Are patients in heart failure trials representative of primary care populations? A systematic review

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Background

Guidelines recommend drug treatment for patients with heart failure with a reduced ejection fraction (HFrEF), however the evidence for benefit in patients with mild disease, such as most in primary care, is uncertain. Importantly drugs commonly used in heart failure account for one in seven of emergency admissions for adverse drug reactions.

Aim

To determine to what extent patients included in studies of heart failure treatment with beta blockers, ACE inhibitors and aldosterone antagonists were representative of a typical primary care population with HFrEF in England.

Design and Setting

Systematic review of RCTs of drug treatment in patients with HFrEF.

Method

MEDLINE, MEDLINE In-process, EMBASE, and CENTRAL were searched from inception to March 2015. We compared the characteristics of the patient's NYHA classification with a primary care reference population with HFrEF.

Results

30 studies were included. Two had incomplete data. None had a 'close match' (<10% deviation from reference study) for NYHA class I disease, 5/28were a close match for NYHA class II, 5/28 for NYHA class III, and 18/28 for NYHA class IV. In general, pre-existing cardiovascular conditions, risk factors and comorbidities were representative of the reference population.

Conclusion

Patients recruited to studies typically had more severe heart failure than the reference primary care population. When evidence from sicker patients is generalised to less sick people, there is increased uncertainty about benefit and also

a risk of harm from overtreatment. More evidence is needed on the effectiveness of treatment of heart failure in asymptomatic patients with NYHA class 1.

Keywords: heart failure, drug treatment, primary health care, guidelines

How this fits in

Heart failure is common in primary care and carries a high morbidity and mortality which is associated with the degree of failure; beta blockers, ACE/ARB and aldosterone antagonists have all been shown to reduce mortality and morbidity, but also carry a significant risk of ADRs. We have shown that patients with heart failure in primary care tend to have mild heart failure, but the evidence for effectiveness for these drugs comes from a population with more severe heart failure. More evidence is needed for the effectiveness of these treatments in populations typical of primary care.

Introduction

Heart failure with reduced ejection fraction (HFrEF) is a common chronic, debilitating disease which has a prevalence of 0.7% and affects 400,000 adults in the United Kingdom (UK) (1). The annual cost of heart failure to the NHS is around 2% of its total budget, and approximately 70% of this total is due to the costs of hospitalisation (2). There is a large variation in clinical presentation of heart failure with some patients having no symptoms at the time of diagnosis, whereas others have significant morbidity. The diagnosis is made based on the presence of signs and symptoms of heart failure and through the use of echocardiography to measure left ventricular ejection fraction (LVEF) ejection fraction (3). A LVEF less than 40% confirms a diagnosis of HFrEF, which has been extensively studied in the literature.

Symptoms of heart failure can be graded using the New York Heart Association (NYHA) functional classification into one of four categories (Table 2) (4). In one study of UK primary care patients with HFrEF, 47% had no symptoms (grade I), 36% had mild symptoms (grade II), 7% had moderate symptoms (grade III), and 10% had severe symptoms (grade IV) (5). Mortality rates from heart failure are high, one UK cohort study reported that 14% (95% C.I. 11% to 18%) of patients died within 6 months of diagnosis (6). Patients with higher NYHA symptom scores have a worse prognosis although even patients with mild heart failure have higher mortality (7).

Several large trials have found a reduction in mortality and hospitalisation in patients with systolic heart failure following treatment with beta blockers, ACE (angiotensin converting enzyme) inhibitors and aldosterone antagonists (8, 9). These drugs have also been shown to be cost effective for the treatment of heart failure (10). This evidence has led to guideline recommendations adopting these treatments for systolic heart failure across the world (2, 7, 11, 12). The National Institute for Health and Care Excellence (NICE) heart failure guideline recommends that all primary care patients with systolic heart failure should be offered beta blockers and ACE inhibitors regardless of NYHA class. This indicator is supported by evidence generalized from higher risk populations (NYHA grades III–IV), in which there is clear evidence of

benefit for beta blockers and ACE inhibitors, however the evidence of benefit in lower risk populations is more equivocal (13, 14).

The applicability of guideline recommendations for management of diseases (including heart failure) in primary care has recently been questioned as this research is rarely conducted in representative populations (13). This question is important in heart failure because the effectiveness of treatment may depend on the severity of disease, and beta blockers and ACE inhibitors carry significant morbidity risk, and account for approximately one in seven emergency hospital admissions due to adverse drug reactions (15).

The aim of our study was to determine to what extent patients included in studies of heart failure treatment with beta blockers, ACE inhibitors and aldosterone antagonists were representative of the NYHA class and other characteristics of a typical primary care population with heart failure in England.

