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FASTTRACK The perindopril in elderly people with chronic heart failure (PEP-CHF) study

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KEYWORDS
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Diastolic heart failure;
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Aims Many patients who receive a diagnosis of heart failure have neither a low left ventricular (LV) ejection fraction nor valve disease. Few substantial randomized controlled trials have been conducted in this population, none has focussed on patients with evidence of diastolic dysfunction and none has shown clear benefit on symptoms, morbidity, or mortality.
Methods and results This was a randomized double-blind trial, comparing placebo with perindopril, 4 mg/day in patients aged $\geq$70 years with a diagnosis of heart failure, treated with diuretics and an echocardiogram suggesting diastolic dysfunction and excluding substantial LV systolic dysfunction or valve disease. The primary endpoint was a composite of all-cause mortality and unplanned heart failure related hospitalization with a minimum follow-up of 1 year. A total of 850 patients were randomized. Their mean age was 76 (SD 5) years and 55% were women. Median follow-up was 2.1 (IQR 1.5–2.8) years. Enrolment and event rates were lower than anticipated, reducing the power of the study to show a difference in the primary endpoint to 35%. Many patients withdrew from perindopril (28%) and placebo (26%) after 1 year and started taking open-label ACE-inhibitors. Overall, 107 patients assigned to placebo and 100 assigned to perindopril reached the primary endpoint (HR 0.919: 95% CI 0.700–1.208; $P = 0.545$). By 1 year, reductions in the primary outcome (HR 0.692: 95% CI 0.474–1.010; $P = 0.055$) and hospitalization for heart failure (HR 0.628: 95% CI 0.408–0.966; $P = 0.033$) were observed and functional class ($P < 0.030$) and 6-min corridor walk distance ($P = 0.011$) had improved in those assigned to perindopril.
Conclusion Uncertainty remains about the effects of perindopril on long-term morbidity and mortality in this clinical setting since this study had insufficient power for its primary endpoint. However, improved symptoms and exercise capacity and fewer hospitalizations for heart failure in the first year were observed on perindopril, during which most patients were on assigned therapy, suggesting that it may be of benefit in this patient population.

Introduction

Many patients receive a clinical diagnosis of heart failure but have neither a low left ventricular ejection fraction (LVEF) nor important valve disease.[1] The clinical diagnosis of heart failure is probably incorrect in some but many have evidence of diastolic LV dysfunction as a potential cause of their symptoms.[1,2] There are no robust, generally agreed diagnostic criteria for diastolic heart failure.[3] Compared with patients with heart failure and a low LVEF, such patients are usually older, more often women, more commonly have a history of hypertension but are less likely to have a history of myocardial infarction (MI).[4] Epidemiological studies suggest that mortality rates may be somewhat lower in patients with diastolic heart failure but that the rate of hospitalization may be similar. The EuroHeart Failure Survey, which was conducted during the recruitment period of this study, suggested that 10% patients with heart failure and preserved LV systolic function would die and 22% would be readmitted within 12 weeks of a hospital admission caused or complicated by heart failure.[4] Other recent hospital discharge surveys have reported a 1 year mortality of 22–27% and re-admission rates for heart failure of up to 52%.[1,5–8]

Most randomized controlled trials have focussed on treatment for heart failure due to LV systolic dysfunction (LVSD). Outcome in subsets of patients who did not have substantial LVSD that were included in trials of ACE-inhibitors showed inconsistent effects.[9,10] A study of 66 patients suggested that perindopril could improve exercise tolerance in older patients with heart failure and a normal LVEF.[11] The DIG trial suggested that digoxin might reduce hospitalization for heart failure but not mortality in a substudy of 988 patients with an LVEF >45% but reported a mortality of

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only 7% and hospitalization for heart failure of <20% in the first year of follow-up.[12–14] A trial of beta-blockers in 158 older patients with heart failure but without substantial LVSD after MI reported a mortality of 76% at 2.5 years in the placebo group, which was reduced to 56% in those treated with propranolol.[15] However, uncertainty exists about the value of beta-blockers for the management of chronic heart failure (CHF) and preserved LV systolic function.[16] The CHARM-preserved study, which enrolled 3023 patients, of whom 20% were receiving ACE-inhibitors, reported an annual rate of cardiovascular death or heart failure hospitalization of 9.1% in patients assigned to placebo compared with 8.1% in those assigned to candesartan, a difference that approached statistical significance ($P = 0.118$).[17] The failure of trials to show substantial benefit in this group of patients may reflect inclusion of many patients whose symptoms were either due to problems such as respiratory disease, obesity or varicose veins, the possibly transitory nature of heart failure in patients with preserved LV systolic function, or a lower rate of cardiovascular events.[2,18,19]

