Send Orders for Reprints to reprints@benthamscience.ae

REVIEW ARTICLE

Heart Failure Pharmacotherapy and Supports in the Elderly - A Short Review

Sepehr Shakib[1,*] and Robyn A. Clark[2]

[1]*Department of Clinical Pharmacology, School of Medicine, Faculty of Health Sciences, Medical School South, University of Adelaide, Adelaide 5005;* [2]*School of Nursing and Midwifery, Flinders University, Office: Room N212, Sturt Campus North Wing, Adelaide 5001, Australia*

ARTICLE HISTORY

Received: November 30, 2015
Revised: December 18, 2015
Accepted: January 11, 2016

DOI: 10.2174/1573403X12666160622102802

Abstract: Heart failure is predominantly a disease of the elderly with an increasing prevalence with increasing age. Increasing age is also associated with increased multi-morbidity such that elderly heart failure patients typically have five to six comorbidities in addition to heart failure. Elderly patients are also more likely to have heart failure with preserved ejection fraction (HF*p*EF), and there are fewer evidence-based treatments with proven efficacy in HF*p*EF. Hence the management of heart failure in these patients is largely about managing the symptoms of heart failure, along with the other cardiovascular and non-cardiovascular comorbidities. Any proposed treatments need to be considered for the potential for reduced benefit due to the competing risk of morbidity and mortality from the patient's other conditions. In patients with heart failure, health related quality of life is impacted by both comorbidities and frailty, and frailty is associated with an increased risk of emergency department visits and hospitalisation. Frailty may also be associated with increased adverse reactions to medications. Although newer guidelines have more information on the management of these comorbidities there are still many areas of uncertainty and potential treatment conflicts. Further research is required on the interactions between different comorbidities, their treatments and heart failure and its management.

Keywords: Heart failure, cardiac, elderly, comorbidity, pharmacotherapy.

INTRODUCTION

Heart failure is predominantly a disease of the elderly with increasing prevalence with increasing age [1]. The average age of a heart failure patients in the UK is currently 77 years [2]. The prevalence of multi-morbidity also increases with age [3]. Elderly heart failure patients typically have five to six comorbidities in addition to their heart failure [4-6].

Elderly patients are also more likely to have heart failure with preserved ejection fraction (HF*p*EF) [5], and there are fewer evidence-based treatments with proven efficacy in HF*p*EF [5]. Patients with HF*p*EF are often perceived as being less critically ill, but they have similar mortality [7] and similar or increased health care costs compared to those with reduced ejection fraction (HF*r*EF) [7, 8].

Hence the management of heart failure in elderly patients is largely about managing the symptoms of heart failure, along with the other cardiovascular and non-cardiovascular comorbidities, and to a lesser extent improving prognosis. Any proposed treatments need to be considered for the potential for reduced benefit due to the competing risk of morbidity and mortality from the patient's other conditions.

The aim of this paper is to present a summary of the current evidence in relation to what is known about the pharmacological and non-pharmacological treatment and management of the elderly person with heart failure. From this review we hope to identify the gaps and make recommendations for future research on an internationally growing clinical issue.

COMORBIDITIES IN HEART FAILURE PATIENTS

Elderly patients with heart failure can have a number of cardiovascular comorbidities (ischemic heart disease, hypertension, hyperlipidemia, atrial fibrillation, cerebrovascular disease) and non-cardiovascular comorbidities (diabetes, renal impairment, chronic obstructive pulmonary disease (COPD), osteoarthritis, malignancies, gout, anemia, obstructive sleep apnea, depression). The prevalence of these varies in different studies depending on the age, gender, and characteristics of the population studied [5, 9]. Some studies have shown more non-cardiovascular than cardiovascular comorbidities [10] particularly as patients get older. Also elderly patients with heart failure are as likely to have hospitalisations due to non-cardiovascular causes than heart failure exacerbations [11].