Methods

A literature search was undertaken to identify randomised controlled trials of systolic heart failure drugs. MEDLINE, MEDLINE In-process, EMBASE, and CENTRAL were searched from inception to March 2015. The search strategy for MEDLINE is shown in supplementary data Appendix 1 and this was modified for other databases. Titles and abstracts were screened by two authors independently according to the following pre-specified inclusion and exclusion criteria.

Inclusion criteria were randomised controlled trials (RCTs) which included patients with HFrEF. Intervention drugs included angiotensin-converting enzyme inhibitors (ACE inhibitors), beta blockers, angiotensin II receptor blockers (ARBs) and aldosterone antagonists (e.g. spironolactone and eplenerone). There were no language restrictions. Exclusion criteria were studies with a follow-up of less than six weeks, those comprising a single-dose regimen, and studies not judged to be generalizable to a primary care population (such as one study of patients on dialysis). Disagreements were resolved through discussion or by a third researcher, and full text articles were retrieved for each abstract meeting these criteria.

Data were extracted from each included study into a template which included study design, intervention, inclusion and exclusion criteria, baseline characteristics, primary outcome and mortality data. Data extraction was checked by a second researcher and any disagreements were resolved through discussion or by a third researcher. Authors were contacted for individual level data. No authors shared individual level data and our difficulties accessing these data have been described elsewhere (16). Study exclusion was guided by pre-defined exclusion criteria as described.

We used data from the largest study on the prevalence of heart failure in the UK (the Echocardiographic Heart Study of England Screening (EHES)) study (5). This study randomly selected a large population of 6286 people aged 45 years and over, and was the best fit to an English population of five studies of heart failure prevalence that we identified (17, 18, and 19). The EHES study had a high participation rate of

63% (3960 patients) and wide geographical spread of populations which was representative of inner-city, urban, suburban, and rural communities. The EHES study was used as the 'reference population' throughout this study.

For each study we analysed the NYHA class, baseline cardiovascular risk factors, baseline cardiovascular comorbidities and use of heart failure drugs. These outcomes were compared between the reference study and each extracted study. Each patient-specific variable was compared to the reference study in terms of prevalence or frequency of use. To allow quantification of similarity between the selected study population and the reference study population, we assessed the percentage deviation and allocated this as being a 'close match', 'fair match' or 'poor match'. If the extracted study population had a ≤10% deviation from the reference study, it was termed as a 'close match', if the deviation was 11-20%, it was termed a 'fair match', and if the deviation was >20%, it was termed a 'poor match'. These parameters were set-out *a priori*. For example, if a study reported 10% class 1, 25% class 2, 40% class 3 and 25% class 4, to assess close match we applied a 10% absolute deviation (i.e. 0-20%, 15-35%, 30-50% and 15-35% respectively) and compared it to classes in the reference population (47%, 36%, 7% and 10% respectively), we have shown this worked example in the table 1. For each of the appendices, the studies were organised in descending order according to the similarity or 'closeness of match' they shared with the reference population.

Results

Literature searching identified 6785 studies, 4433 after de-duplication (Figure 1). Thirty RCTs met the inclusion criteria, representing 43,454 patients with HFrEF. Characteristics of included studies are shown in Table 3. Of the included studies, 13 investigated beta-blockers, 8 ACE-inhibitors, 6 ARBs and 4 spironolactone. One study compared ACEi and ARBs (ELITE I, 2000). Of the 30 extrapolated studies, sample size ranged from 59 – 5010 participants. Follow up ranged from 3 – 73 months.

The reference population is shown in Table 4. The overall mean age was 69 years, and was 81% male. Most patients had NYHA class 1 (47%) and only 17% of patients had class 3 or 4.

NYHA class

Table 5 shows heart failure RCTs compared to the reference population, stratified by NYHA class. 28/30 studies had complete data on NYHA classes. None of the studies had a 'close match' (green bar) for NYHA class I disease, 3/28 (11%) displayed a 'fair match' (amber bar), and 25/28 (89%) a 'poor match' (red bar). For NYHA class II 5/28 (18%) studies has a 'close match', 9/28 (31%) a 'fair match' and 14/28 (48%) a 'poor match'. For NYHA class III, 5/28 (18%) displayed a 'close match', 3/28 (11%) a 'fair match', and 20/28 (71%) a 'poor match'. For NYHA class IV, 18/28 (64%), displayed a 'close match', and 7/28 (25%) had a 'poor match'.

Baseline cardiovascular risk factors

Cardiovascular risk factors were largely representative of the reference population (supplementary data Appendix 2). 25/30 (83%) of the studies had a 'close match' to the age of the reference population, which was a mean of 69 years. 19/30 studies (63%), had a 'close match' with the proportion of the reference population who were male, which was 81%. The majority of extracted studies, 20/30 (67%), did not present ethnicity data. Of those that did, 7/10 (70%) had a 'close match' and 3/10 (30%) had a 'poor match' with the reference population which was 97% white. 23/30 (77%) extracted studies did not present smoking status data. Of the 7 that did, 1/7 (14%) had a 'fair match' and 6/7 (86%) a 'poor match' to the reference population of whom 69% were smokers. A family history of premature myocardial infarction was not reported in any of the studies.