Accordingly, we conducted a randomized controlled trial in older people diagnosed with and treated for heart failure, who had echocardiographic evidence of diastolic LV dysfunction to determine whether treatment with perindopril could improve outcome compared with placebo.[20]

Methods

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) was a double-blind, multi-centre, international, randomized controlled trial comparing the effects of perindopril and placebo in patients with diastolic heart failure.[20] Patients were enrolled at 53 centres in Bulgaria (3), Czech Republic (5), Hungary (10), Ireland (1), Poland (26), Russia (1), Slovakia (2), and the UK (5). The principal investigator was a physician for the care of the elderly or general internal medicine in 10 centres and a cardiologist in 43 centres.

The steering committee (see Appendix) designed the trial. The study was approved by the local Ethics Committee of each participating institution and by appropriate National Ethics Committees and Regulatory Authorities. All patients provided written informed consent. An independent data safety and monitoring board (DSMB) reviewed the progress of the study to advise the Steering Committee on whether the study should be continued, stopped for futility, or stopped because of safety issues.

Patients

Patients had to be aged ≥70 years and treated with diuretics for a clinical diagnosis of CHF due to LV diastolic dysfunction as defined below and to have had a cardiovascular hospitalization within the previous 6 months. Patients had to be able to walk without the aid of another person in order to exclude very frail patients who might not respond to any treatment. Patients with a wall motion index of <1.4, roughly equivalent to an LVEF of 40%, were excluded. As there are no widely agreed criteria for the diagnosis of diastolic heart failure, at least three out of nine clinical and at least two out of four additional echocardiographic criteria were required. Clinical criteria were: exertional breathlessness; orthopnoea or paroxysmal nocturnal dyspnoea; ankle swelling; improved breathlessness with diuretic therapy; increased jugular venous pressure; prior episode of clinical pulmonary oedema; prior MI; cardiothoracic ratio >0.55; and previous radiological pulmonary oedema. Echocardiographic criteria were: an LV wall motion index of 1.4–1.6 inclusive, roughly equivalent to an LVEF fraction between 40 and 50%, since abnormal diastolic dysfunction is often associated with some impairment of systolic function; a left atrial diameter >25 mm/m^2 body surface area or >40 mm because chronic elevation of LV filling pressure should lead to atrial dilatation; an interventricular septum or posterior LV wall ≥12 mm in thickness suggesting hypertrophy, a common cause of impaired diastolic function or, finally, evidence of impaired LV filling by at least one of the criteria recommended by the European Society of Cardiology Study Group on Diastolic Heart Failure. These included an E/A ratio <0.5 or deceleration time of >280 ms from the mitral inflow pattern or an isovolumic relaxation time of >105 ms. These criteria effectively exclude patients with atrial fibrillation (AF) and therefore, in a protocol modification early in the course of the study, this arrhythmia was counted as equivalent to evidence of impaired LV filling by Doppler.

Important exclusion criteria were haemodynamically significant valve disease, stroke within the previous month, sitting systolic arterial pressure <100 mmHg, serum creatinine >200 μmol/L or potassium >5.4 mmol/L, history of ACE-inhibitor intolerance or use of an ACE-inhibitor or angiotensin receptor blocker within the previous week, potassium-sparing diuretics (other than low-dose spironolactone), or potassium supplements.

Study procedures

At baseline, a medical history was taken from each patient, current therapy recorded, and a physical examination and echocardiogram done. Blood was taken to measure haemoglobin, electrolytes and renal function and, in a substantial proportion of patients from the UK and Poland, N-terminal pro-brain natriuretic peptide (NTproBNP; $n = 375$). Most patients also had a 6-min corridor walk test at baseline ($n = 773$). Diuretics were withheld for 24 h and blood pressure was measured every hour for 6 h after a test dose of 2 mg of perindopril. Thereafter, eligible patients were randomly assigned from a computer-generated list in blocks of four within treatment centres to placebo or perindopril through a centrally administered process, concealed from the study investigators. The study medication was provided in externally indistinguishable tablets.