*Address correspondence to this author at the Department of Clinical Pharmacology, Mail Delivery Point 22, Royal Adelaide Hospital, North Terrace, ADELAIDE, South Australia, 5005; Tel: +61 8 8222 2763;
Fax: +61 8 8222 2907; E-mail: ssshakib@gmail.com

1573-403X/16 $58.00+.00

Comorbidities in this population are important for a number of reasons:

1. They may affect the use of treatments for heart failure e.g. renin-angiotensin agents which may exacerbate renal dysfunction, beta-blockers which may worsen shortness of breath in patients with reversible airways disease, severe renal impairment which can complicate diuretic management.
2. The medications used to treat comorbidities may cause a heart failure exacerbation e.g. non-steroidal anti-inflammatory medications or prednisolone used to treat gout, some chemotherapy agents which can reduce left ventricular function e.g. trastuzumab, anthracyclines, or others which are given with large fluid loads e.g. cisplatin, steroids used for exacerbation of chronic obstructive airways disease.
3. The medications used to treat the comorbidities may interact with heart failure medications e.g. nitrates used to treat angina and diuretics for heart failure both worsen postural hypotension, beta-blockers may impact on the benefit of beta-agonists used for treatment of obstructive airways disease.
4. Comorbidities such as cognitive impairment and depression may be associated with poor self-care interfering with the patient's ability to manage their heart failure [12].
5. Other comorbidities, if poorly treated, can create a chaotic therapeutic environment where step-wise increments of heart failure management can become lost in the need to manage acute exacerbations of other conditions.

Often due to the complex nature of the treatments and comorbidities multiple effects can occur in the same patient e.g. a patient with chronic renal impairment and COPD may be prescribed tiotropium, and because this agent is renally cleared, it may accumulate resulting in worsening anticholinergic adverse effects such as dry mouth. The dry mouth may result in the patient drinking excessively, which may exacerbate their heart failure. Their diuretic management is then complicated by the presence of renal impairment and ensuring that they do not become over-diuresed, resulting in worsening renal function. Alternatively, the patient may attribute their dry mouth to their diuretic, and the subsequent poor compliance may result in heart failure exacerbation and hospitalisation.

FRAILTY IN HEART FAILURE PATIENTS

Frailty is a related but different issue to comorbidity that also occurs commonly in elderly heart failure patients. There is no standard definition of frailty, but it is recognised as a state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems [13]. Most definitions use the Fried phenotype of low grip strength, low energy, slow walking speed, low physical activity and unintentional weight loss [14], whereas others use the model of cumulative deficits such as disability, disease, physical and cognitive impairments, psychological risk factors and geriatric syndromes e.g. falls, delirium, urinary incontinence [15]. There is an overlap between comorbidities and frailty, but patients may have reduced function, and disability that may be independent of any defined comorbidities e.g. slowed gait, or contributed to by multiple comorbidities.

In patients with heart failure, health related quality of life is impacted by both comorbidity [16] and frailty [17]. Frailty is associated with an increased risk of emergency department visits and hospitalisation [18]. Frailty may also be associated with increased adverse reactions to medications [19]. Alternatively hospitalisation for new onset heart failure can be followed by sustained functional decline [20]. Hence considerations of frailty are important in the management of elderly heart failure patients as this can impact on their quality of life, hospitalisation, function, and treatment.

SURVIVAL IN ELDERLY HEART FAILURE PATIENTS

Although older heart failure patients would be expected to have worse survival, there is a paucity of long term cohort data specifically for this population and even less information from clinical trials. Considerations of life expectancy are important in terms of whether treatments should be initiated or ceased, either for heart failure or for the associated comorbidity. Population studies [21] provide a global overview, but do not accurately account for comorbidities or severity of heart failure.

Clinical trials of heart failure interventions in the elderly do provide additional information about predictors of mortality [22, 23], however participants are often not representative of typical elderly patients. There is evidence that factors such as comorbidity [24], poor functional status [20, 25, 26] and frailty [27], which are often absent in clinical trial participants, have an impact on mortality. The evidence for these is often derived from small studies, making it difficult to generalise to specific patients. Overall the best available evidence would appear to be that elderly patients with heart failure have a poor prognosis e.g. majority of geriatric outpatients with new heart failure die within 3 years [24]. Furthermore it appears that those elderly patients with severe heart failure e.g. NYHA 4, or severe frailty or functional impairment e.g. those with unintentional weight loss, geriatric syndromes, limited mobility due to fatigue, or in residential aged care irrespective of heart failure severity, should be treated as palliative [24].

