Heart Fail Rev (2006) 11:141–146
DOI 10.1007/s10741-006-9488-6

The treatment of heart failure with preserved ejection fraction ("diastolic heart failure")

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Abstract Unlike heart failure with a low ejection fraction, there is no evidence-based treatment for heart failure with preserved ejection fraction which improves clinical outcomes. Indeed, the only evidence for any treatment effect comes from small studies with verapamil where this drug increased exercise capacity and reduced a heart failure score. Large trials are presently underway which are examining the effect of treatment with an ACE inhibitor, ARB and aldosterone antagonist in patients with heart failure and preserved ejection fraction.

Keywords Heart failure · Diastolic · Ejection fraction · Preserved · Drug treatment

Aims of treatment in the patient with heart failure and preserved ejection fraction ("diastolic heart failure")

Though there are many reports of different agents improving indices of "diastolic function", the significance of such observations is doubtful, as with all reports of surrogate outcomes. Firstly, it is very difficult to know what exactly many non-invasive indices actually measure [1–4]. Secondly, the relationship between these and symptoms, functional capacity or clinical outcome is unclear [1–4]. Thirdly, drugs such as phosphodiesterase inhibitors, that increase mortality, can be shown to improve non-invasive measures of diastolic function [5, 6].

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Consequently, as with heart failure associated with systolic dysfunction, it is improvement in patient well-being and outcome, rather than in ejection fraction, that is important. In other words, we are looking for treatments that improve symptoms, increase functional capacity, reduce the need for hospital admission and lower mortality. Symptom and morbidity reduction may be particularly important in patients with "diastolic heart failure" as most studies show a better survival than in patients with poor systolic function and demonstrating a reduction in mortality in this type of heart failure may be difficult [7–9].

Evidence based treatment of heart failure and preserved ejection fraction

In striking contrast to heart failure associated with left ventricular systolic dysfunction, there is a paucity of evidence on which treatments should be used in patients with heart failure and preserved left ventricular ejection fraction. Though there are many overviews of the theoretical benefits or hazards of particular treatments [10–14], careful review of the literature reveals only a small number of completed randomised trials [15–19]. Few of these are double-blind and placebo-controlled, most enrolled small numbers of patients are and only one has reported long-term morbidity and mortality outcomes. We review these trials in detail.

Heart rate limiting calcium channel blockers

Conceptually, a drug that slows heart rate and reduces myocardial contractility is therapeutically attractive in patients with diastolic dysfunction [20]. Setaro et al. carried out a small, prospective, randomised cross-over comparison of

verapamil and placebo in well characterised patients with "diastolic heart failure" [15].

Twenty two patients were studied. Patients with symptomatic or occult myocardial ischaemia and asymmetrical left ventricular septal hypertrophy were excluded. We do not know if atrial fibrillation was an exclusion criterion.

Diuretic dose was kept constant but digoxin was withdrawn 7 days before randomised treatment was started. Digoxin withdrawal may be associated with clinical deterioration and we are not told what proportion of patients was receiving digoxin at baseline (and how many of these were randomised to placebo and verapamil in the initial treatment period).

A baseline exercise treadmill exercise test (modified Naughton protocol), CHF score and cardiac radionuclide study were obtained. The radionuclide study included measurement of left ventricular ejection fraction and peak filling rate.

Patients were then randomised to placebo or verapamil. The initial dose of verapamil was 80 mg three times daily for 1 week and, if tolerated, this was increased to 120 mg three times daily (if the initial dose was not tolerated it could be decreased to 80 mg twice daily). The mean daily dose of verapamil taken was 256 (range 160–360 mg).

After 2 weeks of treatment, patients were re-evaluated by a blinded investigator, with repeat clinical examination, CHF scoring, exercise testing and radionuclide scanning.

There was then a 4 day "wash-out" period, followed by cross-over to the second treatment period with similar re-evaluation. Twenty of the 22 patients completed the study (one did not comply and a second developed a supraventricular tachycardia during the placebo phase, requiring open-label verapamil treatment).

