

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 7.6: Treatment of heart failure not due to LV systolic dysfunction

Contents:

Atrial Fibrillation	2
Age	4
Severity	11
Gender	12
Ethnicity	14

Subgroups of heart failure
Atrial fibrillation

Paper	Khand, A. U., Rankin, A. C., Kaye, G. C., & Cleland, J. G. 2000, "Systematic review of the management of atrial fibrillation in patients with heart failure.", <i>European Heart Journal</i> , vol. 21, no. 8, pp. 614-632.
Description	Systematic Review
N=	<ul style="list-style-type: none"> • n=32 trials • n~1600 patients • UK reviewers
Intervention	A range of antiarrhythmic drugs are tested in original studies including Flecainide, Quinadine, Disopyramide, Propafenone, Amiodarone, Digoxin, diltiazem, Practolol, Pindolol, Xamoterol. Also radiofrequency ablation, of which some were placebo controlled, all requiring some measure of HF
Outcomes	Various outcome measures were used, including symptoms, exercise performance, heart rate, beats per Minute, NYHA class change, Adverse events, conversion to sinus rhythm, and maintenance of sinus rhythm. Periods of outcome assessment were not stated

<p>Results</p>	<ul style="list-style-type: none"> • 5 complete trials and 3 subgroup analyses met inclusion criteria. The DAAF trial showed no significant difference in cardioversion rates on digoxin or placebo among 28 patients. Galve et al showed that 2 of 11 patients receiving intravenous amiodarone, converted to sinus rhythm but this still represents a low conversion rate. A beneficial effect of amiodarone over digoxin in reversion to sinus rhythm was demonstrated by Hou et al with 92% and 71% conversion respectively. Diltazem produced a positive response in heart rate among 21 of 22 patients in a study by Goldenberg et al while none of the 15 patients on placebo showed any response, and there were no cardioversions. • In terms of chronic atrial fibrillation, 24 trials were highlighted with outcomes either of cardioversion, maintenance of sinus rhythm, or rate control. Cardioversion rates were recorded as being 31% with ibutilide, dofetilide 10-19%, amiodarone =31% in randomized controlled trial and between 16-66% in uncontrolled trials. One study of electrical cardioversion reported a 70% success rate. Three trials of flecainide, quinidine, and disopyramide showed the chances of remaining in sinus rhythm after 1 year as opposed to placebo. A study of xamoterol showed a reduction in mean day time heart rates and an increase in nocturnal rate, reducing the diurnal range and increasing ejection fraction over 6 months. A randomized trial of amiodarone in addition to digoxin therapy showed improved ventricular rate control but no improvement in survival compared to placebo. Elsewhere Maragno et al showed diltiazem as monotherapy or in combination with digoxin lowered exercise heart rates significantly compared to digoxin as monotherapy. • 3 of five uncontrolled studies on radiofrequency ablation of atrioventricular node and pacemaker implantation described improvements in symptoms and 2 found an increase in exercise capacity. • In terms of antithrombotic treatment a previous review suggested that in patients with AF and chronic HF there is a greater absolute benefit with warfarin therapy. Most studies have excluded patients with HF and therefore there is lack of clinical trial evidence to guide therapy. • The landmark trials of B blockers in heart failure (US carvedilol HF study, MDC, CIBIS, Australia and New Zealand HF research group) have not reported any interaction between the presence of AF and benefits on mortality. • There is no evidence to suggest that digoxin has any effect on cardioversion in atrial fibrillation in the presence or absence of HF, and similarly B blockers and diltiazem have not been shown to affect rates of cardioversion in chronic HF • The trade-off between benefits and risks of pacemaker implantation appears to be positive in patients with intractable symptoms and poor rate control despite pharmacological intervention. • The effective management of AF can only be achieved with effective management of HF and conversely the effective treatment of AF is a necessary component of the effective treatment of HF
<p>Comments</p>	<ul style="list-style-type: none"> • A good descriptive review with separate analysis of acute and chronic AF in HF patients, with data separated into that from RCTs and that from other study designs <p>The outcomes of the review are widely applicable to all HF patients with Atrial fibrillation, as many interventions are assessed.</p>
<p>Reference</p>	<p>171</p>
<p>Studies included</p>	<p>DAAF (1997), Hou (1995), Clemo (1998), Kumar (1996), Andrivet (1994), Goldenberg (1994), Heywood (1991), Stambler (1996), Falk (1997), Deedwani (1998), Van Gelder (1991), Tieleman (1996), Gosselink (1992), Mostow (1990), Van Geldner (1989), Sodermark (1975), Karlson (1988), Porterfield (1989), Middelkauf (1992), Crijns (1991), Kudoh (1993), Yahalom (1997), Christorescu (1986) Marango (1988), Brignole (1998), Twidale (1993), Brignole (1994), Edner (1995), Heinz (1992), Twidale (1988)</p>