As stated above, elderly patients are more likely to have HF*p*EF, and non-cardiovascular causes of death occur more frequently in patients with HF*p*EF compared to those with reduced ejection fraction [28].

EVIDENCE FOR PHARMACOLOGICAL TREATMENT

Heart Failure with Reduced Ejection Fraction

Elderly patients have been poorly represented in clinical trials demonstrating the benefits of ACE inhibitors and beta-blockers, the cornerstones of the management of heart failure with reduced ejection fraction. The median age of participants in the original ACE inhibitor trials approximated 60

years [29], and approximately a third of patients in the landmark beta blocker studies were "elderly" (defined in different studies as being above between 59 and 71 years old) [30]. Even though older patients may be enrolled in these studies they are not representative of typical patients, as they do not reflect real world psychological or clinical profiles or functional status.

There is evidence of "elderly" heart failure patients having a higher overall mortality but similar relative risk reduction from beta blockers [30]. In recent years, studies such as the SENIORS study have attempted to recruit an elderly cohort by including only those patients aged ≥70 years. Despite this, the median age of those enrolled was 75 years, the majority were men (63%) and the majority had a left ventricular ejection fraction of ≤ 35% (64.5%). This does not reflect the demographic profile of elderly heart failure that has a much higher median age with a higher proportion of women and a higher prevalence of HF*p*EF. The SENIORS study demonstrated the benefit of beta blockers in this population, however, the reduction in the primary endpoint of all-cause mortality or cardiovascular hospital admission was less than in previous beta blocker studies [HR 0.86, 95% CI 0.74-0.99; p=0.039], and the reduction in mortality was not significant (HR 0.88, 95% CI 0.71-1.08; P=0.21). This was partly due to the lesser benefit of beta blockers in preserved ejection fraction, as well as the older patients having a competing risk of death from other comorbidities.

There have been few studies which have randomised patients to different doses of heart failure interventions to assess the impact of treatment intensity on outcomes [31], and there is even less information on the risks and benefits of treatment intensity in elderly patients with HF*r*EF. Some evidence is available from the TIME-CHF trial which randomised patients to either symptom-guided or Brain Natriuretic Peptide (BNP) guided therapy, with the latter group resulting in patients being prescribed higher doses of ACE inhibitor, angiotensin receptor blocker and beta blocker therapy [32]. More intensive treatment did not result in improved outcomes such as survival, hospital free survival or heart failure hospital free survival in heart failure patients aged 75 years or over, but was associated with more treatment related serious adverse events. Furthermore the difference in this outcome was significantly different compared to those aged less than 75 years (P<0.02 for interaction).

In summary, although few typical elderly HF*r*EF patients were enrolled in landmark trials of heart failure interventions, the evidence of benefit can be extrapolated to this population. The size of the benefit may be reduced by competing risk for mortality and hospitalisation by other conditions, and the best available evidence suggests that increased intensity of pharmacological interventions is not associated with additional benefits, and may be associated with harms.

Heart Failure with Preserved Systolic Function

Heart failure with preserved systolic function has been variably classified as ejection fraction (EF) >40%, >45%, >50% and ≥55% [5] although the recent guidelines define this as heart failure with an ejection fraction of ≥ 50% [5, 9]. Patients with EF between 40-50% represent an intermediate group, who are often treated for underlying risk factors, comorbidities, and pharmacological management similar to HP*r*EF.

There have been few large-scale studies assessing the impact of pharmacological interventions on patients with HF*p*EF [33-35]. Due to the negative results on trials conducted to date, current recommendations for the control of risk factors such as hypertension, myocardial ischemia, and atrial fibrillation remain unchanged [5, 9]. Diuretics are also recommended for symptomatic management due to volume overload. A meta-analysis has reported the benefits of ACE inhibitors in patients with preserved left ventricular ejection fraction, however, although a significant reduction in all-cause mortality was seen (OR 0.52; 95% CI 0.41-0.64, P<0.01), death due to worsening of heart failure, heart failure related rehospitalisation and all cause hospitalisation were not affected [36].