Effect of verapamil on measures of systolic and diastolic function

Left ventricular ejection fraction did not change (baseline 60 $\pm$ 9%, placebo 60 $\pm$ 10%, verapamil 62 $\pm$ 8%, respectively). Peak filling rate increased from baseline (1.85 $\pm$ 0.45 edv/s) with verapamil (2.29 $\pm$ 0.54 edv/s, $P < 0.05$) but did not change during placebo treatment (2.16 $\pm$ 0.48 edv/s), though the between treatment group comparison was not statistically significant. There was also a suggestion of a "carry-over" effect of verapamil on peak filling rate in those receiving this treatment before placebo.

Effect of verapamil on blood pressure and heart rate

Average systolic blood pressure did not differ significantly between groups. Diastolic blood pressure at baseline was 84 $\pm$ 6 mmHg, 79 $\pm$ 6 mmHg during treatment with verapamil ($P < 0.05$) and 82 $\pm$ 8 mmHg at the end of the placebo period. The corresponding mean heart rates were: baseline 79 $\pm$ 11, verapamil 71 $\pm$ 11 ($P < 0.05$) and placebo 78 $\pm$ 9 beats/minute. Verapamil did not reduce peak heart rate or systolic blood pressure during exercise.

Effect of verapamil on CHF score and functional capacity

The mean baseline CHF score was 6.7 $\pm$ 1.7. After treatment with verapamil this decreased, significantly, to 3.8 $\pm$ 1.6 whereas, following placebo treatment the score increased to 6.1 $\pm$ 1.9 ($P < 0.01$).

In the 12 patients capable of exercise, the mean treadmill time (minutes) was 10.7 $\pm$ 3.4 at baseline, 13.9 $\pm$ 4.3 after verapamil ($P < 0.05$) and 12.3 $\pm$ 4 after placebo. The between treatment group comparison was also significant ($P < 0.01$).

Very similar improvements in symptoms and exercise tolerance were also reported by Hung et al. in an almost identical study. In that study, treatment with verapamil improved the CHF score from 5.5 to 3.5 and increased exercise tolerance from 7.4 minutes to 8.3 minutes on treadmill testing [16].

Beta-blockers

As with verapamil, beta-blockers, drugs with heart rate slowing and negatively inotropic actions might be expected to improve diastolic function. Aronow et al. examined the effect of propanolol on outcome in 158 elderly ($\geq$62 years) patients with heart failure and a left ventricular ejection fraction (LVEF) $\geq$0.40 [17]. In contrast to the study of Setaro et al., with verapamil, patients with coronary heart disease were not excluded and, in fact, all patients had a prior Q wave infarction. Another important difference in enrolment criteria was that all patients were receiving baseline diuretic and beta-blocker therapy. A third of patients were in atrial fibrillation. 79 patients were randomised to receive propranolol and 79 did not to receive propanolol. This open design is clearly a crucial issue. Follow-up was for 32 months.

The initial dose of propranolol was 10 mg per day. The dose was increased by 10 mg increments at 10 day intervals until the target dose of 30 mg three times daily was reached.

Two dimensional echocardiography was carried out at baseline, before randomisation and after one year of treatment. LVEF and left ventricular mass were measured by a blinded echocardiographer. Mortality and the composite endpoint of death or non-fatal myocardial infarction (MI) were also assessed by intention to treat.

Propanolol was discontinued by 11 of 79 patients (14%) because of adverse effects (worsening CHF in 7 and hypotension in 4).

There was a significantly greater increase in LVEF and greater reduction in left ventricular mass with propanolol.

After a follow-up of 2.7 years, 44 out of 79 (56%) propranolol treated patients died, compared to 60 out of 79 randomised to no propranolol (76%, $P = 0.007$). The respective figures (rates) for death or MI were 47 (59%) and 65 (82%) [$P = 0.002$].

These are clearly favourable results though the lack of placebo control and highly selected patient group must be pointed out. The beneficial action of beta-blockers in post-MI patients is well recognised and the findings of this study might have been anticipated. Similarly, the composite death or MI end-point, while important, is perhaps not the most relevant one in the more general population of patients with normal LVEF heart failure.