Subgroups of heart failure

Age

Paper	Simpson, K. L. & McClellan, K. J. 2000, "Losartan: a review of its use, with special focus on elderly patients.", <i>Drugs & Aging</i> , vol. 16, no. 3, pp. 227-250.
Description	Systematic Review
N=	<ul style="list-style-type: none"> • n=96 references, but many of these epidemiological or pharmacokinetic based, and probably half of the remainder based on hypertensive patients. Various types of studies are included in the review depending on the focus of each section. For the efficacy part mostly RCTs are used where the patient population is elderly, or post hoc subgroup analysis of RCTs are used • n=? patients. There are no details given of populations involved in original trials, or definition of elderly cohort, although >65 years tended to be a common cut off for subgroup analysis in many trials • Oceanian reviewers.
Intervention	The intervention of losartan is reviewed both as a stand alone therapy compared to ACEi, and also in combination with ACEi Vs placebo, all in elderly HF populations
Outcomes	The major outcomes are mortality and morbidity, also effects on exercise capacity and tolerability are reviewed where data available
Results	<ul style="list-style-type: none"> • Losartan decreases systemic vascular resistance and pulmonary capillary wedge pressure, and increased cardiac index in HF patients, but this is in general HF population rather than elderly cohort • The findings from ELITE II with an elderly HF population showed no benefit over ACEi in all cause mortality, or sudden death, heart failure mortality, MI, stroke, or non-cardiovascular death. • There is no specific analysis given of the efficacy of losartan in terms of benefiting exercise capacity, or functional status in elderly patients. • Adverse drug reactions are a common cause of hospitalisation for elderly patients, but tolerability of Losartan appears to be better than ACEi in elderly HF patients with treatment discontinuation at 0% Vs 3.8% with ACEi (due to cough) in the ELITE I trial (p<0.002), and in ELITE II a higher number of patients on captopril discontinued because of adverse events. • There is no evidence to suggest that for elderly patients losartan be started or titrated in any different way than is generally recommended. • Preliminary evidence suggests that the efficacy of ARBs is not diminished in elderly patients despite the tendency for the renin-angiotensin system to decline with age
Comments	<p>No details given of populations involved in original trials The sections on heart failure are directly appropriate to the sub-group of elderly HF patients given the focus of the review and the selection of original papers included No assessment of study quality. No details are given of the patient numbers in many of the trials reviewed</p>
Reference	173

Studies included	Crozier (1995), Pitt (1997) ELITE, Pitt (1999) ELITE II, Cowley (1998), Dickenstien (1995), Lang (1997), Vescovo (1998), Warner (1999), Hamroff (1997), Hamroff (1999), Horiuchi (1999), Burrell (1997), Dickerstein 1999).
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Paper	Aronow, W. S., Mercado, A. D., & Epstein, S. 1998, "Effect of benazepril on complex ventricular arrhythmias in older patients with congestive heart failure, prior myocardial infarction, and normal left ventricular ejection fraction", <i>American Journal of Cardiology</i> , vol. 81, no. 11, pp. 1368-1370.
Description	Randomised Controlled Trial
N=	n=60, benazapril =30, no treatment =30 Age =82 yrs, Male =24%, LV ejection fraction =61%, >30 ventricular premature complexes per hour =100% USA
Intervention	Oral Benazapril at either 20, 30 or 40 mg/day depending on patients blood pressure and serum creatinine levels
Outcomes	The endpoints were changes in cardiac function with a >70% reduction in the average number of ventricular premature complexes and hour, or a >90% reduction in the number of runs of VT per 24 hours, both assessed at 6 months
Results	<ul style="list-style-type: none"> • There were no significant differences in the rates of ventricular premature complexes 26% Vs 19%, or the number of runs of ventricular tachycardia 25% Vs 14% between the benazapril and no treatment group respectively
Comments	<p>Relatively small trial, with no significant outcomes. Not a proven therapy The outcomes of trial are applicable to most of the older HF population who have survived a previous Q wave myocardial infarction Lack of assessment of the effects of excluding patients who died</p>