Baseline cardiovascular comorbidities

The majority of the studies, 23/30 (77%), reported the presence of pre-existing angina but 13/30 (43%) studies did not report the presence of previous myocardial infarction, pre-existing hypertension, or diabetes mellitus (supplementary data Appendix 3). In general, pre-existing cardiovascular conditions recorded in the extracted studies were representative of the reference population. When comparing for the presence of pre-existing myocardial infarction, 10/17 (59%) of the extracted

studies had a ‘close match’, 6/17 (35%) had a ‘fair match’ and 1/17 (6%) had a ‘poor match’ to the reference population which reported a prevalence of 53%. A similar trend was noted for hypertension, of which, 7/17 (41%) of the extracted studies had a ‘close match’, 3/17 (18%) had a ‘fair match’ and 7/17 (41%) had a ‘poor match’ to the reference population (reported prevalence, 39%).

For diabetes mellitus 7/17 (41%) of the extracted studies had a ‘close match’, 6/17 (35%) had a ‘fair match’ and 4/17 (26%) had a ‘poor match’ to the reference population (reported prevalence, 15%). As mentioned, the presence of angina was recorded in only seven studies. Of which, 3/7 (43%) had a ‘close match’, 3/7 (43%) had a ‘fair match’ and 1/7 (14%) had a ‘poor match’ to the reference population (reference population reported prevalence, 36%).

Use of heart failure drugs.

The use of important heart failure drugs varied significantly across the analysed studies (supplementary data Appendix 4). 20/30 (67%) studies did not report data on the use of aspirin. Of the remaining 10, 5/10 (50%) had a ‘close match’, 4/10 (40%) a ‘fair match’, and 1/10 (10%) had a ‘poor match’ to the reference population of whom 53% took regular aspirin.

22/30 (73%) of extracted studies did not report data on the use of calcium channel blockers (CCBs). Of the remaining 8, 4 (50%) had a ‘close match’ and 4 (50%) had a ‘fair match’ to the reference population (which reported CCB usage in 21%).

A large proportion of the extracted studies investigated beta-blockers and ACE inhibitors directly, and therefore not assessed for prevalence of use of these therapies compared to the reference population. Of the 18 studies which did not study beta-blockers, 11 studies did report data on the proportion of patients using beta-blockers, and only 3 (27%) had a ‘close match’ to the reference population (reference population reported frequency, 13%).

Of the 22 studies that did not directly study ACE inhibitors, 8 studies (36%) did not report prevalence of use. Therefore only 14 (47%) could be assessed for ACE

inhibitors, all of which had a 'poor match' to the reference population (reference population reported frequency, 26%).

11/30 (37%) studies did not report data on the proportion of patients using digoxin; of the remaining 19, 2 (11%) had a 'close match', 2 (11%) had a 'fair match' and 15 (79%) had a 'poor match' to the reference population (reference population reported frequency, 7%).

Spironolactone and eplenerone were the study drug in 4/30 studies and these were therefore not assessed for similarity to the reference population. Of the remaining 26 studies that did not directly investigate these agents, 10 (39%) did not report prevalence of use data. As such, only 16 studies could be assessed for spironolactone and eplenerone use, all of which had a 'poor match' to the reference population (reference population reported frequency, 36%).

We examined the six studies that were a close match for NYHA class II participants for evidence of benefit for this class. Only one study (MERIT) reported outcomes by NYHA class II (20), the remaining studies reported pooled outcomes for all NYHA classes. MERIT reported no significant mortality reduction, but a reduction in 2 out of 4 secondary outcomes (development of CHF and hospitalisations).

Discussion

Summary

83% of the reference population representing a primary care population with HFrEF had mild symptoms in NYHA class I and II, however none of the 30 studies were matched closely with NYHA class 1, and only 5/28 (18%) studies were a 'close match' with NYHA class II symptoms. For patient characteristics of age, sex, ethnicity, previous MI, hypertension, diabetes and angina; > 40% studies were closely matched to the reference population. For patient characteristics of smoking

status, family history of premature heart disease, and the use of beta blockers, ACE inhibitors and the aldosterone antagonists spironolactone and eplenerone; <30% of studies were closely matched to the reference population. In this way, we have shown that these studies are not typically representative of the primary care population in England, with patients with more severe heart failure being over-represented.

