

Ageing of the United States Population: Impact on Heart Failure

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Abstract The United States population, particularly among older age groups, continues to expand. Because the incidence of heart failure increases with age, largely due to the development of heart failure risk factors such as hypertension and coronary artery disease, the epidemic of heart failure is likely to grow further in the coming decades. This article will review the epidemiology of heart failure among older adults, the influence of an aging population on heart failure prevalence and phenotype, the complications in management for a larger and older heart failure population, and the potential implications of these changes for health care costs and delivery. Ultimately, these challenges demand research

into optimal therapeutic strategies for older heart failure patients, including improved prevention and treatment of the major causes of heart failure, an increasing role for palliative care, and innovations in patient-centered health care delivery.

Keywords Heart failure · Aging · Epidemiology · Treatment

Introduction

The United States population has more than doubled from 150 million people in 1950 to approximately 310 million in 2010. The Census Bureau projects that the U.S. population will continue to grow, to almost 440 million persons by year 2050 [1]. Although increased births and immigration have accounted for much of this recent expansion, the proportion of patients >65 years of age is increasing at a greater rate than the total population. While the total population increased by 9.7 % between 2000 and 2010, those >65 years of age increased by 15.1 %. Furthermore, the greatest proportional increases over this 10-year period occurred in the oldest age groups, with a 29.9 % increase in those 85–94 years of age and a 25 % increase in those >95 years of age [2]. Future mortality trends are difficult to predict. While some assert that life expectancy is approaching its natural limit and obesity-related mortality is slowing life expectancy gains, the steady increase in life expectancy observed over the past century has not wavered in recent years [3].

This increase in the aging population has implications for heart failure. Over the next two decades, the proportional increase in the prevalence of heart failure will likely exceed that of other cardiovascular diseases and is likely driven by the aging of the population (see Table 1) [4]. The estimated prevalence of heart failure based on the National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2008 was 5,700,000 among Americans ≥ 20 years of age

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Table 1 Projections of crude cardiovascular disease (CVD) prevalence (%), 2010–2030, in the United States

Year	All CVD*	Hypertension	CHD	HF	Stroke
2010	36.9	33.9	8.0	2.8	3.2
2015	37.8	34.8	8.3	3.0	3.4
2020	38.7	35.7	8.6	3.1	3.6
2025	39.7	36.5	8.9	3.3	3.8
2030	40.5	37.3	9.3	3.5	4.0
% Change	9.9	9.9	16.6	25.0	24.9

Data generated from the National Health and Nutrition Examination Survey (NHANES) and United States Census Bureau, reprinted from Heidenreich PA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123(8):933–44, with permission from Wolters Kluwer. CHD, coronary heart disease; HF, heart failure

*This category includes hypertension, CHF, HF, and stroke

[5]. Approximately 80 % of these patients were >65 years of age. As of 2012, an estimated 2.4 % of the U.S. population has heart failure, with prevalence increasing with age such that, among those 80 years and older, almost 12 % of both men and women have heart failure [5]. This progressive increase in heart failure prevalence with older age is shown in Table 2 [6] and is reflected in a similar increase in death due to heart failure with increasing age (see Fig. 1) [7]. Therefore, as the population of individuals >65 years of age grows, the population of heart failure patients will likely mirror those increases. A study using Census and NHANES data projected that an additional 3 million individuals would develop heart failure by 2030 [4].

How much the prevalence of heart failure grows will depend not only on the changes in population size and makeup, but also on a variety of other factors that influence the development of heart failure, the type of heart failure, and the length of time with which patients live with the disease. We will subsequently review a variety of these factors.

