Contemporary Management of Heart Failure in the Elderly

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Abstract

The foundation of the treatment of heart failure with reduced ejection fraction (HFREF) is a number of pharmacotherapies that have been shown to reduce morbidity and mortality in large randomized multinational clinical trials. These include ACE inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and more recently, a combined angiotensin receptor blocker neprilysin inhibitor, sacubitril/valsartan. In select cases digoxin, ivabradine and hydralazine with isosorbide dinitrate have a role to play in the treatment of HFREF. On this foundation other more advanced treatments such as implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) are recommended in guidelines for the treatment of HFREF (i.e. an ejection fraction of ≤ 40%) and for a select few there remains the option of mechanical circulatory support and cardiac transplantation. The efficacy of pharmacotherapy does not vary by age and each of these therapies should be considered in all patients, irrespective of age. Other factors such as co-morbidities like renal dysfunction may limit the use of some of these drugs in the elderly. Decision making with regards to device therapy is more complex; the likelihood of competing non-cardiovascular causes of death and life expectancy need to be considered. Despite multiple treatment options for HFREF, the options for heart failure with preserved ejection fraction (HFPEF) are limited. In the absence of robust outcomes data from a large randomized trial, a mineralocorticoid receptor antagonist is a reasonable therapy to reduce the risk of hospitalization for HF in HFPEF.

Key points

Heart failure with reduced ejection fraction is treated with a number of pharmacotherapies that reduce morbidity and mortality regardless of age

Older patients have more comorbidities and may be more likely to develop side effects such as hypotension but these side effects can be managed

Heart failure with preserved ejection fraction may be more common in the elderly but as yet no therapies have been proven to reduce morbidity and mortality

1. Introduction

With advances in the understanding of the pathophysiology of heart failure (HF) there have been major advances in the treatment of HF and particularly heart failure with reduced ejection fraction (HFREF), i.e. patients with an ejection fraction of ≤ 40%. Less progress has been made with heart failure with preserved ejection fraction (HFPEF- patients with an ejection fraction of > 50%), a form of HF for which there are few effective therapies. Despite improvements in both pharmacotherapy and device therapy for HF it remains a major cause of morbidity and mortality in the elderly. Although the average age of patients with HF is 77 years[1], early landmark clinical trials were designed with age related exclusion criteria[2,3]. While the narrow inclusion and exclusion criteria improve the internal validity of the trials, the external validity is consequently limited and clinicians must extrapolate the results to populations underrepresented or not studied in the trials such as the elderly.

Delivery of treatments recommended by the guidelines, be those drugs or devices, is complex and frequently limited by comorbidities, limited physiological reserve, altered drug metabolism and the side effects of the treatment. Importantly with respect to devices, the potential benefit over the expected remaining years of life must be carefully considered. In this review we will focus on the management of HF in the older population. We will review the pharmacological therapies that are recommended for the treatment of HF in the major international guidelines. We will also discuss the issues surrounding selection of patients for device therapy, mechanical circulatory support and cardiac transplantation.

2. Heart failure in the elderly

Heart Failure (HF) is one of the major cardiovascular causes of mortality and morbidity worldwide. It is predominantly a disease of the elderly with the incidence rising after the age of 60 and peaking around the age of 75 years[1]. Due to the aging population, the incidence is increasing and with longer survival due to more effective therapies being used, prevalence is also rising[1]. Furthermore, the burden of comorbidity is rising with 87% of patients having at least three other comorbidities[1], but declines in the very elderly presumable due to survivor bias[4].

While in young patients, HF is often labelled as idiopathic, with a dilated cardiomyopathy, in the elderly, hypertension and ischemia tend to be the predominant etiologies in those with HFREF[5]. The normal process of ageing also causes progressive changes in cardiac structure and function, leading to diminished chronotropic and ionotropic responses, myocyte hypertrophy, increased intracardiac and filling pressures, and increased afterload.[6] Consequently, HFPEF is more common in the elderly[4]. Age-associated myocardial and vascular wall stiffness may lead to increased filling pressure in a stiff ventricle, resulting in pulmonary oedema[6]. Coexisting comorbidities common in the elderly e.g. atrial fibrillation, have potential to trigger acute decompensation in a heart with limited cardiac reserve. Coupled with this, older patients are also more likely to suffer from other comorbidities such as renal disease, diabetes, chronic lung disease and atrial fibrillation, directly and indirectly contributing to the myocardial damage, and adding to the complexity of HF.