MANAGEMENT OF ELDERLY PATIENTS WITH HEART FAILURE

As can be seen from the discussion above, the management of heart failure in elderly patients is a difficult balancing act of understanding the patient's heart failure and associated comorbidities, understanding the potential benefits and risks associated with the interventions which have been shown to be of benefit, monitoring carefully for adverse effects which may be more common in the elderly, and considering this in the context of the patient's frailty and functional limitations, and potential survival.

Elderly patients with HF*r*EF should be initiated on evidence-based pharmacological and non-pharmacological interventions. They are more likely to develop medication related adverse effects, particularly due to frailty and their comorbidities e.g. reversible obstructive airways disease for beta blockers, or age related renal impairment e.g. for ACE inhibitors, angiotensin receptor antagonists, aldosterone antagonists. Hence, they need to be monitored more closely for these potential adverse effects. They may also be less likely to report some adverse effects e.g. postural hypotension, shortness of breath, lethargy, bradycardia, as they may believe that it is related to the underlying heart failure, or due to other comorbidities or medications. Other medication adverse effects may be more detrimental in the frail elderly e.g. postural hypotension may precipitate falls which may cause fractures in those with osteoporosis, anorexia due to digoxin may cause malnutrition in those with borderline nutritional intake, nocturia due to diuretics may lead to falls as elderly patients attempt to ambulate at night in the dark.

Although there is no direct evidence assessing the impact of dose escalation of evidence-based therapies in elderly patients with HF*r*EF, the best available evidence would suggest that treatment should be symptom driven, and that intensification of treatment to doses achieved in clinical trials in younger patients may be associated with no benefit, and some potential harm. This conclusion is congruent with observations regarding the morbidity and mortality of comorbidities, and frailty in this population, and the fact that some of these may be exacerbated with greater intensity of treatment e.g. postural hypotension leading to falls and decreased mobility, worsening renal impairment.

In patient with *HFpEF* pharmacological treatment is aimed primarily at the management of fluid overload with diuretics, and the control of risk factors such as myocardial ischemia, hypertension and atrial fibrillation.

It can be seen that although audits have found reduced guideline compliance in patients with chronic heart failure [37], many have HF*p*EF where the evidence for ace inhibitors and beta blockers is unclear, and patients are more likely to have contraindications such as renal impairment, reversible airways disease, and postural hypotension. Patients may also be on submaximal doses of pharmacological agents, and this may be an appropriate strategy for elderly patients.

From the discussion above, it is clear that the management of elderly patients with chronic heart failure is much more about the management of comorbidities including heart failure, in the setting of frailty, functional impairment and limited survival, and hence strategies which manage the patient holistically, and have impacts across multiple comorbidities would be preferred.

A systematic review has demonstrated that strategies which incorporate follow-up by a specialised multidisciplinary team reduce mortality, heart failure hospitalisation and all cause hospitalisations [38]. These strategies often involve not only specialist follow-up but also nurse-led clinics, home visits, education, self-management guidelines, dietary and social services consultations, and medication review. Although the focus of these interventions is on heart failure management, some of the interventions e.g. medication review, dietary advice, self-management guidelines, would also be beneficial for the patient's other comorbidities. In this systematic review, the strategies which evaluated cost were found to be cost saving. There also evidence that disease management programs may be less costly and more effective in moderately frail patients [39] compared to non-frail or mildly frail patients. A multidisciplinary model which including other specialties e.g. general physicians, clinical pharmacologists, pharmacists combined with electronic decision support tool has been demonstrated to achieve excellent evidence-based management outcomes for not only heart failure, but a number of other comorbidities seen commonly in this population as well [40].

The literature on the benefit of home medication reviews in patients with heart failure is unclear with a large randomised trial demonstrating increased hospitalisation [41], but other reviews [42], and observational data [43] supporting this intervention. This intervention has a slightly different model in different countries, but essentially involves a pharmacist visiting the patient in their own home to review their medications. They are able to reconcile medication lists from different sources, and check these against what the patient is actually taking; assess patient compliance, medication packaging storage, and whether any inappropriate non-prescribed medications are being taken e.g. non-steroidal anti-inflammatory medications; remove out of date medications with the patient's permission; assess the use of puffers and other medication administration devices; provide education about medications, and provide a report to other team members about suggestions to improve medication management. Although unequivocal evidence of benefit has not been demonstrated, in patients struggling with medication management, or at high risk of medication misadventure e.g. immediately post-discharge from hospital with multiple medication changes, the pharmacist is able to make a number of useful interventions [44].