Table 2 Incidence of heart failure* by age and sex FHS, 1980–2003

Cases/1,000 Person-Years		
Age	Men	Women
65–74	9.2	4.7
75–84	22.3	14.8
85–94	43.0	30.7

Data reproduced as published by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services

*Based on physician review of medical records and strict diagnostic criteria

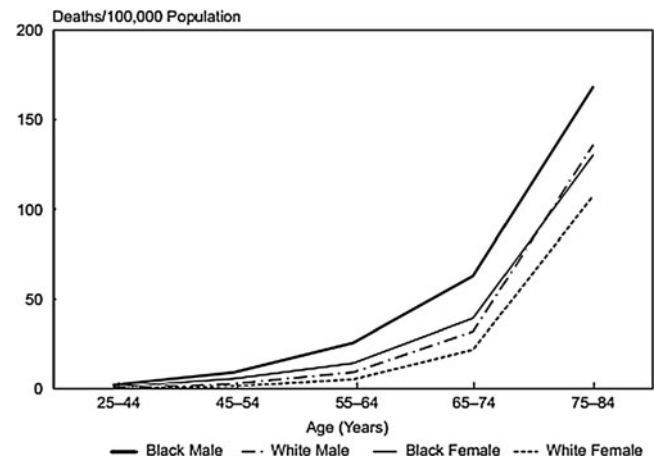


Fig. 1 Death rates for heart failure as the underlying cause by age, race, and sex, U.S., 2008. Data are reproduced as published by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services

Impact of Age on Heart Failure Etiology

The increasing prevalence of heart failure among older Americans is multifactorial in etiology. One contributor is the increasing prevalence of common risk factors for heart failure, such as hypertension and coronary artery disease. In addition, these conditions are occurring at younger ages, providing a greater duration of time for the development of heart failure. Heart failure causes that occur later in life, such as calcific aortic stenosis and impaired cardiac relaxation, also contribute to increased heart failure prevalence among older populations.

Hypertensive Heart Disease

There is a continuous association between systolic blood pressure and incident heart failure in adults >65 years of age [8]. In an adjusted hazards model with data from a cohort of over 4,000 participants without heart failure, prehypertension was associated with greater risk of heart failure (hazards ratio [HR] 1.63, 95 % CI 1.23–2.16), and this risk increased for stage I hypertension (HR 2.21, 95 % CI 1.65–2.96) and stage II hypertension (HR 2.60, 95 % CI 1.85–3.64) [8]. Data from the Framingham Offspring Study estimated that the lifetime risk for heart failure was twofold greater for men and women with systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 100 mm Hg [9]. The population-attributable risks for incident heart failure have been estimated at 21.6 % for systolic blood pressure >140 mm Hg [10]. Because the prevalence of hypertension increases with age and because hypertensive heart disease tends to represent an accumulation of years of pressure overload, heart failure due to hypertensive heart disease disproportionately affects older Americans and is predicted to increase in the coming years.

Although the prevalence of hypertension has remained stable over the 10-year period from 1999 to 2008, the percentage of patients aware of their diagnosis has increased from 69.6 % to 80.6 % over that time period [11]. Additionally, the proportion of adults with controlled blood pressure has increased from 31.6 % to 48.4 % [11]. If the proportion of older hypertension patients with blood pressure control improves over time, this could diminish the incidence of hypertensive heart disease among older Americans, thereby offsetting some of the heart failure increase predicted from a larger older population.

Ischemic Heart Disease

Coronary artery disease is a significant risk factor for the development of heart failure. In a cohort of 676 patients from the Framingham Heart Study who had an incident myocardial infarction between 1970 and 1999, heart failure occurred in 22.4 % of the patients. Additionally, the incidence of heart failure following acute myocardial infarction has increased for each of the last 3 decades, with the 5-year event rate at 19.6 % from 1970 to 1979, 21.5 % from 1980 to 1989, and 33.9 % from 1990 to 1999 [12]. It is likely that improved treatments for acute myocardial patients, while reducing death rates, have contributed to an increase in the incidence of postmyocardial heart failure.