Strengths and limitations

This study is the first systematic review to determine whether the types of patients included in studies of treatments for HFrEF were representative of a typical primary care population with HFrEF in England. We used a large study as the reference population (5) which randomly selected and screened the population for HFrEF and our systematic review method was robust. Whist this cohort study was published 15 years ago and the characteristics of the primary care population and treatments have changed, it is closer to the time when the included RCTs were undertaken. We had initially intended to obtain individual level data for each NYHA class from each of the 30 identified studies; however, we faced obstacles in terms of non-disclosure of further information from authors, who either failed to reply to repeated attempts to make contact or were unwilling for us to access their trial data (16). There may be some overlap between classes, such as class 1 and 2, which may have led to misclassification in either the reference study or the included trials. We only included trials which recruited patients with heart failure, there is a possibility that some trials with a subgroup of patients with heart failure may not have been identified.

Comparison with existing literature

This study concurs with the findings of Steel et al, who reported that out of 48 studies cited in the NICE guidance on heart failure treatment, 43 (90%) were studies of uncertain relevance to patients in primary care (14). These findings are particularly important as there is evidence that of heart failure treatments may be less effective in patients with less severe heart failure (16, 21, 22), and these drugs do account for significant morbidity.

Implications for research and/or practice

The underrepresentation of patients with HFrEF and mild or absent symptoms in clinical trials has implications for general practitioners who should weigh the potential benefits of initiating treatment in those with absent or mild symptoms against the risks of an adverse drug reaction which are significant, although all degrees of heart failure have raised mortality and morbidity. By extrapolating data from studies of patients with more severe disease, patients and clinicians may misinterpret the potential benefits and risks. It is important that the risks and benefits are stratified by NYHA disease class.

More studies are needed using individual patient data analysis by heart failure severity, as most of the outcomes in the current studies were not reported by NYHA class. This should be complimented by observational studies using, for example, the CRPD dataset which primarily recruit from primary, rather than secondary care.

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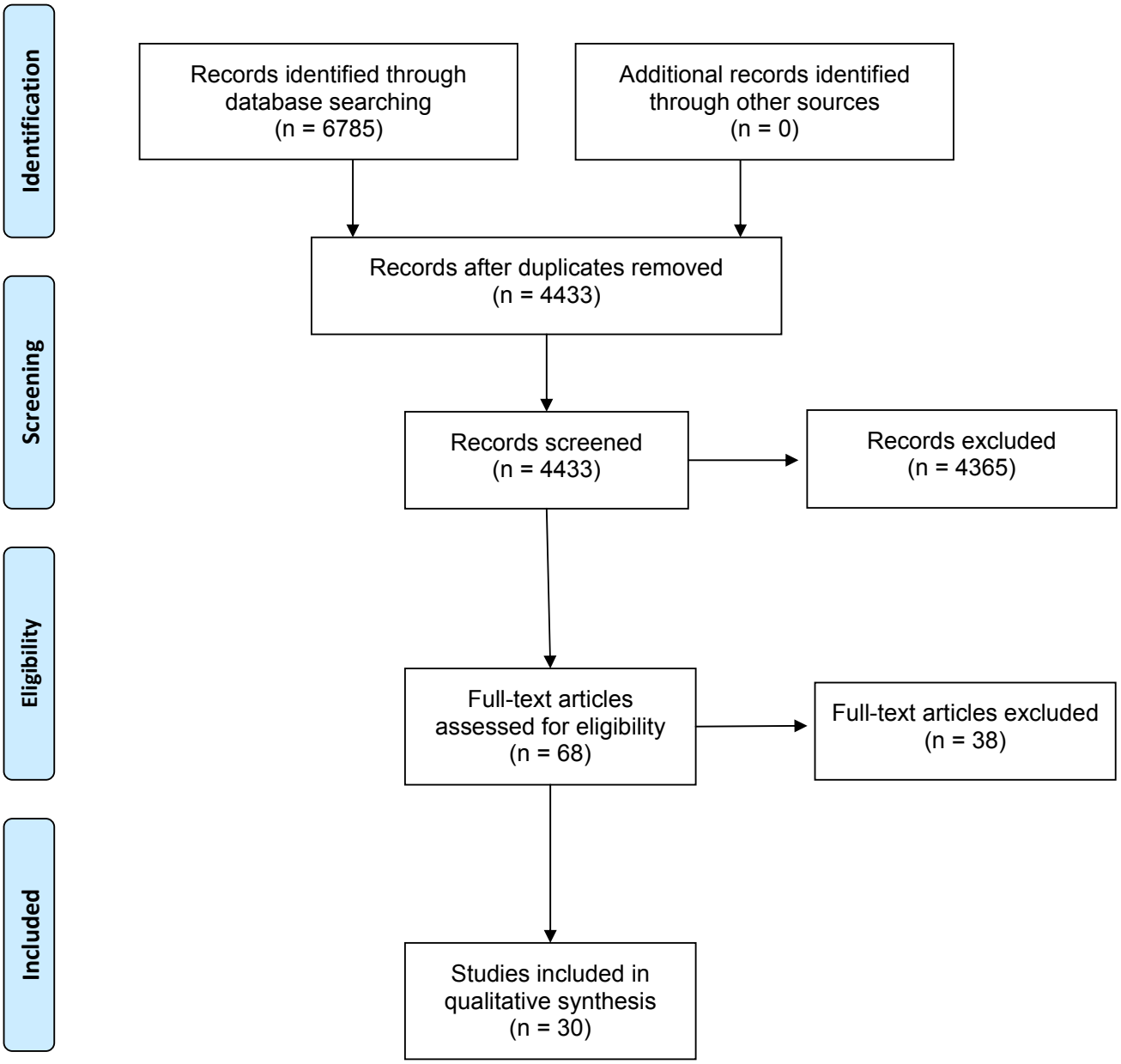
Figure 1: PRISMA diagram