Paper	Azzolini, A., Guffanti, E., Ronzitti, M., Tantalò, L., Colantoni, A., & Pizzorni, C. 1990, "Ibopamine in the treatment of mild chronic heart failure in elderly patients. A double-blind, placebo-controlled study", <i>Cardiology</i> , vol. 77, no. Suppl 5, pp. 89-95.
Description	Randomised Controlled Trial
N=	n=52, Ibopamine=28, Placebo=24 Age =66yrs, Male =64%, NYHA class II =100%, Cardiothoracic ratio =0.55, Ischaemic origin of HF =54% Italy
Intervention	An intervention of ibopamine at 300mg/day, Vs placebo in elderly HF patients for a 12 week period
Outcomes	The main outcome measures relate to changes to exercise capacity, primarily duration, with secondary measures of clinical status and cardiac function parameters, measured at 1, 4, 6, 8, and 12 weeks
Results	<ul style="list-style-type: none"> • At 12 weeks there was a significant increase in exercise time with ibopamine compared to placebo with a 57 secs improvement Vs 23 secs with placebo (p<0.02) • There was a non significant improvement in distance walked in 6 minutes with ibopamine 84m Vs 62 m on placebo. • There were no significant differences in standardised symptoms score, nor were there any between group differences in end systolic or diastolic diameter. • No patient required hospitalisation, and no deaths occurred during the study
Comments	<p>The study results can only be seen to be relevant to the older cohort of HF patients with mild symptoms, except those with valvular disease, angina, or concomitant COPD</p> <p>Lack of control over concomitant use of diuretic</p> <p>relatively small sample size</p> <p>Short outcome assessment time</p> <p>There were no significant differences in the rates of adverse events between the groups</p> <p>It is not certain that these effects can be extrapolated to more severe HF or whether this will hold with concomitant use of other HF therapies</p>

Paper	Barabino, A., Galbariggi, G., Pizzorni, C., & Lotti, G. 1991, "Comparative effects of long-term therapy with captopril and ibopamine in chronic congestive heart failure in old patients", <i>Cardiology</i> , vol. 78, no. 3, pp. 243-256.
Description	Randomised Controlled Trial
N=	n=150, Captopril =52, Ibopamine =49, Placebo =49 Age =75yrs, Male =49%, Ischaemic origin of HF =70%, NYHA class II =37%, class III =45%, class IV =18% Italy
Intervention	Either Ibopamine at 300 mg/day, or captopril at 50-75 mg/day orally Vs placebo as a continuous treatment for 6 months
Outcomes	The primary outcome was change in distance walked in 6 minutes, with NYHA class, and symptoms self reported all at 6 months, as well as adverse effects recorded. Also mortality and morbidity were recorded as part of an open label trial to a mean 20 months
Results	<ul style="list-style-type: none"> • There was a significant improvement in distance walked in 6 minutes in both captopril and ibopamine groups compared with placebo with 104m (99% CI 90.2 – 118.2) and 100m (74.9 – 124.7) improvement Vs 19m on placebo (p<0.01 for both) with no significant difference between the active interventions. • NYHA class was seen to improve more frequently in both the captopril and ibopamine groups 54% (99% CI 35.4 – 71.5) and 46% (26.3 – 64.1) compared to 21% in placebo (p<0.01 in both comparisons), again the comparison between these (p>0.05) • The most frequent symptoms recorded were fatigue (95%), dyspnoea (92%) and fluid retention (92%). • The haemodynamic variables did not show any clinically significant changes • The difference in the rates of adverse event reported was not statistically significant. Similarly although the total discontinuation rate was high at 16% there was no excess in any of the groups • In long term follow up of open label therapy there were no significant differences in any individual items of Morbidity or mortality, but as a combined endpoint there was significant benefit of both active therapies (p<0.01) although this was not a pre-specified outcome.
Comments	<p>Mortality as assessed by survival curves showed no significantly different outcomes between either active agent or placebo</p> <p>The study was not designed to assess morbidity or mortality.</p> <p>Exercise test adopted is in patient regulated</p> <p>Ibopamine should be considered a valid alternative to ACEi where these present safety issues.</p> <p>Study in absence of B blocker treatment</p> <p>The results of the study can be widely seen to be relevant to most elderly HF patients, although caution is required when considering patients with valvular disease, recent MI, or pulmonary, hepatic, or renal disease.</p>