Fortunately, many advances have been made in the primary prevention of coronary artery disease. As was stated above, the proportion of U.S. patients with hypertension who have controlled blood pressure is increasing, which is an important modifiable risk factor for the prevention of coronary artery disease. Additionally, NHANES data indicate that statin use has increased among adults with high LDL levels from 19.6 % in 1999–2000 to 27.3 % in 2001–2002 and 35.9 % in 2003–2004. This trend is accompanied by an increasing proportion of patients who are achieving their target LDL levels according to ATP III guidelines [13]. Finally, the prevalence of cigarette smoking has declined substantially in recent years; in 1965, 41.9 % of adults Americans were smokers, as compared with 20.9 % in 2005 [14]. As several of the cardiovascular risk factors have improved, the incidence of acute myocardial infarction has decreased. In a cohort of 46,086 myocardial infarction patients from Kaiser Permanente Northern California between 1999 and 2008, the incidence of age- and sex-adjusted myocardial infarction decreased from 287 cases per 100,000 person-years in 2000 to 208 cases per 100,000 person-years in 2008 [15]. Continued improvements in modifiable coronary artery disease risk factors may decrease, or at least delay, the incidence of coronary artery disease, thereby offsetting expected increases in heart failure prevalence in an aging population.

Valvular Disease

In contrast to hypertension and coronary artery disease, certain causes of heart failure do not typically appear until later in life. One example is valvular heart disease. Among the elderly population in the U.S., senile calcific aortic disease is a common condition and leads to heart failure. Data from the Framingham Heart Study demonstrated that valvular heart disease increases the risk of heart failure by >50 % among men and women, and that 7 %–8 % of heart failure could be attributed to valvular disease [16].

Changes in Heart Failure Phenotype

Older heart failure patients are more likely to have heart failure with preserved left ventricular ejection fraction (LVEF) [17]. In a sample of patients >65 years of age from the Cardiovascular Health Study with congestive heart failure who had assessments of left ventricular systolic function, 55 % of patients had normal LVEF, and 25 % had mildly reduced LVEF. Among women in the study, 67 % had normal LVEF, as compared with 42 % of men [18]. On the basis of limited existing studies, the epidemiology of HF appears to be shifting in recent years, with an increasing proportion of patients with heart failure having normal LVEF [19, 20••].

Impact of Aging on Heart Failure Management

Pharmacotherapies

While treatment guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers, and aldosterone receptor antagonists for heart failure patients with reduced LVEF, older patients were underrepresented in the randomized trials on which these recommendations were based [21]. Medical therapies for heart failure and reduced LVEF may not always be tolerated in older patients. For instance, in a prospective study of 1,030 heart failure patients >70 years of age, advanced age was a predictor of poor tolerability of beta blockers, and the reasons for beta blocker discontinuation included worsening heart failure, symptomatic hypotension, bradycardia, and wheezing [22]. Hyperkalemia resulting from the introduction or up-titration of ACEI, ARB, or spironolactone is more common among older individuals, due to impaired physiologic renal reserve or overt renal disease [23]. Recognition of these treatment considerations among the elderly can be seen in current practice patterns. Data from the Euro Heart Failure Survey II demonstrate that octogenarians were less commonly prescribed ACEI or ARB, beta blockers, and spironolactone at

hospital discharge after an admission for heart failure, in comparison with younger patients. Additionally, they were prescribed lower doses [24•].

Device Therapies

Increasing age also has important implications in the application of heart failure therapies such as implantable cardioverter-defibrillators (ICDs). The majority of participants in randomized controlled trials for the primary prevention of sudden cardiac death were <65 years of age, raising the question of whether such devices have similar risks and benefits in older individuals with heart failure. Data from a pooled analysis among elderly patients enrolled in the MADIT-II, DEFINITE, and SCD-HeFT trials showed a nonsignificant reduction in all-cause mortality for primary prevention ICD implantation among older patients [25]. As the risk of death from causes other than sudden cardiac death increases among elderly patients with heart failure, the overall survival benefit conferred by invasive therapies such as ICDs may not extend to older heart failure patients [26•].