3. Pharmacological treatment of heart failure with reduced ejection fraction

Elderly patients tend to be under-represented in landmark clinical trials of therapies currently recommended for the treatment of HF in the guidelines, with the mean age being in the 60s (Figure 1). Additionally, pharmacological treatment in elderly patients with HF is frequently limited by comorbidities such as renal dysfunction or hypotension. Elderly patients are also more likely to take multiple medications, and polypharmacy is associated with increased risk of drug interactions and adverse side effects. Although the incidence of side effects varies by age, the methods to deal with these do not differ in older compared to younger patients and the same principles apply. We would suggest following the recommendations in the guidelines with regards to dealing with side effects of the major classes of pharmacotherapy for HF.[7] While diuretics are recommended for all with signs and symptoms of congestion, other medications recommended by guidelines aim to improve morbidity and mortality[8,9].

3.1 ACE inhibitors and angiotensin receptor blockers

The first major breakthrough in the treatment of HFREF came with the finding that angiotensin converting enzyme (ACE) inhibitors improved mortality in patients with HFREF[3,10]. The guidelines recommend that all patients with HFREF are commenced on an ACE inhibitor[8,9]. Although there have not been age specific analyses of the two main trials that underpin the use of ACE inhibitors, a meta-analysis, including these two trials and a number of other smaller trials, has shown that the efficacy of ACE inhibitors is similar across age groups (Figure 2)[11]. ACE inhibitors improve mortality, and in particular in the elderly, reduce

hospitalizations for HF. Angiotensin receptor blockers (ARBs) are an alternative to ACE inhibitors in those who cannot tolerate ACE inhibitor[8,9]. In the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity trial (CHARM), the ARB candesartan was similarly effective across the age range in patients who could not tolerate an ACE inhibitor in the CHARM-Alternative arm of the program[12,13]. The efficacy of these drugs in the elderly with HFREF is not in question given the vast number of patients studied in multiple trials with no evidence of any age by treatment interaction. ACE inhibitors and ARBs can cause renal dysfunction, hyperkalaemia and hypotension. As older patients tend to have poorer renal function and often have issue with low blood pressure, these side effects can be more pronounced in the elderly. However, with careful monitoring of fluid status (ensuring that the patient is not dry), consideration of other therapies that may be causing renal dysfunction or hypotension, these issues can be overcome.

3.2 Beta-blockers

Beta-blockers reduce mortality and morbidity in symptomatic patients with HF and current guidelines recommend combination of ACE inhibitors and beta-blocker as soon as diagnosis of HFREF is made[8,9]. The major clinical trials that have demonstrated the benefit of beta-blockers have been conducted in relatively young populations by current standards. However, in contrast to ACE inhibitors and ARBs, beta-blockers have been specifically tested in an elderly population in the SENIORS trials. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure study (SENIORS) included only patients at the age of 70 or above[14]. Use of beta-blocker nebivolol, when

compared to placebo, was associated with 14% reduction in all cause mortality and hospitalization (hazard ratio [HR] 0.86 95% confidence interval [CI] 0.74-0.99, p= 0.039)[26]. This was mainly driven by the reduction in hospitalizations and not mortality, which was not reduced by nebivolol (HR 0.88, 95% CI 0.71–1.08; p= 0.21). In recognition of the higher prevalence of HFPEF in the elderly, the SENIORS investigators enrolled patients with HFPEF and HFREF[15], however only 35% had ejection fraction (EF) of > 35%, therefore despite there being no interaction between EF and the efficacy of nebivolol, the small number of patients with EF of ≥ 40% has meant that this therapy is not considered for the treatment of HFPEF by the guidelines. SENIORS did however provide valuable information on the safety and tolerability of beta-blockers in the elderly. As expected, there was more bradycardia and hypotension compared to placebo in the nebivolol group but drug discontinuation rates and dose achieved were similar in the beta-blocker and placebo groups[15]. Finally, a comparison of the tolerability of bisoprolol and carvedilol in the those >65 years of age, confirmed that these drugs can be used and up titrated in this age group[16].