General practice and primary care management plans that have a planned structured and holistic approach have also been shown to be associated with a reduced time to next hospitalisation [45].

TELEPHONE SUPPORT AND TELEMONITORING

Meta-analyses of randomized controlled trials and cohort studies have found that remote monitoring of heart failure can reduce mortality and hospitalizations compared with usual care [46-48]. It has been suggested that frequent monitoring may work in a health maintenance mode by improving titration of and compliance with therapy or in an early crisis-detection mode and enabling timely intervention [49]. There is a great need to investigate which particular technologies are most effective and whether remote monitoring interventions are effective in particular subsets of the heart failure population: including those who, for example, have mild cognitive impairment [50], or older individuals [51].

Only half (50%) the studies in a recent Cochrane review that investigated telephone support and telemonitoring recruited patients aged over 70 years. These findings suggest a systematic bias in recruiting older heart failure patients in trials; despite the appropriateness of recruiting them.

It is may be thought that the frailty of the elderly population, in particular the degenerative musculoskeletal and sensory (auditory/visual) changes as well as increased number and severity of comorbidities, both biomedical and psychosocial, would impair functional ability to the extent that it would impede participation in remote monitoring programs. Previous studies that have focused on patient adherence as opposed to the outcomes for telemonitoring generally report positive outcomes for the elderly with heart failure. Results from these studies have consistently identified that elderly patients are able to effectively use the remote monitoring technology. They have reported that elderly patients can adapt quickly to telephone monitoring, find its use an acceptable part of their healthcare routine, and are able to maintain good adherence for at least 12 months. These findings would support the use of telephone support and telemonitoring as part of a comprehensive multidisciplinary heart failure management program for elderly people [52]. High rates of adherence to remote monitoring for heart failure was also found in a more recent study with an even older sample of patients aged over 65 years (mean 78 years) [53].

CONCLUSION

In summary, few typical elderly heart failure patients have been enrolled in landmark trials of heart failure interventions and only little evidence of benefit can be extrapolated to this population. The size of the benefit may be reduced by competing risk for mortality and hospitalisation by other conditions, and the best available evidence suggests that increased intensity of pharmacological interventions is not associated with additional benefits, and may be associated with harms.

Newer guidelines have more information on the management of heart failure and common comorbidities [5, 9] there are still many areas of uncertainty and potential treatment conflicts for the elderly heart failure patient [6]. Further multidisciplinary research is required on the interactions between different comorbidities, their treatment and management for the very complex and often frail elderly heart failure patient.

LIST OF ABBREVIATIONS

EF	=	Ejection Fraction
HR	=	Hazard Ratio
OR	=	Odds ratio
HF*p*EF	=	Heart failure with preserved ejection fraction
HF*r*EF	=	Heart failure with reduced ejection fraction

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Curtis LH, Whellan DJ, Hammill BG, *et al*. Incidence and prevalence of heart failure in elderly persons, 1994-2003. Arch Intern Med 2008; 168(4): 418-24.

[2] de Giuli F, Khaw KT, Cowie MR, Sutton GC, Ferrari R, Poole-Wilson PA. Incidence and outcome of persons with a clinical diagnosis of heart failure in a general practice population of 696,884 in the United Kingdom. Eur J Heart Fail 2005; 7(3): 295-302.

[3] Marengoni A, Angleman S, Melis R, *et al*. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011; 10(4): 430-9.

[4] Krum H, Gilbert RE. Demographics and concomitant disorders in heart failure. Lancet 2003; 362(9378): 147-58.

[5] Yancy CW, Jessup M, Bozkurt B, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62(16): e147-239.

[6] Caughey GE, Roughead EE, Shakib S, Vitry AI, Gilbert AL. Comorbidity and potential treatment conflicts in elderly heart failure patients: a retrospective, cross-sectional study of administrative claims data. Drugs Aging 2011; 28(7): 575-81.