Comorbidities

Comorbidities among the elderly can have a significant impact on heart failure management. In a sample of >200,000 Medicare beneficiaries with heart failure >65 years of age, over 40 % had ≥ 5 comorbidities. Of this cohort, more than 70 % had ischemic heart disease, over 30 % had diabetes, and approximately 20 % had chronic kidney disease [27••]. Not only do these comorbidities contribute to the greater intolerance of medications and increased complications of devices that are efficacious in younger populations with heart failure and reduced LVEF, but also this increasing prevalence of multimorbidity in progressively older populations results in competing risks of morbidity and mortality due to causes other than heart failure. As a result, heart failure therapies that confer significant mortality benefits in younger heart failure populations may be less germane to older patients with multiple comorbidities

Frailty

In parallel with the increased prevalence of comorbidities among older heart failure patients, frailty is increasingly common. Frail patients have decreased physiologic reserves [28], loss of weight and muscle mass, weakness, poor endurance, slowness, and low physical activity levels [29]. Data from the Cardiovascular Health Study show that heart failure and frailty are related; frail patients have significantly higher odds of heart failure than do nonfrail patients (OR 7.51, CI

4.66–12.12) [30]. Frailty is an independent predictor of death among patients with heart failure [31] and can lead to impaired quality of life and functional status [17]. These relationships between advancing age, frailty, increased vulnerability to a variety of stressors, lower quality of life, and higher mortality should alter the approach to management for older patients with heart failure, as compared with their younger counterparts.

Shared Decision Making, Advanced Planning, and Palliative Care

Given that older patients may not tolerate or benefit from guideline-recommended heart failure therapies and may have greater degrees of comorbidity and frailty, shared decision making among physicians and patients becomes increasingly important. The American Heart Association Scientific Statement on Decision Making in Advanced Heart Failure advocates that physicians have discussions about goals of care and advanced planning with patients that may be part of routine care, driven by worsening heart failure symptoms, considerations of advanced therapies, and the diagnosis of new comorbidities, among other things [32]. This process should focus on the outcomes that are most important to older patients, including not only survival, but also relief of symptoms, quality of life, and living at home. Central to the decision-making process is understanding that “doing everything” is not always the best approach for each patient. For many older patients with progressive heart failure, a more palliative approach focused on symptom relief, comfort, and support may be preferred.

Effect of Aging and Heart Failure on Resource Utilization

The growing population of older adults with heart failure and a high incidence of comorbidity will likely contribute to the increasing costs and hospitalizations accounted for by individuals with heart failure. One study estimated the lifetime cost of heart failure care at initial diagnosis to be \$109,541 per person, with the majority of this cost, or a mean of \$83,980, attributed to hospitalizations. Patients with comorbid conditions such as diabetes and cerebrovascular disease and with heart failure with normal LVEF (i.e., features more common in older patients) had higher costs than did patients with reduced LVEF and without these comorbidities [33]. In a study of Medicare beneficiaries with heart failure >65 years of age, the annual likelihood for hospital admission was 35 %, but among patients with 5 comorbidities, the likelihood increased to 72 %, and among patients with >10 comorbidities, the likelihood

was 94 %. Therefore, with increasing prevalence of heart failure in older populations with multimorbidity, it is likely that annual hospitalization rates will continue to rise [34]. In 2010, the direct costs attributed to heart failure were \$24.7 billion, and this amount is projected to increase to \$77.7 billion by 2030 [4].