564 **Table 1:** Example assessment of an extracted paper compared to the reference
565 population

	class 1	class 2	class 3	class 4
Reference population (%)	47	36	7	10
Extracted study (%)	10	25	40	25
Extracted study with 10% deviation (%)	0-20	15-35	30-50	15-35
Closeness of match (%)	>20%	11-20%	>20	11-20%
Closeness of match (label)	poor	fair	poor	fair

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568 **Table 2:** New York Heart Association classes of heart failure (4).

Class	**Patient Symptoms**
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

569 **Table 3:** Characteristics of included studies (References: 23-51)

Study ID	**Comparison**	**Number of participants**	**Primary outcome**	**Follow up**

AREA-CHF 2009	Canrenon Placebo	231 236	Change in LV diastolic volume	12 months
BEST 2003	Bucindolol Placebo	114 112	Death and heart failure hospitalisation composite	19 months
Borghi 2013	Ramipril Zofenopril	73 102	Survival	73+/-14 months
CARNEBI 2013	Carvedilol Bisoprolol Nebivolol	61 crossover	NYHA class, biochemistry and physiological testing	6 months (2 x 3 crossover)
CELICARD 2000	Celiprolol Placebo	62 62	Functional score - Goldman score	12 months
CHARM Added 2003	Candesartan Placebo	1011 1014	Cardiovascular death or unplanned hospital admissions for worsening CHF	34 months
CHARM Alterative 2003	Candesartan Placebo	1273 1271	Cardiovascular death or unplanned hospital admissions for worsening CHF	41 months
CIBIS 1994	Bisoprolol Placebo	320 321	All-cause mortality	23 months
CIBIS 1999	Bisoprolol Placebo	1327 1320	All-cause mortality	16 months
Cicoira 2002	Spironolactone Placebo	54 52	Physiological/functional improvement	12 months
Cohn 2001	Valsartan Placebo	2511 2499	All-cause mortality and combined mortality and morbidity	23 months
Colucci 1996	Carvedilol Placebo	232 134	Disease progression and death composite	12 months
COMET 2003	Carvedilol Metoprolol	1511 1518	All-cause mortality	58 months
Dalla-Volta 1999	Delapril Enalapril	88 91	Physiological/functional improvement	12 months
ELITE II 2000	Losartan Captopril	1578 1574	All-cause mortality	18 months
Kum 2008	Add on Irbesartan Placebo	50 50	6MHW, Minnesota (QoL), peak exercise capacity on treadmill	12 months
Liu 2014	Metoprolol Conventional therapy	77 77	NYHA class, LVESD, LVEDD, LVEF, 6-min walking distance, medication safety	6 months
MAIN CHF II 2014	Bisoprolol Carvedilol	21 14	Clinical and functional status, mortality rate	8 months
MERIT-HF 1999	Metoprolol CR Placebo	1990 2001	All-cause mortality	12 months
Munich 1991	Captopril Placebo	83 87	Cardiovascular-cause mortality	33 months
Pitt 1999	Spironolactone Placebo	822 841	All-cause mortality	24 months
Rieger 1999	Candesartan 4mg Candesartan 8mg Candesartan 16mg	211 208 212 213	Increase in exercise tolerance, reduction in NYHA class	3 months

	Placebo			
SENIORS 2005	Nevovitol Placebo	1067 1061	All-cause mortality and time to first CVD admission	21 months
SOLVD 1991	Enalapril Placebo	1285 1284	Clinical and functional status, mortality rate	41.4 months
SOLVD 1992	Enalapril Placebo	2111 2117	Clinical and functional status, mortality rate	37.4 months
Sturm 2000	Atenolol Placebo	51 49	Worsening heart failure or death	24 months
US Carvedilol 2001	Carvedilol Placebo	Black: 127, Not Black: 569 Black:90, Not Black: 308	Ethnicity (self-reported), ejection fraction, clinical status and major clinical events	15 months
Yodfat 1991	Captopril Placebo	41 43	Functional status	3 months
Zannad 1998	Fosinopril Placebo	122 132	Cardiovascular mortality and event-free survival	12 months
Zannad 2011	Eplenerone Placebo	1364 1373	Cardiovascular mortality and event-free survival	21 months