3.3 Mineralocorticoid receptor antagonists

The mineralocorticoid receptor antagonists (MRA) spironolactone and eplerenone have been tested in two large randomized trials in patients with HFREF. Spironolactone was tested in the Randomized ALdactone Evaluation Study (RALES) in a population with New York Heart Association Class (NYHA) class III and IV HFREF[17]. Spironolactone reduced the risk of death in all ages (Figure 2). The MRA eplerenone was similarly effective in patients in NYHA class

II (Figure 2) [18]. MRAs, as with ACE inhibitors and ARBs may cause renal dysfunction and hyperkalaemia, though they can be managed in the same way. Currently MRAs are indicated in patients who are receiving an ACE inhibitor or an ARB plus a beta-blocker and still remain symptomatic (NYHA class II or higher)[8,9].

3.4 Sacubitril/valsartan

Sacubitril/valsartan is the first in class of the angiotensin receptor neprylisin inhibitors (ARNI). This drug is an ARB (valsartan) combined with a neprilysin inhibitor (sacubitril). The aim of the drug is to both inhibit the renin-angiotensin-aldosterone system with valsartan and augment the natriuretic peptides through neprilysin inhibition. As such, it should not be prescribed at the same time as an ACE inhibitor or an ARB, and before commencing it patients must be off their ACE inhibitor for 36 hours. In the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial sacubitril/valsartan was superior to the ACE inhibitor enalapril in reducing cardiovascular (CV) death or HF hospitalizations, and all-cause mortality[19]. The mean age of patients was 64 years, however nearly 1 in 5 patients (18.6%) were aged 75 years or older[20]. The beneficial effect of sacubitril/valsartan was consistent across the spectrum of age for all of the endpoints studied, including all-cause mortality (Figure 2)[20]. The major guidelines differ slightly in their interpretation of the trial with the European guidelines recommending that an ARNI should be initiated in those who are still symptomatic despite an ACE inhibitor or an ARB, a beta-blocker and a MRA while the US guidelines are more lenient, allowing it to be used in place of an ACE inhibitor or an ARB earlier on in the treatment of HFREF. Sacubitril/valsartan is similar to all

other inhibitors of the renin-angiotensin-aldosterone system in that it can cause hypotension, renal impairment and hyperkalaemia. However, renal dysfunction and severe hyperkalaemia are less common with sacubitril/valsartan than enalapril and their incidence is no different across the different age groups[20]. Hypotension was a more frequent side effect and more common with sacubitril/valsartan than enalapril, but was not more common in the elderly (Figure 3)[20]. Finally there has been some concern that there is a theoretical risk that as neprilysin breaks down amyloid-ß peptides that inhibition of neprilysin may increase the risk of Alzheimer's type dementia. However, in a retrospective analysis of PARADIGM-HF the rates of reported dementia were no different to a number of other trials of medications for heart failure including ARBs, statins and direct renin inhibitors.[21]

3.5 Ivabradine

The I*f* channel inhibitor ivabradine is used for the treatment of HFREF when the patient is in sinus rhythm and either cannot take a beta-blocker (for example due to a contraindication such as asthma or bradycardia) or a heart rate of >70 bpm despite maximal tolerated dose of beta-blockers. This is on the basis of the Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial (SHIFT)[22] that demonstrated that ivabradine reduced the composite endpoint of CV death or HF hospitalization (although this was mainly through a reduction in HF hospitalizations). In an analysis of age groups the authors found no difference in the efficacy of ivabradine by age[23].

3.6 Digoxin

Digoxin has been used for the treatment of HF for thousands of years. The Digitalis Investigation Group (DIG) study examined the efficacy of digoxin in patients with HFREF and in the ancillary study, those with HFPEF[24]. Digoxin failed to reduce all cause mortality (the primary endpoint) but did reduce the secondary endpoints of HF mortality or HF hospitalization, HF hospitalization and all cause hospitalizations, and these effects were the same across all ages[25].