Future Directions

The unique aspects of heart failure and its management among older Americans suggest a variety of areas where further research and direction is needed. First, new therapies are needed to treat older patients with heart failure, especially given the disproportionate increase in heart failure with normal LVEF. Clinical trials of ARBs [35], beta blockers [36], and ACEI [37] have not demonstrated mortality benefits or improvement in rates of hospitalizations in patients with heart failure with normal LVEF. At present, volume control with diuretic therapy, sodium restriction, and blood pressure control are the mainstays of treatment [38]. Additional research and clinical trials are needed to improve outcomes and quality of life for patients with heart failure and normal LVEF. Second, the effectiveness of accepted therapies for heart failure with reduced LVEF needs to be assessed for older patients with comorbid conditions, who have largely been excluded from randomized clinical trials. The health care system will need to be prepared to manage an increasing number of older patients with multimorbidity and frailty, coping with the higher resource use associated with their care and exploring alternative systems of care that can more efficiently meet the needs of these complex patients. Third, this expanding cohort of older patients with progressive disease and persistent symptoms such as dyspnea and pain will necessitate an increased focus on symptom reduction and palliative care. A study of veterans with heart failure demonstrated a high incidence of pain, shortness of breath, and low energy levels, suggesting the need for more intensive pain management and symptom relief measures for heart failure patients [39]. The role of palliative care in older patients with advanced heart failure has been far less developed than in cancer [40], and further work documenting the synergistic effect of adding palliative care to the clinical care of patients with advanced heart failure is needed. Finally, exploring ways to encourage high-quality shared decision making will be necessary to ensure that therapeutic decisions chosen from an expanding list of medical options (e.g., left ventricular assist devices) are best aligned with patient values, goals, and preferences.

Conclusion

Because the greatest increases in population are occurring among the oldest age groups, the prevalence of heart failure is projected to expand significantly in the coming decades, by an estimated 50 % (an additional 3 million persons) by 2030 [4]. A larger and older heart failure population has important implications for management, since poorly tolerated therapies, multiple comorbidities, and higher rates of heart failure with normal LVEF (for which there are limited proven interventions) all complicate treatment in older patients. These trends will challenge existing systems of care. Therefore, future research and health policy must work to improve efficiency in health care delivery and optimize quality of life for the growing population of older patients with heart failure.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. United States Census Bureau. Projections of the Population by Selected Age Groups and Sex for the United States: 2010 to 2050. 2008. Available at www.census.gov/population/www/projections/summarytables.html. Accessed July 2012.
2. Werner CA. The Older Population: 2010. The 2010 Census Briefs, November 2011.
3. National Institute on Aging NIH, U.S. Department of Health and Human Services, U.S. Department of State. Why Population Aging Matters: A Global Perspective. 2007:1–32.
4. Heidenreich PA, Trogon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123(8):933–44.
5. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220.
6. National Institutes of Health: NHLBI. Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases.