Abbreviations: 6MHW: 6-Minute Hall Walk, AREA-CHF: Anti-remodelling effect of canrenone in patients with mild chronic heart failure, BEST: Beta-Blocker Evaluation in Survival Trial, CARNEBI: Multiparametric comparison of CARvedilol, vs. NEbivolol, vs. BIsoprolol in moderate heart failure, CELICARD: Treatment of heart failure with celiprolol, a cardioselective beta blocker with beta-2 agonist vasodilatory properties, CHARM: Candesartan in Heart failure - Assessment of moRtality and Morbidity, CHF: Congestive Heart Failure, CIBIS: Cardiac Insufficiency Bisoprolol Study, COMET: Carvedilol Or Metoprolol European Trial, CVD: Cardiovascular Disease, ELITE: Evaluation of Losartan in the Elderly, LV: Left Ventricle , LVEDD: Left Ventricular End-Diastolic Diameter, LVEF: left Ventricular Ejection Fraction, LVESD: Left Ventricular End-Systolic Diameter, MAIN CHF: Multistep Administration of bisoprolol IN Chronic Heart Failure, MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure, NYHA: New York Heart Association, SENIORS: Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure, SOLVD: Studies of Left Ventricular Dysfunction

Table 4: Summary of the ejection fraction <40% cohort for the reference population: 'Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening (EHES) study: a population based study'.

Characteristic	Total (n=72)
Age, mean in year (SD)	69 (9)
Women	14 (19%)
Men	58 (81%)
Ever smoked	50 (69%)
Non-white	105 (3%)
Any electrocardiogram abnormality	2 (3%)
Height, mean in metres (SD)	1·71 (0·09)
Weight, mean in kilograms (SD)	80.8 (14·6)
Heart rate, mean in beats per min (SD)	77.3 (17.8)
Forced expiratory volume at 1 s, mean in litres (SD)	2·11 (0·76)
Forced vital capacity, mean in litres (SD)	2·55 (0·85)
Systolic blood pressure, mean in mm□Hg (SD)	148·4 (21·1)
Diastolic blood pressure, mean in mm□Hg (SD)	87.1 (12.3)
New York Heart Association class	
1	34 (47%)
2	26 (36%)
3	5 (7%)
4	7 (10%)
History	
Myocardial ischaemia	38 (53%)
Angina	26 (36%)
Hypertension	28 (39%)
Diabetes	11 (15%)
Family myocardial ischaemia (age <65 years)	25 (35%)
Medication taken	
ACE Inhibitors	19 (26%)
Diuretics	26 (36%)
β-blockers	9 (13%)
Calcium antagonists	15 (21%)
Aspirin	38 (53%)
Digoxin	5 (7%)

602
603 **Table 5:** NYHA classification in heart failure RCTs compared to the reference
604 population.

		NYHA Class (% of 'reference population') (Reference 5, Davies et al, 2001).			
Heart Failure RCTs	**N-value**	**I (47%)**	**II (36%)**	**III (7%)**	**IV (10%)**
SOLVD 1992	4228	11-20%	<10%	<10%	<10%
Munich 1991	170	11-20%	11-20%	11-20%	<10%
Borghi 2013	175	11-20%	11-20%	11-20%	<10%
US Carvedilol 1996	1094	>20%	<10%	>20%	<10%
Liu 2014	154	>20%	<10%	>20%	<10%
CHARM Added 2003	2548	>20%	<10%	>20%	<10%
MERIT-HF 1999	3991	>20%	<10%	>20%	<10%
Zannad 1998	254	>20%	>20%	<10%	<10%
CELICARD 2000	124	>20%	11-20%	>20%	<10%
CHARM Alterative 2003	2028	>20%	11-20%	>20%	<10%
SENIORS 2005	2128	>20%	11-20%	>20%	<10%
SOLVD 1991	2569	>20%	11-20%	>20%	<10%
COMET 2003	3029	>20%	11-20%	>20%	<10%
Cicoira 2002	106				
CARNEBI 2013	183	>20%	>20%	<10%	>20%
MAIN CHF II 2014	59	>20%	>20%	<10%	>20%
Colucci 1996	366	>20%	>20%	<10%	>20%
Zannad 2011	2737	>20%	>20%	>20%	<10%
Sturm 2000	100	>20%	>20%	>20%	<10%
Cohn 2001	5010	>20%	>20%	>20%	<10%
CIBIS 1994	641	>20%	>20%	>20%	<10%
CIBIS 1999	2647	>20%	>20%	>20%	<10%
ELITE II 2000	3152	>20%	11-20%	>20%	>20%
Kum 2008	100	>20%	11-20%	>20%	>20%
Rieger 1999	844	>20%	>20%	11-20%	>20%
BEST 2003	226	>20%	>20%	>20%	>20%
Dalla-Volta 1999	179	>20%	>20%	>20%	>20%
AREA-CHF 2009	382	>20%	>20%	>20%	>20%
Pitt 1999	1663	>20%	>20%	>20%	>20%
Yodfat 1991	84				