Patients were reviewed weekly for the first 5 weeks to ensure that treatment was tolerated and to check serum potassium and creatinine. The dose of perindopril was increased to 4 mg once daily at the second follow-up visit if no clinical contraindication, such as hypotension or worsening renal function existed. Study medication was reduced or discontinued if serum creatinine rose to >250 μmol/L or by >50 μmol/L from baseline or potassium rose to >5.5 mmol/L. Patients were reviewed at 8, 12, and every 12 weeks thereafter until 1 year follow-up, then according to the investigator's judgment until the end of the study. The structure of the case report form did not plan regular visits after 1 year. At each visit, patients' New York Heart Association (NYHA) class was reassessed, weight, heart rate and blood pressure measured, and a blood sample taken for serum sodium, potassium, and creatinine. The 6-min corridor walk test ($n = 642$) and tests for NTproBNP ($n = 278$) were repeated at 1 year.

The protocol aimed to recruit 1000 patients and follow them for at least 1 year. No interim analyses were planned. However, enrolment was lower than anticipated. The DSMB also noted a lower than expected event rate and a high-rate of cessation of blinded therapy with open-label ACE-inhibitor use and recommended that recruitment be stopped since they considered that the study could not reach statistical power on its primary endpoint without a large increase in the sample size. The Steering Committee agreed to stop recruitment but decided that all patients should be followed until the last patient had completed 1 year follow-up, in order to retain power for other outcomes of interest, including the effect on symptoms and functional capacity.

Endpoints

The primary endpoint was the composite of all-cause mortality or unplanned heart failure related hospitalization using a

time-to-first-event analysis. This included hospitalizations for worsening signs and/or symptoms of heart failure due to declining renal function, acute vascular events, arrhythmias, infection, or unknown causes. Potential qualifying events were independently classified by MT and JGFC, blind to treatment allocation. Pre-specified secondary endpoints included the individual components of the primary endpoint, cardiovascular mortality, worsening heart failure requiring hospitalization or an increase in diuretic treatment, hospital bed-days for cardiovascular reasons, hospital bed-days for any reason, and change in NYHA class between baseline and 1 year.

Subgroup analyses

Pre-specified subgroup analyses were age, sex, wall motion abnormality (WMA) above or below 1.6, and dose of perindopril tolerated. However, only 9% of patients failed titration to 4 mg of perindopril and only 15% had a wall motion index <1.6, and therefore these subgroup analyses were considered futile. Subgroup analysis according to serum creatinine and NTproBNP above and below median, systolic blood pressure above or below 140 mmHg and presence or absence of a history of MI were not pre-planned but were considered of interest. One-year outcome for the primary endpoint composite was used for these analyses.

Statistics

The study was based on epidemiological data that existed at the time of planning. These data suggested that older patients with heart failure and a recent hospital admission had an annual mortality of 10–20%, a re-admission rate for heart failure of 30%, and a risk of death or re-admission of about 50%.[1,5,6] We considered that patients invited and agreeing to participate in a clinical trial would have a lower event rate but that this would be compensated for by a broad primary endpoint definition and by the inclusion only of patients with documented cardiac dysfunction who required diuretic therapy. The assumption was that perindopril could reduce this rate to 40% with a predicted HR of 0.74. The study required 451 primary endpoints overall and approximately 500 patients per group to demonstrate a benefit using a two-sided test at $P < 0.05$ and a power $(1 - \beta)$ of 0.9. All analyses used the intention-to-treat principle. Logrank tests for analysis of the time to occurrence of the primary endpoint, the Kaplan–Meier method for measuring the cumulative distribution over time and Cox's proportional-hazards model to assess risk reduction for the primary and secondary clinical endpoints were used. Event rates with 95% CI are reported. Descriptive statistics were done on NYHA class, 6-min corridor walking test, and NTproBNP. Changes from baseline were analysed and compared between groups using analyses of covariance or Fisher's exact test.

Results

Between 2000 and 2003, 852 patients were enrolled and received a 2 mg test dose of perindopril, which was tolerated by all patients. Subsequently, 424 patients were randomized to perindopril and 426 to placebo (*Figure 1*). Two patients were not randomized for non-medical reasons. At the end of the study, vital status was known for all except four patients who were lost to follow-up after 38, 112, 112, and 131 weeks. The mean follow-up was 26.2 months (range, excluding deaths, 12.0–54.2) during which 207 (24.4%) patients reached a primary endpoint and 109 (12.8%) died. Calculations indicate that the power of the study to show statistical significance on the primary endpoint was only 35%.