[7] Wong DT, Clark RA, Dundon BK, Philpott A, Molaee P, Shakib S. Caveat anicula! Beware of quiet little old ladies: demographic features, pharmacotherapy, readmissions and survival in a 10-year cohort of patients with heart failure and preserved systolic function. Med J Aust 2010; 192(1): 9-13.

[8] Liao L, Jollis JG, Anstrom KJ, *et al*. Costs for heart failure with normal vs reduced ejection fraction. Arch Intern Med 2006; 166(1): 112-8.

[9] McMurray JJ, Adamopoulos S, Anker SD, *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14(8): 803-69.

[10] van der Wel MC, Jansen RW, Bakx JC, Bor HH, Olderikkert MG, van Weel C. Non-cardiovascular co-morbidity in elderly patients with heart failure outnumbers cardiovascular co-morbidity. Eur J Heart Fail 2007; 9(6-7): 709-15.

[11] Muzzarelli S, Leibundgut G, Maeder MT, *et al*. Predictors of early readmission or death in elderly patients with heart failure. Am Heart J 2010; 160(2): 308-14.

[12] Cameron J, Worrall-Carter L, Page K, Riegel B, Lo SK, Stewart S. Does cognitive impairment predict poor self-care in patients with heart failure? Eur J Heart Fail 2010; 12(5): 508-15.

[13] Xue QL. The frailty syndrome: definition and natural history. Clin Geriatr Med 2011; 27(1): 1-15.

[14] Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56(3): M146-56.

[15] Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001; 1: 323-36.

[16] Franzen K, Saveman BI, Blomqvist K. Predictors for health related quality of life in persons 65 years or older with chronic heart failure. Eur J Cardiovasc Nurs 2007; 6(2): 112-20.

[17] Buck HG, Riegel B. The impact of frailty on health related quality of life in heart failure. Eur J Cardiovasc Nurs 2011; 10(3): 159-66.

[18] McNallan SM, Singh M, Chamberlain AM, *et al*. Frailty and healthcare utilization among patients with heart failure in the community. JACC Heart Fail 2013; 1(2): 135-41.

[19] Mangoni AA. Predicting and detecting adverse drug reactions in old age: challenges and opportunities. Expert Opin Drug Metab Toxicol 2012; 8(5): 527-30.

[20] Formiga F, Chivite D, Sole A, Manito N, Ramon JM, Pujol R. Functional outcomes of elderly patients after the first hospital admission for decompensated heart failure (HF). A prospective study. Arch Gerontol Geriatr 2006; 43(2): 175-85.

[21] Jhund PS, Macintyre K, Simpson CR, *et al*. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation 2009; 119(4): 515-23.

[22] Manzano L, Babalis D, Roughton M, *et al*. Predictors of clinical outcomes in elderly patients with heart failure. Eur J Heart Fail 2011; 13(5): 528-36.

[23] Huynh BC, Rovner A, Rich MW. Long-term survival in elderly patients hospitalized for heart failure: 14-year follow-up from a prospective randomized trial. Arch Intern Med 2006; 166(17): 1892-8.

[24] Oudejans I, Mosterd A, Zuithoff NP, Hoes AW. Comorbidity drives mortality in newly diagnosed heart failure: a study among geriatric outpatients. J Card Fail 2012; 18(1): 47-52.

[25] Delgado Parada E, Suarez Garcia FM, Lopez Gaona V, Gutierrez Vara S, Solano Jaurrieta JJ. Mortality and functional evolution at one year after hospital admission due to heart failure (HF) in elderly patients. Arch Gerontol Geriatr 2012; 54(1): 261-5.

[26] Gastelurrutia P, Lupon J, Altimir S, *et al*. Fragility is a key determinant of survival in heart failure patients. Int J Cardiol 2014; 175(1): 62-6.

[27] Cacciatore F, Abete P, Mazzella F, *et al*. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. Eur J Clin Invest 2005; 35(12): 723-30.

[28] Rickenbacher P, Pfisterer M, Burkard T, *et al*. Why and how do elderly patients with heart failure die? Insights from the TIME-CHF study. Eur J Heart Fail 2012; 14(11): 1218-29.

[29] Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995; 273(18): 1450-6.