	<10% deviation from reference study
	11-20% deviation from reference study

	>20% deviation from reference study
	Insufficient information to calculate deviation

Supplementary data

Appendix 1: MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp angiotensin-converting enzyme inhibitors/
12. angiotensin-converting enzyme inhibitor$.mp.
13. exp enalapril/
14. (alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or derapril or enalapril or fosinopril or idapril or imidapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril).mp.
15. 11 or 12 or 13 or 14 or 15
16. exp adrenergic beta-antagonists/
17. (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).mp.

18. (beta adj2 (antagonist? or receptor? or adrenergic? block$)).tw.
19. adrenergic beta antagonist?.tw.
20. 16 or 17 or 18 or 19
21. exp angiotensin II type 1 receptor blockers/
22. exp losartan/
23. (angiotensin receptor blocker$ or angiotensin II receptor blocker$ or angiotensin receptor antagonist$ or angiotensin II receptor antagonist$ or candesartan or eprosartan or irbesartan or losartan or olmesartan or tasosartan or telmisartan or valsartan).mp.
24. 18 or 19 or 20 or 21 or 22 or 23
25. exp Heart Failure/
26. (heart adj2 failure*).tw.
27. (congestive adj2 heart).tw.
28. (cardiac adj2 failure*).tw.
29. (myocardial adj2 failure*).tw.
30. 25 or 26 or 27 or 28 or 29
31. 10 and 30 and 15
32. 10 and 30 and 20
33. 10 and 30 and 24
34. 31 or 32 or 33
35. 34 and 2005:2012.(sa_year).
36. remove duplicates from 35

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696 **Appendix 2:** Prevalence of CVD risk factors in heart failure RCTs compared to the
697 reference population

	CVD Risk Factors (% of 'reference population') (Reference 5, Davies et al, 2001).					
Heart Failure RCTs	**N-value**	**Age (69+/-9yrs)**	**Male (81%)**	**White (97%)**	**Smoker (69%)**	**FH of MI< 65(35 %)**
CHARM Added 2003	2548	<10%	<10%	<10%	11-20%	
SOLVD 1992	4228	<10%	<10%	<10%	>20%	
Pitt 1999	1663	<10%	<10%	<10%		
MERIT-HF 1999	3991	<10%	<10%	<10%		
CHARM Alterative 2003	2028	<10%	11-20%	<10%	>20%	
Borghi 2013	175	<10%	11-20%	<10%	>20%	
SOLVD 1991	2569	<10%	<10%	11-20%	>20%	
Zannad 2011	2737	<10%	<10%	11-20%		
Zannad 1998	254	<10%	11-20%	<10%		
CARNEBI 2013	183	<10%	<10%			
US Carvedilol 1996	1094	<10%	<10%			
COMET 2003	3029	<10%	<10%			
Munich 1991	170	<10%	<10%			
Cohn 2001	5010	<10%	<10%			
CIBIS 1994	641	<10%	<10%			
CIBIS 1999	2647	<10%	<10%			
AREA-CHF 2009	382	<10%	<10%			
ELITE II 2000	3152	<10%	11-20%	11-20%		
SENIORS 2005	2128	<10%	11-20%		>20%	
BEST 2003	226	11-20%	<10%		>20%	
Rieger 1999	844	<10%	11-20%			
MAIN CHF II 2014	59	<10%	11-20%			
Liu 2014	154	<10%	11-20%			
Kum 2008	100	<10%	11-20%			
Dalla-Volta 1999	179	11-20%	<10%			
Sturm 2000	100	11-20%	<10%			
Colucci 1996	366	11-20%	<10%			
CELICARD 2000	124	11-20%	<10%			

Yodfat 1991	84	<10%	>20%			
Cicoira 2002	106	<10%	>20%			

	<10% deviation from reference study
	11-20% deviation from reference study
	>20% deviation from reference study
	Insufficient information to calculate deviation

698

699 **Appendix 3:** Prevalence of comorbidities in heart failure RCTs compared to the

