop outs makes subsequent assessment of outcomes difficult
Results	<ul style="list-style-type: none"> • There was a positive effect of pentoxifylline on clinical status with 66.6% improving NYHA class, 16.6% remaining unchanged and 16.6 % deteriorating, compared to 10%, 53%, and 37% in the placebo group respectively (p=0.01). • There was a non significant trend towards a improvement in exercise performance with pentoxifylline (p=0.1). • There was a significant improvement in LV ejection fraction from baseline with pentoxifylline compared with placebo 7.8% Vs 0.9% (p=0.04%). • There was a marginally significant decrease in plasma Fas/APO-1 levels -3.2U/mL, versus 0.34 U/mL with placebo (p=0.05), but not with TNF-α concentration. • The inability of pentoxifylline to reduce circulating TNF- α does not exclude the possibility that it may not be operating through suppression of myocardial TNF- α. • The inability of pentoxifylline to reduce circulating TNF- α does not exclude the possibility that it may not be operating through suppression of myocardial TNF- α.
Comments	The study results are only applicable to HF patients with idiopathic dilated cardiomyopathy.
Reference	162

Paper	Wojnicz, R., Nowalany-Kozielska, E., Wojciechowska, C., Glanowska, G., Wilczewski, P., Niklewski, T., Zembala, M., Polonski, L., Rozek, M. M., & Wodniecki, J. 2003, "Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy: two-year follow-up results.", <i>Circulation</i> , vol. 104, no. 1, pp. 39-45.
Description	Randomised Controlled Trial
N=	n=84, IT group =41, placebo =43 Age =40 yrs, Male =82%, LV ejection fraction =24%, atrial fibrillation =13% Poland
Intervention	Immunosuppressive therapy (IT) trailed was Prednisone at 0.2 mg/kg/day and azathioprine at 1 mg/kg/day as continuous treatment for 100 days Vs placebo.
Outcomes	Out comes measured at up to 2 years included the primary composite endpoint of Cardiac death, heart transplantation, or readmission. With other endpoints being changes in LV dimensions and function, and clinical status by NYHA score.
Results	<ul style="list-style-type: none"> • The IT group and placebo groups did not differ significantly in primary composite end point of cardiac death / transplant / hospitalisation with 22.8% Vs 20.5% respectively. • There was a significant improvement in LV ejection fraction with IT Vs placebo from 3 months all the way to 2 years at which improvement was 20.1 % compared to 6% on placebo (p<0.001). • There was a non significant trend towards benefit of IT with respect to changes in NYHA class (p=0.097) at 3 months but at 2 years there was a improvement in median value in the IT group from III to I, and only from III to II in placebo arm (p=0.005). • Of the adverse drug effects reported increased body weight >5kg due to steroid treatment was reported in 34% of patients, and 4.9% developed hypertension. • As a comparison to the non randomised population without inflammatory cardiomyopathy with 34% improvement at 2 years compared to 30% in the placebo arm of the trial, it is possible that in these patients there was not true ongoing myocarditis nut merely transient auto immunity.
Comments	The patients included in the study are notably younger than the average HF population, and any outcomes of the study can only be related to the sub group of patients with dilated cardiomyopathy of inflammatory origin. Invasive procedure required to assess up-regulation of HLA, limits clinical relevance.
Reference	163

Paper	Lewis, B. S., Rabinowitz, B., Schlesinger, Z., Caspi, A., Markiewicz, W., Rosenfeld, T., Sclarovsky, S., & Ermer, W. 1999, "Effect of isosorbide-5-mononitrate on exercise performance and clinical status in patients with congestive heart failure. Results of the Nitrates in Congestive Heart Failure (NICE) Study", <i>Cardiology</i> , vol. 91, no. 1, pp. 1-7.
Description	Randomised Controlled Trial
N=	n=136, ISMN =67, placebo =69 Incomplete details of demographics given but age =57yrs, and all had coronary artery disease by inclusion criteria Israel
Intervention	50 mg/day of long-acting isosorbide-5-mononitrate was given Vs placebo for 24 weeks in patients with mild to moderate HF
Outcomes	A range of outcome measures were studied primarily changes in exercise performance, with LV function, QOL and neurohormonal profile studies at both 12 and 24 weeks. In addition total adverse events were reported at 24 weeks
Results	<ul style="list-style-type: none"> • Total treadmill time with ISMN Vs placebo was significantly improved at 12 weeks (p=0.087) but not 24 weeks (p=0.32), until correction for baseline exercise time, ejection fraction and study centre were adjusted for. • In pre-specified subgroup of patients with higher LV ejection fraction (31-40%) Vs (20-30%) there was increased benefit on exercise time but still not significant with baseline characteristics • There were no significant changes in HF functional class between treatment arms (p=0.66), QOL, LV ejection fraction, or plasma NE or ANP levels. • Serious side effects were equally common in both ISMN and placebo groups 7 and 8 events respectively • Other adverse events occurred at similar rates in total, however there was a significant increase in the frequency of headache in the ISMN group 19% Vs 0% (p=0.0001)
Comments	<p>QOL assessment used a self rating questionnaire with a visual analogue scale with no details of validation 116/136 patients available for full 24 week follow up, with last observation carried forward where data missing Findings of the study are applicable to most HF patients in NYHA classes II=III, although cannot be extrapolated to patients with recent MI, angina pectoris, hypertension, or valvular disease No significant results, as higher than expected baseline exercise time and improvement with placebo, possibly due to baseline therapy Additive assessment with ACEi</p>