[30] Dulin BR, Haas SJ, Abraham WT, Krum H. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. Am J Cardiol 2005; 95(7): 896-8.

[31] Packer M, Poole-Wilson PA, Armstrong PW, *et al*. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999; 100(23): 2312-8.

[32] Pfisterer M, Buser P, Rickli H, *et al*. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009; 301(4): 383-92.

[33] Massie BM, Carson PE, McMurray JJ, *et al*. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008; 359(23): 2456-67.

[34] Cleland JG, Tendera M, Adamus J, *et al*. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006; 27(19): 2338-45.

[35] Yusuf S, Pfeffer MA, Swedberg K, *et al*. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362(9386): 777-81.

[36] Fu M, Zhou J, Sun A, *et al*. Efficacy of ACE inhibitors in chronic heart failure with preserved ejection fraction--a meta analysis of 7 prospective clinical studies. Int J Cardiol 2012; 155(1): 33-8.

[37] Komajda M, Follath F, Swedberg K, *et al*. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003; 24(5): 464-74.

[38] McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol 2004; 44(4): 810-9.

[39] Pulignano G, Del Sindaco D, Di Lenarda A, *et al*. Usefulness of frailty profile for targeting older heart failure patients in disease management programs: a cost-effectiveness, pilot study. J Cardiovasc Med 2010; 11(10): 739-47.

[40] Ho TH, Caughey GE, Shakib S. Guideline compliance in chronic heart failure patients with multiple comorbid diseases: evaluation of an individualised multidisciplinary model of care. PLoS One 2014; 9(4): e93129.

[41] Holland R, Lenaghan E, Harvey I, *et al.* Does home based medication review keep older people out of hospital? The HOMER randomised controlled trial. BMJ 2005; 330(7486): 293.

[42] Ponniah A, Anderson B, Shakib S, Doecke CJ, Angley M. Pharmacists' role in the post-discharge management of patients with heart failure: a literature review. J Clin Pharm Ther 2007; 32(4): 343-52.

[43] Roughead EE, Barratt JD, Ramsay E, *et al*. The effectiveness of collaborative medicine reviews in delaying time to next hospitalization for patients with heart failure in the practice setting: results of a cohort study. Circ Heart Fail 2009; 2(5): 424-8.

[44] Lövgren S, Clark RA, Angley M, Ponniah AP, Colley D, Shakib S. Timeliness and clinical impact of hospital-initiated medication reviews. J Pharm Pract 2009; 39(4): 269-73.

[45] Vitry AI, Nguyen TA, Ramsay EN, *et al*. General practitioner management plans delaying time to next potentially preventable hospitalisation for patients with heart failure. Intern Med J 2014; 44(11): 1117-23.

[46] Inglis SC, Clark RA, McAlister FA, *et al*. Structured telephone support or telemonitoring programmes for patients with chronic heart failure. Cochrane Database Syst Rev 2010; 8(August 2010): 1-138.

[47] Klersy C, De Silvestri A, Gabutti G, Regoli F, Auricchio A. Meta-Analysis of remote Monitoring of Heart Failure Patients J Am Coll Cardiol 2009; 54(18): 1683-94.

[48] Inglis SC, Clark RA, McAlister FA, Stewart S, Cleland JGF. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: Abridged Cochrane Review. Eur J Heart Fail 2011; 13(9): 1028-40.

[49] Anker SD, Koehler F, Abraham WT. Telemedicine and remote management of patients with heart failure. Lancet 2011; 378(9792): 731-9.

[50] Cameron J, Ski CF, Thompson DR. Cognitive impairment in chronic heart failure and the need for screening. Am J Cardiol 2011; 107(10): 1547.

[51] Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med 2002; 162(15): 1682.

[52] Clark RA, Yallop JJ, Piterman L, *et al*. Adherence, adaptation and acceptance of elderly chronic heart failure participants to receiving healthcare by telemonitoring. Eur J Heart Fail 2007; 9(11): 1104-11.

[53] Guzman-Clark JRS, Servellen Gv, Chang B, Mentes J, Hahn TJ. Predictors and Outcomes of Early Adherence to the Use of a Home Telehealth Device by Older Veterans with Heart Failure. Telemed J E Health 2013; 19(3): 217-23.