700 reference population

		Prevalence of CVD (% of 'reference population') (Reference 5, Davies et al, 2001).			
Heart Failure RCTs	**N-value**	**MI (53%)**	**HTN (39%)**	**DM (15%)**	**Angina (36%)**
AREA-CHF 2009	382	<10%	<10%	<10%	
ELITE II 2000	3152	<10%	<10%	<10%	
CHARM Added 2003	2548	<10%	<10%	11-20%	11-20%
MERIT-HF 1999	3991	<10%	<10%	<10%	
COMET 2003	3029	11-20%	<10%	<10%	11-20%
SOLVD 1991	2569	11-20%	<10%	11-20%	<10%
SOLVD 1992	4228	>20%	<10%	<10%	<10%
CHARM Alterative 2003	2028	<10%	11-20%	11-20%	11-20%
Zannad 2011	2737	<10%	11-20%	11-20%	>20%
SENIORS 2005	2128	<10%	>20%	<10%	
CIBIS 1994	641	<10%	>20%		<10%
Sturm 2000	100		>20%	<10%	
Pitt 1999	1663	<10%			
CIBIS 1999	2647	<10%			
Kum 2008	100	11-20%	>20%	>20%	
Munich 1991	170	11-20%	>20%		
Cohn 2001	5010		>20%	11-20%	
Borghi 2013	175		>20%	11-20%	
Rieger 1999	844		11-20%		
Colucci 1996	366	11-20%			
CELICARD 2000	124	11-20%			
Liu 2014	154			>20%	
BEST 2003	224			>20%	
MAIN CHF II 2014	56			>20%	
Dalla-Volta 1999	179				
Zannad 1998	2737				
CARNEBI 2013	183				
Yodfat 1991	84				
US Carvedilol 1996	1094				
Cicoira 2002	106				

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Appendix 4: Use of heart failure drugs in heart failure RCTs compared to the reference population

			Heart Failure Drugs (% of 'reference population') (Davies et al, 2001).				
Heart Failure RCTs	**Study Drugs**	**Number of Participants**	**Aspirin (53%)**	**CCBs (21%)**	**B-blockers (13%)**	**Digoxin (7%)**	**ACEi (26%)**
ELITE II 2000	Losartan, Captopril	3152	<10%	<10%	<10%		
Rieger 1999	Candesartan, Placebo	844	<10%		11-20%	>20%	>20%
SOLVD 1992	Enalapril, Placebo	4228		11-20%	11-20%	<10%	
CHARM Alternative 2003	Candesartan, Placebo	2028	<10%		>20%	>20%	
CHARM Added 2003	Candesartan, Placebo	2548	<10%		>20%	>20%	>20%
SENIORS 2005	Nebivolol, Placebo	2128	11-20%	<10%		>20%	>20%
Pitt 1999	Spironolactone, Placebo	1663	11-20%		<10%	>20%	>20%
SOLVD 1991	Enalapril, Placebo	2569		11-20%	<10%	>20%	
Kum 2008	Irbesartan add-on, Current drugs	100	11-20%		>20%	<10%	
AREA-CHF 2009	Canrenone, Placebo	382		11-20%	>20%	11-20%	>20%
MERIT-HF 1999	Metoprolol CR/XL, Placebo	3991	<10%			>20%	>20%
COMET 2003	Carvedilol, Metoprolol	3029	11-20%			>20%	>20%
Zannad 2011	Eplenerone, Placebo	2737			>20%	11-20%	>20%
Sturm 2000	Atenolol, Placebo	100	>20%			>20%	>20%
Cohn 2001	Valsartan, Placebo	5010			>20%	>20%	>20%
CIBIS 1994	Bisoprolol, Placebo	641				>20%	>20%
CIBIS 1999	Bisoprolol, Placebo	2647				>20%	>20%
BEST 2003	Bucindolol, Placebo	226				>20%	>20%
Zannad 1998	Fosinopril, Enalapril	254				>20%	
CARNEBI 2013	Carvedilol, Nebivolol, Bisoprolol	183					>20%
Liu 2014	Metoprolol, Routine treatment	154					

Dalla-Volta 1999	Delapril, Enalapril	179					
Munich 1991	Captopril, Placebo	170					
Colucci 1996	Carvedilol, Placebo,	366					
CELICARD 2000	Celiprolol, Placebo	124					
MAIN CHF II 2014	Bisoprolol, Carvedilol	59					
US Carvedilol 1996	Carvedilol, Placebo	1094					
Yodfat 1991	Captopril, Placebo	84					
Borghi 2013	Zofenopril, ramipril	175					
Cicoira 2002	Spironolactone, Placebo	106					

	<10% deviation from reference study
	11-20% deviation from reference study
	>20% deviation from reference study
	Insufficient information to calculate deviation
	Drug investigated and therefore not assessed