3.7 Hydralazine and isosorbide dinitrate

The combination of hydralazine and isosorbide dinitrate has been studied in randomized trials[26,27]. While in the era prior to ACE inhibitors the combination was beneficial[26], when tested against an ACE inhibitor it failed to improve outcomes[27]. However, the subgroup of patients of African descent did appear to gain benefit and in the subsequent African-American Heart Failure Trial (A-HeFT)[28], the combination reduced the primary endpoint of all cause death or HF hospitalization. This is thought to be because patients of African descent are less responsive to ACE inhibitors due to lower levels of activation of the renin-angiotensin-aldosterone system. As such hydralazine and isosorbide dinitrate remain an option for those unable to take or tolerate an ACE inhibitor, an ARB or an ARNI[8,9].

4. Device and surgical therapy in HFREF

4.1 Implantable cardioverter defibrillators and cardiac resynchronization therapy

While the foundation of treatment of HFREF remains pharmacotherapy, in select patients implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) are indicated. However, the use of these device

therapies in the elderly is complex. Briefly, ICDs are indicated in a primary prevention setting if the patient is symptomatic (NYHA class II-III) with reduced EF (≤ 35%) despite 3 months of treatment with optimal medical therapy (OMT)[8,9]. An important additional criterion is that patients should have good functional status and should be expected to survive for more than 12 months. This is to ensure that the benefits of ICDs are likely to be realized. This can therefore often be a barrier to elderly patients. In the setting of secondary prevention ICDs are recommended in patients who have recovered from a ventricular arrhythmia, and again, who are expected to survive for more than 12 months and have good functional status[8,9].

Data on primary prevention in the elderly is limited and conflicting[29–31]. While many of the trials showed significant reduction in mortality in comparison to medical therapy alone, they predominantly included younger patients. The decision to implant an ICD in the elderly includes taking account of likely benefit, potential harms (both of the procedure and then the device itself which can fire inappropriately) and cost has been reviewed elsewhere[32]. While the use of ICDs in patients with an ischemic aetiology, which is more common in the elderly, is less controversial, their use in non-ischemic aetiology of HF is difficult[33]. Certainly the risk/benefit ratio in the whole population, and in particular the elderly, is questionable given contemporary rates of sudden death with modern pharmacotherapy[34,35].

4.2 Cardiac resynchronization therapy (CRT)

Cardiac resynchronization therapy (CRT) has been shown to improve quality of life, and reduce morbidity and mortality in selected patients with HF. Current guidelines recommend CRT in patients with EF ≤ 35%, wide QRS (≥ 130 ms) who remain symptomatic (NYHA II-IV) despite OMT[8,9]. Similar to the trials of medical therapies, trials of CRT have tended to include younger patients, though subsequent analyses have not shown any difference in efficacy by age[36–38]. As with pharmacotherapy, the incidence of adverse events following ICD or CRT implantation such as pocket infection or haematoma formation is higher in elderly patients[39]. In addition to considering efficacy in the elderly, side effects and dealing with side effects of device implantation must be taken into account during the decision making process.

4.3 Coronary artery bypass grafting

In patients with coronary artery disease and HFREF, over a 10 year follow up, coronary artery bypass grafting was superior to optimal medical therapy and therefore is recommended in the guidelines as a therapeutic option for these patients[40]. However, much like ICDs and CRT, the benefit of surgery must be considered in light of potential life expectancy (the benefit takes a number of years to become apparent) and the competing risk of non-cardiovascular causes of death. As such the efficacy of coronary artery bypass grafting appears to be greater in younger patients[41].