The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) randomised 2128 patients ≥70 years with CHF and either a documented LVEF ≤0.35 or a hospital admission for CHF within 12 months [18]. The treatment comparison was the beta-blocker nebivolol versus placebo. The primary outcome was the composite of death or cardiovascular hospitalisation. A subgroup analysis was reported for patients with a LVEF of ≤ 0.35 or > 0.35 ($n = 752$). The nebivolol:placebo hazard ratio was 0.87 (95% CI 0.73–1.05) for the LVEF ≤ 0.35 subgroup and 0.82 (95% CI 0.63–1.05) for the LVEF > 0.35 subgroup (interaction p value 0.42). In other words, SENIORS suggests that nebivolol may be beneficial in patients with a relatively preserved LVEF, though the cut point of 0.35 used in this analysis is unconventional and clearly led to inclusion of patients with systolic dysfunction in the "preserved" LVEF subgroup. A further analysis, using a higher LVEF cut point, would be valuable.

The place of beta-blockers in the treatment of diastolic heart failure is, therefore, still unclear and really should be clarified.

Angiotensin converting enzyme (ACE) inhibitors

Angiotensin II is thought to play a causal role in left ventricular hypertrophy (LVH), reduces left ventricular (LV) relaxation and increases LV stiffness. ACE-inhibitors are known to reduce LVH and to improve diastolic filling. Some patients with heart failure with preserved ejection fraction also have diabetes, coronary artery disease or both, where ACE inhibitors also have beneficial effects. Consequently, there are good theoretical reasons why ACE inhibitors (and angiotensin receptor blockers—see below) might be beneficial in heart failure with preserved ejection fraction.

One small trial has compared treatment with enalapril to no treatment with enalapril in 21 elderly patients (mean age 80 years) with NYHA Class III CHF associated with prior Q-wave myocardial infarction but a "preserved" LVEF (> 0.50) [19]. All patients were in sinus rhythm and treated with furosemide but no other cardiac drug. The target dose of enalapril was 10 mg twice daily (by week 5 of titration). A chest X-ray, echocardiogram and modified Bruce protocol treadmill exercise test were performed at baseline and after 3 months of treatment.

The effects of enalapril on NYHA Class, exercise time, radiographic cardiothoracic ratio and echocardiographic LVEF were reported. All of these measures improved, significantly, in the enalapril group but not the control (no enalapril) group. Similarly, left ventricular mass fell after enalapril treatment (from 313 ± 43 g to 280 ± 46 g, $P < 0.001$) but not in the control group (306 ± 51 to 309 ± 55 g). Peak mitral Doppler E/A ratio increased with enalapril (from 0.6 ± 0.1 to 0.7 ± 0.1, $P < 0.001$) but not in the control group (0.6 + 0.2 to 0.6 + 0.2). Resting systolic and diastolic blood pressure fell during enalapril treatment (but not in the control group). Again, while encouraging, these findings must be treated with caution. Firstly, within-group rather than between-group differences are described. Secondly, only 21 patients were studied. Thirdly, the study had an open design though the chest X-ray and echocardiographic measures were made by a blinded observer.

Of course, there is reason to believe that, in patients with prior myocardial infarction, an ACE inhibitor is of benefit in reducing the risk of future vascular events. Whether ACE inhibitors reduce morbidity/mortality in patients with "diastolic heart failure" is a question currently addressed in a long-running randomised controlled trial, the Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) study. PEP-CHF planned to recruit 1000 patients >70 years with CHF and no major left ventricular systolic dysfunction (LVEF < 0.40 or wall motion index <1.4). Patients also had to have echocardiographic evidence of left atrial enlargement, left ventricular hypertrophy or "diastolic dysfunction" (Doppler criteria) [20]. The primary endpoint is death or CHF hospitalisation and the trial is finally due to report in 2006.

Angiotensin receptor blockers (ARB)

ARBs are the first class of drug to be properly studied in heart failure with preserved ejection fraction.

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme had 3 component trials, one of which enrolled 3024 patients with a LVEF >0.40 (CHARM-Preserved) [21]. In all 3 trials, candesartan was compared to placebo and the primary endpoint of each individual trial was cardiovascular death or CHF hospitalisation. Because CHARM-Preserved was the first, large, prospective outcome trial in patients with preserved ejection fraction heart failure, its findings are described in detail.