Paper	De, B., V, Mets, T., Romagnoli, M., & Derde, M. P. 1994, "Captopril treatment of chronic heart failure in the very old", <i>Journal of Gerontology</i> , vol. 49, no. 3, p. M148-M152.
Description	Randomised Controlled Trial
N=	n=50, captopril =25, placebo =25 Age =84yrs, Male =78%, LV ejection fraction =38%, NYHA class II =36%, class III =30%, class IV =34% Belgium
Intervention	An intervention with Captopril 50mg /day given orally as a continuous treatment Vs placebo.
Outcomes	The main outcome criteria were the Boston score and distance covered in 6 minute walk test at 3 weeks 3 months and 6 months
Results	<ul style="list-style-type: none"> • The Boston scores were available for 47 patients and the difference from baseline to the end of treatment (including those who dropped out) was a reduction • Of 3.6 points in the captopril group (ie improvement) Vs 0 points in the placebo group (p<0.001) • There was no significant difference in the distance walked in 6 minutes between the groups (p=0.073) • There were only 2 cases of adverse reactions reported with rash being reported shortly after initiation of treatment.
Comments	<p>The results of this study can be widely applied only to the very old HF patients without significant comorbidity</p> <p>High drop out rate</p> <p>50% of patients reported to have a combined aetiology</p> <p>Early terminated study due to the positive effects of captopril to limit uncontrolled chronic HF</p> <p>Given the relatively high LV ejection fraction scores it was considered that many of the patients suffered from diastolic dysfunction</p> <p>The Boston HF classification allowed a better distinction of degrees of heart failure compared to the 4 point NYHA scale</p> <p>The proportion of patients remaining on medication after 6 months was not significantly different</p> <p>The study provides further evidence for the usefulness of ACEi therapy for chronic HF in the very old patient</p>
Reference	172

Paper	Luparini, R. L., Celli, V., & Piccirillo, G. 1999, "Carvedilol in elderly patients with chronic heart failure, a twelve week randomised, placebo controlled trial", <i>Archives of Gerontology and Geriatrics</i> , vol. 29, pp. 275-282.
Description	Randomised Controlled Trial
N=	n=40 carvedilol =20, placebo =20 Age =77yrs, Male =73%, NYHA class II =22%, class III =65%, class IV =13%, Ischaemic HF origin =75% Italy
Intervention	Carvedilol at 50mg/day was given orally for 12 weeks Vs placebo
Outcomes	Cardiac function was measured by echocardiography and by electrocardiogram, cognitive function was evaluated by the mini mental state examination, functional ability was evaluated by the activities of daily living scale, and routine blood chemistry tested glucose and lipid metabolism and kidney and liver function all at 4 and 12 weeks
Results	<ul style="list-style-type: none"> • Carvedilol reduced both systolic -9.5 mmHg Vs $=2$ mmHg and diastolic blood pressure -7 mmHg Vs $+1$ mmHg compared with placebo, both comparisons ($p<0.005$). • There was a significant reduction in the LV ejection fraction amongst patients treated with carvedilol compared to placebo 5.5% Vs 0.5% ($p<0.005$) at 12 weeks
Comments	<p>The results are widely applicable to elderly HF patients given the spread of aetiologies included in the trial</p> <p>No blinding</p> <p>The analysis only including patients who completed the study protocol</p> <p>A well controlled study</p> <p>Small sample size.</p> <p>Cardiovascular variables showed no significant differences between treatment arms</p> <p>There were no statistically significant changes in cognitive or functional scores between the study groups.</p>
Reference	174