4.4 *Valve surgery and interventions*

In selected patients valve interventions such as surgical valve replacement or repair may be indicated in patients with heart failure due to valvular disease and

in those patients in whom valve disease is worsening their heart failure[7,42]. The percutaneous treatment of aortic stenosis has become widespread and may be the favoured option in the elderly with more comorbidity who are unable to undergo surgical valve repair or replacement. More recently percutaneous techniques for the treatment of mitral valve regurgitation have shown promise in clinical trials although the mean age of enrolled patients remains relatively young[43]

5. Cardiac Transplantation and Mechanical Circulatory Support

Left ventricular assist devices (LVADs) and cardiac transplantation are important therapies for advanced HF. Although their availability remains limited to specialized centers, the worldwide number of LVAD implants is increasing. While some centers have strict age related criteria for LVAD implantation, the literature on outcomes in the elderly remains inconclusive and rates of use after the age of 65 years are low with data derived mainly from registries[44]. Similarly for cardiac transplantation age is not a contraindication but advancing age is an incremental risk factor. As a result, few patients in the UK have been transplanted above the age of 65 years although worldwide older patients do receive transplants[45]. The use of cardiac transplantation and LVADs in the elderly is a topic of much debate as the potential benefit of the therapies again must be weighed with their highly invasive nature and high incidence of serious side effects.[46]

6. Heart failure with preserve ejection fraction (HFPEF)

This review has tended to focus on the patients with HFREF, primarily because much of the evidence base is in this group. HFPEF is also challenging to diagnose correctly and patients are often older and have more comorbidities.[47] However, in

older age groups the proportion of patients with HFPEF is higher, reaching 50% in some series. This group is particularly problematic as there are no clinical trials that have demonstrated a benefit of any one therapy in this group. ACE inhibitors[48], ARBs[49,50], MRAs[51] and ivabradine[52] have all been tested in this group, a trial of sacubitril/valsartan in HFPEF is ongoing[53]. The best current evidence comes from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study[51], where the MRA spironolactone was compared to placebo in patients with HF and EF of ≥45%. The trial was conducted in North America, Russia and Georgia, and there was doubt as to the diagnosis and adherence to therapy in Russia and Georgia centres. However, in the North American patients there was a reduction in HF hospitalization with spironolactone. In the absence of any other therapy that alters outcomes, the use of spironolactone in this group of patients would seem reasonable as is recommended in the guidelines[9].

7. Summary

The management of HFREF and HFPEF in the elderly follows that of patients of any age. The pharmacotherapies that are recommended in the guidelines on the treatment of HF are also indicated in the elderly and are similarly efficacious in this population. Although age per se is not a contraindication to any device or surgical treatment for HF, decision making about these therapies is more difficult. There should be careful consideration of the potential benefits to the patient, in terms of potential gain in life expectancy, before a decision is made.

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Table. Guideline recommended therapies for the treatment of symptomatic (NYHA class II-IV) heart failure with reduced ejection fraction. Therapies are added sequentially if the patient remains symptomatic.[7,9,54]

Step 1 - First line therapy	**Comments**
ACE Inhibitors (or ARB in those intolerant of ACE inhibitors	ARBs can be used in those intolerant of ACE inhibitors because of side effects such as cough
Beta blockers	
Step 2 - Second line therapy – ongoing symptoms NYHA class II-IV	
Mineralocorticoid receptor antagonists	
Step 3 - Third line therapy – ongoing symptoms NYHA class II-IV	
Ivabradine (heart rate >=70bpm)	Can be used with a betablocker if there is inadequate heart rate control and the patient is in sinus rhythm
Sacubitril/valsartan	Not to be prescribed with an ACE inhibitor or ARB. ACE inhibirors should be stopped 36 hours prior to intiation of sacubitril/valsartan
Isosorbide dinitrate/Hydralazine	
Digoxin	
Step 3 - Device therapy	
Implantable cardioverter defibrillator (ICD)	At any time a patient with an ejection fraction <=35% may be eligible for an ICD is they have a primary prevention indication
Cardiac resynchronization therapy (CRT)	CRT is recommended if the patient remains symptomatic with a reduced ejection fraction despite optimal medical therapy with an ACE inhibitor or ARB, betablocker and MRA. CRT is recommended if the QRS duration is ≥ 130 msec and left bundle branch block is present (in sinus rhythm) and can be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or in patients in atrial fibrillation
Step 4 - Cardiac transplantation/ LVAD	Reserved for select populations after extensive workup in a specialist centre

Figure 1. Mean age of participants in clinical trials of pharmacotherapies that are recommended in guidelines for the treatment of heart failure with reduced ejection fraction and that have been shown to improve morbidity and mortality[2,12,56–61,14,18,19,22,24,26,28,55].