ACE inhibitor use at baseline was 19%, and beta-blocker use 56%, in each group. The median duration of follow-up was 36.6 months. The primary outcome occurred in 333 of

1514 patients in the candesartan group compared to 366 of 1509 in the placebo group i.e. 22.0% vs 24.4%; representing a relative risk reduction of 11%, hazard ratio (HR) 0.89, 95% confidence intervals (CI) of 0.77 to 1.03, $p = 0.118$. The annualised event rates were 8.1% in the candesartan group and 9.1% in the placebo group. In a pre-specified covariate-adjusted analysis, the HR was 0.86 (0.74 to 1.00), $p = 0.051$ (Fig. 1).

There was no difference in the number of individuals experiencing CV deaths (170 vs 170) (HR of 0.99, 95% CI of 0.80 to 1.22, $p = 0.918$), or non-CV deaths in the candesartan group compared to the placebo group (74 vs 67) (HR of 1.10, 95% CI of 0.79 to 1.52, $p = 0.589$). The number of individuals who were hospitalised for CHF (as a primary cause reported by the investigator) at least once was lower in the candesartan group compared to the placebo group (230 vs 279; $p = 0.017$). In addition, the number of individuals hospitalised more than once for heart failure was also lower in the candesartan group (98 vs 122; $p = 0.093$), so that the total number of hospitalisation for CHF was 402 in the candesartan group and 566 in the placebo group ($p = 0.014$). In the candesartan group, 912 patients had 2510 hospital admissions for any reason while 922 placebo patients had 2545 hospitalisations ($p = 0.627$ for patients and $p = 0.794$ for admissions). Directionally similar results were obtained in the additional pre-specified analyses utilising the investigator-reported outcomes. However, the reduction in the composite outcome of CV death and hospitalisation for heart failure was more clear and nominally significant (324 in the candesartan group and 372 in the placebo group; HR of 0.85, 95% CI of 0.73 to 0.98; $p = 0.028$) (Table 1).

There was no heterogeneity of treatment effects in the various subgroups examined. Two subgroups are noteworthy. Among those not receiving an ACE inhibitor at baseline, there were 253/1218 (20.8%) individuals experiencing a primary outcome with candesartan compared to 283/1229 (23.0%) with placebo (HR of 0.88, 95% CI of 0.75 to 1.05). Among those receiving an ACE inhibitor at baseline, the corresponding numbers were 80/296 (27.0%) and 83/280 (29.6%) (HR 0.89, 95% CI of 0.65 to 1.21, interaction test comparing these HRs as $p = 0.97$). Among those with an LVEF between >40% and ≤50%, 106/536 (19.8%) experienced CV death or CHF hospitalisation in the candesartan group compared to 131/536 (24.4%) in the placebo group (HR 0.78; 95% CI of 0.60 to 1.01). Among those with an LVEF >50%, 227/978 (23.2%) experienced a primary event in the candesartan group compared to 235/973 (24.2%) in the placebo group (HR of 0.95, 95% CI of 0.79 to 1.14; p for interaction = 0.21). Thus, while CHARM-Preserved did not show a reduction in the risk of the primary outcome, it did suggest that candesartan had some beneficial action on patients with heart failure and preserved ejection fraction, namely on hospital admission for worsening heart failure. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) study (see below) will provide more information on the effects of an ARB in this type of CHF.

Digoxin

Surprisingly, the second largest trial experience with any anti-failure therapy in patients with "diastolic heart failure" was with digoxin [22]. At first sight, digoxin would seem an unsuitable treatment for this form of heart failure. Classically, digitalis glycosides are thought of as agents which increase cytosolic calcium concentrations which, if not rapidly reversed, should, if anything, impair myocardial relaxation. It is possible, however, that the sympatho-inhibitory, pro-parasympathetic and renin-angiotensin-aldosterone suppressing actions of digoxin are beneficial in CHF [23].