7. National Institutes of Health: NHLBI. Morbidity and Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases.
8. Butler J, Kalogeropoulos AP, Georgiopoulos VV, et al. Systolic blood pressure and incident heart failure in the elderly. The Cardiovascular Health Study and the Health, Ageing and Body Composition Study. *Heart*. 2011;97(16):1304–11.
9. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106(24):3068–72.
10. Kalogeropoulos A, Georgiopoulos V, Kritchevsky SB, et al. Epidemiology of incident heart failure in a contemporary elderly cohort: the health, aging, and body composition study. *Arch Intern Med*. 2009;169(7):708–15.
11. Yoon S, Ostchega Y, Louis T. Recent trends in the prevalence of high blood pressure and its treatment and control, 1999–2008. *NCHS Data Brief*. 2010;48:1–8.
12. Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-Term Trends in the Incidence of Heart Failure After Myocardial Infarction. *Circulation*. 2008;118(20):2057–62.
13. Mann D, Reynolds K, Smith D, Muntner P. Trends in Statin Use and Low-Density Lipoprotein Cholesterol Levels Among US Adults: Impact of the 2001 National Cholesterol Education Program Guidelines. *Ann Pharmacother*. 2008;42(9):1208–15.
14. Committee on Reducing Tobacco Use: Strategies B, Consequences. *Ending the Tobacco Problem: A Blueprint for the Nation*: The National Academies Press; 2007.
15. Yeh RW, Sidney S, Chandra M, et al. Population Trends in the Incidence and Outcomes of Acute Myocardial Infarction. *N Engl J Med*. 2010;362(23):2155–65.
16. Kannel WB. Incidence and epidemiology of heart failure. *Hear Fail Rev*. 2000;5(2):167–73.
17. Murad K, Kitzman D. Frailty and multiple comorbidities in the elderly patient with heart failure: implications for management. *Hear Fail Rev*. 2012;17(4):581–8.
18. Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients ≥ 65 years of age. *Am J Cardiol*. 2001;87(4):413–9.
19. Owan TE, Hodge DO, Herges RM, et al. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2006;355(3):251–9.
20. • Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in Patients Hospitalized with Heart Failure and Preserved Left Ventricular Ejection Fraction - Prevalence, Therapies, and Outcomes. *Circulation*. 2012. *This study describes differences in demographics, comorbidities, prevalence, and outcomes among patients with heart failure and normal ejection fraction versus those with borderline and reduced ejection fraction who are hospitalized for heart failure.*
21. Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med*. 2011;171(6):550–6.
22. Krum H, Hill J, Fruhwald F, et al. Tolerability of beta-blockers in elderly patients with chronic heart failure: the COLA II study. *Eur J Hear Fail*. 2006;8(3):302–7.
23. Muzzarelli S, Maeder MT, Toggweiler S, et al. Frequency and Predictors of Hyperkalemia in Patients ≥ 60 Years of Age With Heart Failure Undergoing Intense Medical Therapy. *Am J Cardiol*. 2012;109(5):693–8.
24. • Komajda M, Hanon O, Hochadel M, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Hear J*. 2009;30(4):478–86. *This study compares the management and outcomes among octogenarians and younger adults hospitalized with heart failure across Europe. Management and outcomes are also compared across time, between 2000–2001 and 2004–2005.*
25. Santangeli P, Di Biase L, Dello Russo A, et al. Meta-analysis: age and effectiveness of prophylactic implantable cardioverter-defibrillators. *Ann Intern Med*. 2010;153(9):592–9.
26. • Alsheikh-Ali AA, Trikalinos TA, Ruthazer R, et al. Risk of arrhythmic and nonarrhythmic death in patients with heart failure and chronic kidney disease. *Am Heart J*. 2011;161(1):204–9.e1. *This study shows that the proportion of patients who die from nonarrhythmic versus arrhythmic death increases among patients with advanced heart failure and chronic kidney disease.*
27. • Ahluwalia SC, Gross CP, Chaudhry SI, et al. Change in comorbidity prevalence with advancing age among persons with heart failure. *J Gen Int Med*. 2011;26(10):1145–51. *This retrospective cohort study of Medicare beneficiaries with heart failure describes the increasing incidence of comorbidities with age.*
28. van Kan GA, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. *Clin Geriatr Med*. 2010;26(2):275–86.
29. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Biol Sci Med Sci*. 2001;56(3):M146–56.
30. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol Ser A Biol Sci Med Sci*. 2001;56(3):M158–66.
31. 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.
32. Allen LA, Stevenson LW, Grady KL, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation*. 2012;125(15):1928–52.
33. Dunlay SM, Shah ND, Shi Q, et al. Lifetime costs of medical care after heart failure diagnosis. *Circ Cardiovasc Qual Outcomes*. 2011;4(1):68–75.
34. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol*. 2003;42(7):1226–33.
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. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26(3):215–25.
37. Cleland JGF, 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.
38. Bhuiyan T, Maurer M. Heart failure with preserved ejection fraction: persistent diagnosis, therapeutic enigma. *Curr Cardiovasc Risk Rep*. 2011;5(5):440–9.
39. Goebel JR, Doering LV, Shugarman LR, Asch SM, Sherbourne CD, Lanto AB, et al. Heart failure: the hidden problem of pain. *J Pain Symptom Manag*. 2009;38(5):698–707.
40. Bekelman DB, Havranek EP. Palliative care for patients with acute decompensated heart failure: an underused service? *Nat Clin Pract Cardiovasc Med*. 2008;5(5):250–1.