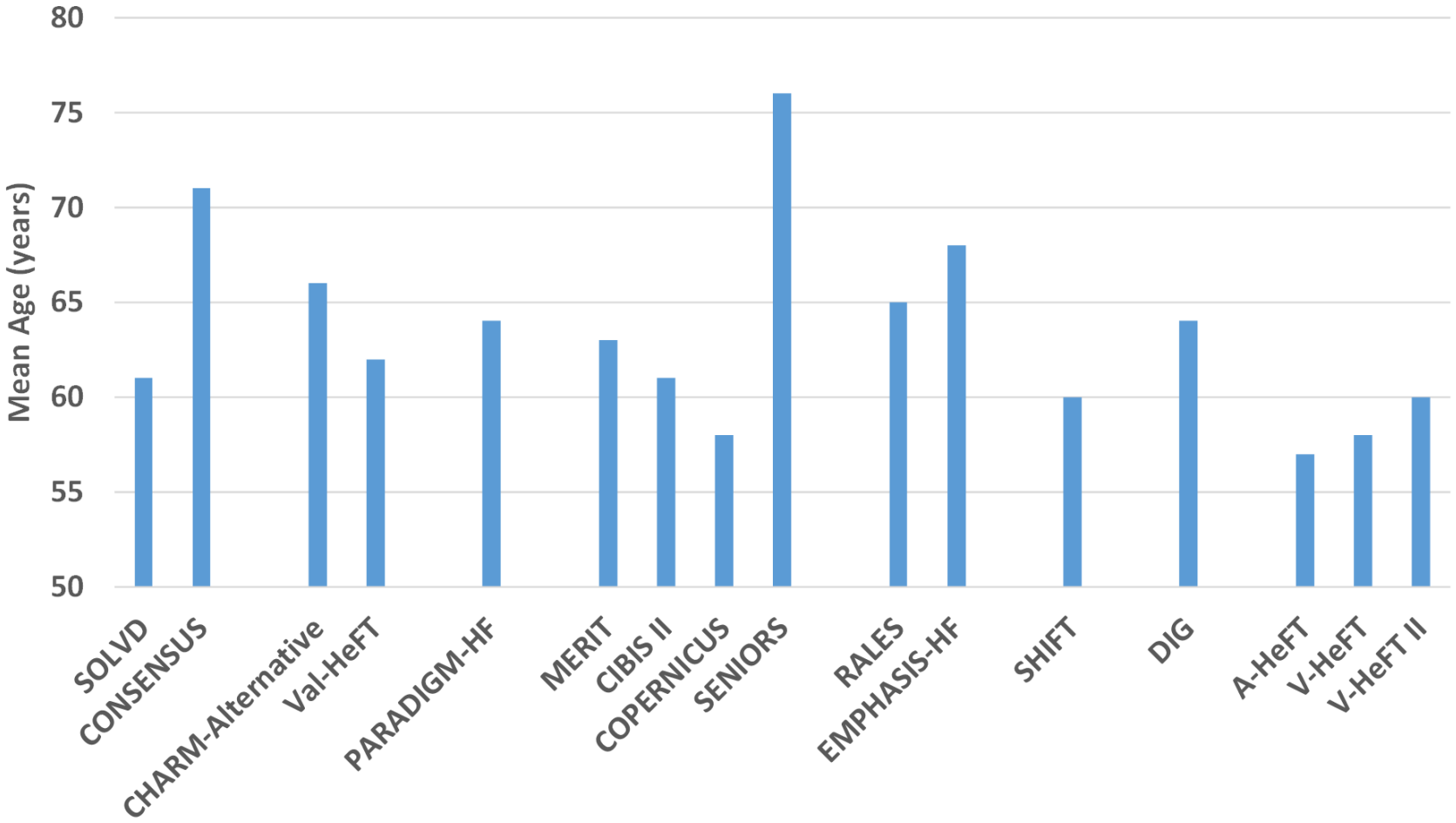

Figure 2. Efficacy of therapies that have been shown to reduce all cause mortality according to age patients with heart failure and a reduced ejection fraction.[11,17–19,62]