As part of the overall Digitalis Investigation Group (DIG) programme, 988 patients with a clinical diagnosis of CHF and an LVEF > 0.45 were randomised to receive placebo ($n = 496$) or digoxin ($n = 492$) in an ancillary trial. By comparison, 3403 patients with CHF and a LVEF of ≤0.45 were randomised to placebo and 3397 to digoxin in the main trial. There were 116 deaths (23.4%) in the placebo group and 115 deaths (23.4%) in the digoxin group in the ancillary trial. For the combined end-point of death or CHF hospitalisation, the results in the ancillary trial (risk ratio with digoxin 0.82, 95% CI 0.63–1.07) were consistent with the findings in the main trial (risk ratio 0.85, 95% CI 0.79–0.91; $P < 0.001$). Unfortunately, no further information on outcome in the preserved LVEF ancillary trial is available. Ahmed et al. in a posthoc analysis reported that serum digoxin levels of 0.5−0.9 ng/dl were associated with better outcomes versus placebo at 60 months, even with an EF > 45% [24]. The findings of the DIG trial are supported, to some extent, by those of the rather curious German and Austrian Xamoterol Study Group trial [25]. This study compared the effects of placebo, xamoterol and digoxin on symptoms, signs and exercise capacity in patients with a spectrum of CHF. LVEF was not reported but 80–90% of patients were in NYHA Class I or II CHF, about half had angina pectoris, only a quarter were taking diuretics and just over a third had radiological cardiomegaly (a cardiothoracic ratio ≥0.52). In other words, it is highly likely that many of these patients had "diastolic heart failure". Digoxin significantly improved breathlessness, tiredness, chest pain, oedema and lung tales [25]. Digoxin also reduced weight and cardiothoracic ratio more than placebo.

New studies in "diastolic heart failure"

Recently the unsatisfactory state of affairs regarding adequate clinical trials in patients with "diastolic heart failure"

has begun to improve. Two more large trials including such patients are underway.

The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) study is the largest to date in patients with CHF and preserved ejection fraction and will investigate the role of irbesartan in reducing mortality and cardiovascular morbidity in subjects with this condition [26]. It is a multicentre, randomised, double-blind, placebo-controlled trial in which approximately 4,100 subjects with CHF and preserved ejection from 24 countries will be evaluated to determine whether irbesartan 300 mg daily is superior to placebo in reducing mortality and cardiovascular morbidity, defined as the occurrence of death from any cause or prespecified cardiovascular hospitalisations. Additional secondary end points include cardiovascular mortality, cause specific mortality and morbidity and change in NYHA functional status, quality of life and plasma N-terminal pro BNP. Patients must be 60 years or older and have a LVEF of $\geq$0.45. In addition, patients in NYHA class II-IV CHF must have had a hospital admission with heart failure within the previous 6 months or, if NYHA clas III or IV, have an abnormal chest radiograph (pulmonary oedema), ECG (left ventricular hypertrophy [LVH] or left bundle branch block) or echocardiogram (LVH or enlarged left atrium). I-PRESERVE began enrolment in June 2002, and will complete after 1440 events have occurred. Comparison of outcomes in I-PRESERVE and CHARM-Preserved should be interesting as the patients randomised in these two trials differ considerably, particularly in relation to sex and age distribution and aetiology of CHF.

Excessive fibrosis may contribute to impaired relaxation and filling of the ventricles in patients with CHF and preserved ejection fraction and aldosterone is thought to play an important role in this extracellular matrix change. The US National Institutes of Health has funded The Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure (TOPCAT) which began enrolling male or female patients aged 50 years or older with heart failure, determined by signs and symptoms in conjunction with a prior hospital admission for heart failure and/or elevated b-type natriuretic peptide level and preserved left ventricular ejection fraction ($\geq$0.45) in 2006. Approximately 4,500 patients will be randomised to placebo or spironolactone 15–45 mg daily. The primary endpoint is a composite of cardiovascular mortality, aborted cardiac arrest or hospitalisation for the management of heart failure [27]. Secondary endpoints include all-cause mortality, new onset of diabetes mellitus or atrial fibrillation, and quality of life. The trial duration is 4.5 years, with 2.5 years for subject enrolment and an additional 2 years of follow-up, allowing for an average subject follow-up of 3.25 years. The trial will have 90% power to detect a relative reduction of 20% in the primary endpoint.