Severity

Paper	Goldstein, S., Fagerberg, B., Hjalmarson, A., Kjekshus, J., Waagstein, F., Wedel, H., Wikstrand, J., & The MERIT-HF Study Group 2001, "Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study", <i>Journal of the American College of Cardiology</i> , vol. 38, no. 4, pp. 932-938.
Description	Randomised Controlled Trial Post Hoc analysis
N=	N =795 patients (from 3991) metoprolol =399, placebo =396. Age =65yrs, Male =77%, Ischaemic origin of HF =64.5%, NYHA class III =90%, class IV =10%, LV ejection fraction =19% International
Intervention	Intervention with metoprolol at a target of 200 mg/day orally Vs placebo
Outcomes	The primary endpoints are all cause mortality and all cause mortality combined with all cause hospitalisation, on a time to first event basis). With other endpoints including change in NYHA class from baseline
Results	<ul style="list-style-type: none"> • There were 45 deaths in patients taking metoprolol (11.7% per patients year) and 72 deaths among patients on placebo (19.1%) HR 0.61 (95% CI 0.42 – 0.89) (p=0.0086) • The combined endpoint of mortality and hospitalisation also demonstrated a treatment benefit with metoprolol Vs placebo 155 and 203 events respectively HR 0.71 (0.57 – 0.87) (p=0.0012) • There was a more favourable change in NYHA functional class in the metoprolol arm compared to placebo, when comparing proportions that have improved, remained stable or deteriorated by one class or more (p=0.0031) • The drug was well tolerated without any evidence of increased withdrawal of drug use due to worsening HF. • When the results of this sub group analysis were pooled with a similar subgroup analysis from the CIBIS II trial and data from the COPURNICUS trial which enrolled LV ejection fraction <25% only, a total of 3800 patients the combined effect showed a benefit in terms of mortality of HR 0.67 (95% CI 0.58 – 0.89) (from figure) but no details of heterogeneity given and 3 trials only included
Comments	<p>The groups included in this analysis were not the basis for randomisation Lack of detail on how drop outs were considered in the subgroup analysis The results of the study are only applicable to a small proportion of the most severe cases of HF in NYHA class III-IV and with very suppressed LV ejection fraction <25% Post Hoc analysis of RCT to test efficacy of metoprolol The beneficial effect on primary endpoints of all cause mortality and hospitalisation appear to be very similar in this cohort to that found in the whole study population In this sub group the number needed to treat in a year to save one life would appear to be 13.</p>

Gender

Paper	Rathore, S. S. 2002, "Sex-based differences in the effect of digoxin for the treatment of heart failure", <i>N Engl J Med</i> , vol. 347, no. 18, pp. 1403-1411.
Description	Cohort study
N=	n=6800, Men=5281, women=1519 Age =65yrs Male =78%, LV ejection fraction =29%, MYHA class I=13%, class II =53%, class III =32%, class IV =2% USA reanalysis of a clinical trial set in USA and Canada
Intervention	The prognostic factor under investigation is male or female sex
Outcomes	The main outcome assessed is all cause mortality, which was the primary endpoint in the clinical trial from which the cohorts are derived. Other endpoints include other classifications for mortality and hospitalisation, all to a mean of 37 months
Results	<ul style="list-style-type: none"> • After multivariate adjustment digoxin therapy was associated with a non-significant reduction in the risk of death among men HR 0.93 (95% CI 0.85 to 1.02) and a significant increase in the risk of death among women with HR 1.23 (1.02 to 1.47) representing a significant interaction between sex and digoxin (p=0.014) with the unadjusted value only just significant in showing a difference of effect between cohorts • In terms of cardiovascular death there appeared to be a difference in the effect of digoxin among women where taking digoxin was associated with an increased risk of death HR 1.24 (1.02 to 1.52) while there was no increased risk among men taking digoxin HR 0.96 (0.87 to 1.06) with the difference being significant with p=0.035 for the interaction • Similarly over the course of the follow up Digoxin therapy reduced death from worsening heart failure among men with a HR of 0.79 (0.68 to 0.92) but with no benefit being apparent for women HR 1.17 (0.87 to 1.56) (p=0.026 for the difference in effect between cohorts). In a similar vein hospitalisations for worsening HF were reduced significantly for men taking digoxin over placebo but no such difference was apparent among the female cohort (p=0.011 for the interaction between sex and digoxin) • There was no significant interaction between sex and digoxin use in terms of other causes of hospitalisation or for a combined endpoint of death or hospitalisation due to worsening heart failure

Comments	<p>Large number of variables to be corrected for with many being interrelated.</p> <p>Women may be less likely to be receptive to treatment with dig due to many clinical characteristics relating to an older female than male cohort, which could not be adequately corrected for statistically.</p> <p>Men received a higher dose of digoxin than women when standardised for body-mass index ($p < 0.001$), although median serum digoxin levels at 12 months showed no significant difference between the groups</p> <p>Prospective randomised trials with stratification for sex are required to definitively test the association of digoxin efficacy with sex, however such trials may be considered unethical as would be designed to show risk rather than benefit</p> <p>A possible mechanism for the differences in risks between the sexes may be some association of digoxin with HRT therapy which was not a variable recorded in the original DIG trial and could therefore not be included in regression analysis</p> <p>Given the number of demographic and clinical differences between men and women at baseline, even with corrections for possible confounders the confidence in the size of interaction may be \nearrow</p> <p>No clear a priori reason for inclusion of the confounding variables used, and multiple testing may have led to spurious associations</p> <p>Disproportionately higher number of men than women in trial may have led to treatment effects being more accurately defined in this cohort with narrower confidence intervals than for the female cohort, making comparison of these groups difficult</p>
Reference	176