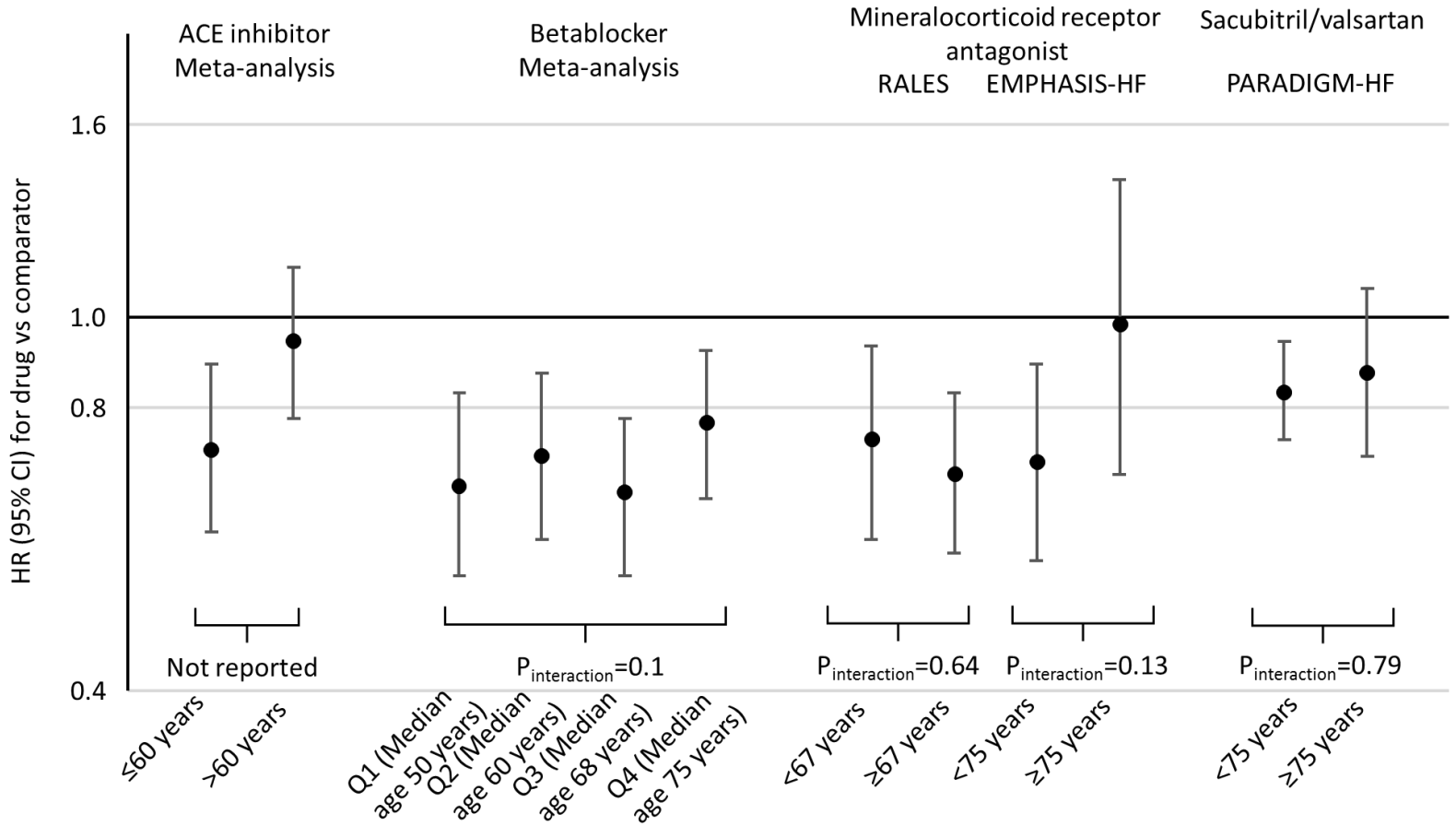

Figure 3. Safety profile of sacubitril/valsartan compared to enalapril according to age. P for interaction for all comparisons >0.05. [20]