Conclusions: Treatment of heart failure and preserved ejection fraction

In summary, the development of treatment for CHF with preserved ejection fraction has been neglected until recently. CHARM-Preserved is the only completed large randomised outcome trial, though the results of a number of ongoing trials are eagerly awaited.

What can we conclude from the limited evidence currently available? There seems to be reasonable evidence that verapamil improves symptoms and exercise time in patients with CHF with preserved ejection fraction. The safety and efficacy of this drug has been generally established in patients with hypertension and coronary heart disease [29].

Similarly, ARBs have established benefits in hypertension, after myocardial infaction, in CHF with reduced ejection fraction and diabetic nephropathy. In CHARM, candesartan also substantially reduced the risk of heart failure hospitalisation in patients with CHF and preserved ejection. In addition, candesartan improved NYHA class in the overall CHARM Programme without evidence of heterogeneity across the component trials or by LVEF.

References

1. Brutsaert DL. Diagnosing primary diastolic heart failure. Eur Heart J 2000;21:94–6.
2. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from “diastolic heart failure” or from misdiagnosis? A prospective descriptive study. BMJ 2000;321:215–8.
3. Vasan RS, Levy D. Defining diastolic heart failure: A call for standardized diagnostic criteria. Circulation 2000;101:2118–21.
4. Caruana L, Davie AP, Petrie M, McMurray J. Diagnosing heart failure. Eur Heart J 1999;5:393.
5. Binkley PF, Shaffer PB, Ryan JM, Leier CV. Augmentation of diastolic function with phosphodiesterase inhibition in congestive heart failure. J Lab Clin Med 1989;3:266–71.
6. Monrad ES, McKay RG, Baim DS, Colucci WS, Fifer MA, Heller GV, Royal HD, Grossman W. Improvement in indexes of diastolic performance in patients with congestive heart failure treated with milrinone. Circulation 1984;6:1030–7.
7. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;7:1565–74.
8. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;21:2282–9.
9. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317–27.
10. Weinberger HD. Diagnosis and treatment of diastolic heart failure. Hosp Pract 1999;3:115–8, 121–2, 125–6.
11. Cody RJ. The treatment of diastolic heart failure. Cardiol Clin 2000;3:589–596.
12. Remme WJ. How to treat diastolic heart failure: a personal point of view. Rev Port Cardiol 1999;5:V117–23.

13. Garcia MJ, Diastolic dysfunction and heart failure: Causes and treatment options. Cleve Clin J Med 2000;10:727–9, 733–8.
14. Vasan RS, Benjamin EJ. Diastolic heart failure—no time to relax. N Engl J Med 2001;1:56–9.
15. Setaro JF, Zaret BL Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol 1990;12:981–6.
16. Hung MJ, Cherng WJ, Kuo LT, Wang CH. Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure. Int J Clin Pract 2002;56(1):57–62.
17. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol 1997;2:207–9.
18. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA. SENIORS Investigators. 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;26:215–25.
19. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. Am J Cardiol 1993;7:602–4.
20. Cleland JG, Tendera M, Adamus J, Freemantle N, Grays CS, Lye M, O'Mahony D, Polonski L, Taylor J. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. The PEP investigators. Eur J Heart Fail 1999;3:211–217.
21. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preservedleft-ventricular ejection fraction: The CHARM-Preserved Trial. Lancet 2003;362:777–81.
22. No authors listed. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 1997;8:525–33.
23. Massie BM, Abdalla I. Heart failure in patients with preserved left ventricular systolic function: do digitalis glycosides have a role? Prog Cardiovasc Dis 1998;4:357–69.
24. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J 2006;27:178–86.
25. No authors listed. Double-blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. The German and Austrian Xamoterol Study Group. Lancet 1988; i:489–93.
26. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, Ptaszynska A, Frangin G, for the I-PRESERVE Investigators. The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial: rationale and design. J Card Fail 2005;11(8):576–85.
27. http://www.topcatstudy.com/
28. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC, for the ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function. J Am Coll Cardiol 2006;47:76–84.
29. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290:2805–16.