Ethnicity

Paper	Kalus, J. S. & Nappi, J. M. 2002, "Role of race in the pharmacotherapy of heart failure", <i>Annals of Pharmacotherapy</i> , vol. 36, no. 3, pp. 471-478..
Description	Systematic Review
N=	<ul style="list-style-type: none">• n=7 trials, 4 vasodilator and 3 B blocker• n=9337 of which 1412 (15%) were black patients
Intervention	The efficacy of vasodilators Hydralazine Isosorbide, ACEi, and of B blockers compared with placebo were studied in HF population in the various studies
Outcomes	Primary endpoint of all cause mortality is reviewed and hospitalisation rates are given where available

<p>Results</p>	<ul style="list-style-type: none"> • In general black patients develop HF at an earlier age and are more likely to have hypertension as a cause for HF • From V-HeFT I comparing Hydralazine isosorbide with prazosin and placebo there were 180 black patients and 450 non black patients. Black patients in the hydralazine isosorbide group had a significantly lower annual mortality rate than those in the placebo group, whereas non black patients derived no survival benefit. • In V-HeFT II 215 black patients and 574 non black patients were randomised to enalapril or Hydralazine isosorbide. There was no significant difference on mortality between the treatment groups amongst the black population, while in the non black population there was a significant benefit with enalapril. • These two findings make it hard to ascertain whether there is a superior response to hydralazine isosorbide or an inferior activity of ACEi in black patients • In total the SOLVD treatment and prevention trials included 800 black patients and 5719 non black patients, overall the RR of mortality was higher among black patients than non black patients regardless of assignment to enalapril RR 1.34 (95% CI 1.08 – 1.66) (p=0.007) or placebo RR 1.15 (1.02 – 1.53) (p=0.03), showing a comparatively higher relative risk with enalapril. A further post hoc study matching the 800 black patients for age, gender, and ejection fraction to 1196 non black patients showed no difference in the relative risk of mortality among black patients and non black patients assigned to enalapril. There was a higher relative risk of hospitalisation among black patients compared to non black patients receiving enalapril. The difference in response to ACEi could be the result of a smaller reduction in blood pressure among black patients • In terms of B blocker therapy for HF patients the US Carvedilol Heart Failure trial programme compared B Blocker therapy to placebo. 217 black and 877 non black patients participated and of the black patients 127 were randomized to B blocker and 90 to the placebo arm. All cause mortality among black and non black groups was similar. Similarly no difference was found in the rate of all cause mortality or hospitalisation, all cause mortality and cardiovascular hospitalisation, and worsening heart failure between the race groups. • The BEST trial had a pre specified subgroup analysis of black patients in which there was no mortality benefit noted HR 1.17 (95% CI 0.89 – 1.53) (p=0.27), whereas in the non black patients B blockers did provide a mortality benefit HR 0.82 (0.70 – 0.96) (p=0.01). • The Metoprolol CR/XL study reported the racial demographics of patients at baseline, but no analysis of the effect of race in this trial have been reported. • Baseline differences in cardiovascular disease severity among black patients cannot be discounted for the different efficacies seen. • Both ACEi and B blockers have been shown to be less effective in reducing blood pressure in black patients than non black patients. • Another possible explanation for the inferior efficacy could be inadequate dosing, or potentially a genetic difference could explain altered response to therapy.
<p>Comments</p>	<p>Well described subgroup analysis of each trial included The results of this review are only directly applicable to the sub-population of black patients with HF Limited search strategy The post hoc analysis of RCTs give potential bias in baseline differences in patients populations as the sub group in question was not the basis for randomisation The US FDA has requested that a placebo controlled trial of BiDil in black patients for a specific licence in black HF patients. The A-HeFT trial will include approximately 600 black patients with HF. Lack of prospective evaluations</p>
<p>Studies included</p>	<p>Cohn (1986) V-HeFT, Cohn (1991) V-HeFT II, SOLVD (1991), SOLVD (1992), Packer (1996) US Carvedilol HF, BEST (2001), Hjalmarson (2000) MERIT-HF.</p>