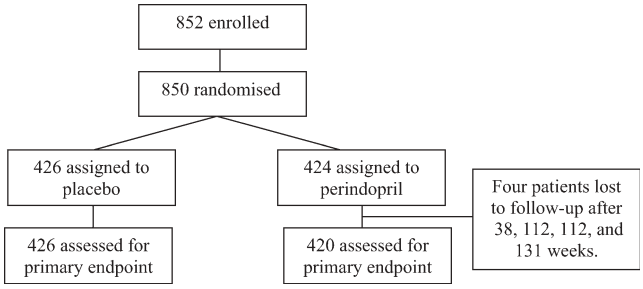

Figure 1 Consort diagram showing result of randomization and patient follow-up.

Study population

Baseline characteristics were similar in the two groups (*Table 1*). Most patients were women, half were aged >75 years, and the oldest patient aged 96 years. Hypertension was common and substantial minorities had other factors potentially contributing to the development of heart failure including ischaemic heart disease, diabetes, and AF. Most patients had mild symptoms, a modestly reduced exercise capacity, and almost half had a systolic blood pressure ≥ 140 mmHg.

Echocardiography demonstrated that most patients had no LV regional WMA, good global systolic function but evidence of LV hypertrophy. The mean left atrial dimension was increased, consistent with a chronic elevation in atrial pressure and a diagnosis of diastolic LV dysfunction. However, fewer than 25% of patients had an E/A ratio <0.5 or a deceleration time criterion >280 msec and only about half an isovolumic relaxation time >105 msec, the criteria set by the European Study Group on Diastolic Heart Failure for older people.[21] The median plasma concentration of NTproBNP was modestly elevated but many patients had values commonly found in older people without a history of cardiovascular disease.[22] Many patients were taking beta-blockers and nitrates. Thiazide were used more often than loop diuretics.

Treatment

At 1 year, almost 90% of patients were treated with perindopril 4 mg. Subsequent to the 1 year visit, 28% of the perindopril group and 26% of the placebo group ceased blinded treatment and by 18 months, 40% of the perindopril group and 36% of the placebo group were not on study treatment. By the end of the study, 35% of patients assigned to perindopril and 37% assigned to placebo were taking open-label ACE-inhibitors.

Primary outcome

For the entire duration of follow-up, 107 (25.1%) patients assigned to placebo and 100 (23.6%) to perindopril experienced a primary outcome event (HR 0.92; 95% CI 0.70–1.21; $P = 0.545$) with annual incidence rates of 13.2 and 12.2%, respectively. If analysis was confined to the first year of follow-up, 65 patients (15.3%) assigned to placebo and 46 (10.8%) assigned to perindopril had a primary outcome event (HR 0.69; 95% CI 0.47–1.01; $P = 0.055$) (*Figure 2A* and *B*).

Table 1 Baseline characteristics. Values are median and IQR or proportions as appropriate

Variable	Placebo ($n = 426$)	Perindopril ($n = 424$)
Age (years)	75 (72–79)	75 (72–79)
Women (%)	57%	54%
Duration of heart failure (months)	11 (2–39)	8 (2–38)
Prior hypertension (%)	337 (79%)	333 (79%)
Prior MI (%)	110 (26%)	116 (27%)
Prior CABG (%)	12 (3%)	27 (6%)
Prior PCI (%)	35 (8%)	30 (7%)
Diabetes (%)	87 (20%)	88 (21%)
NYHA class I/II (%)	317 (74%)	327 (77%)
NYHA III/IV (%)	109 (26%)	97 (23%)
Six-min walk distance (m)	297 (200–380) ($n = 387$)	290 (200–372) ($n = 385$)
Body mass index (kg/m^2)	27.6 (25.3 to 30.7)	27.5 (25.1 to 30.0)
Heart rate (b.p.m.)	73 (66 to 82)	74 (66 to 81)
AF(%)	93 (22%)	79 (19%)
Paced rhythm	23 (5%)	28 (7%)
Systolic BP (sitting) (mmHg)	140 (129–150)	138 (128–150)
Diastolic BP (sitting) (mmHg)	80 (73–88)	80 (74–86)
Wall motion index (units)	2.0 (1.7–2.0)	2.0 (1.7–2.0)
LVEF(%)	64 (56–66)	65 (56–66)
LV end-diastolic dimension (mm)	46 (42–51)	46 (41–51)
Inter-ventricular septal thickness (mm)	13 (12–15)	13 (12–15)
Posterior LV wall thickness (mm)	12 (11–14)	13 (11–14)
Left atrial diameter (mm)	44 (41–48)	45 (41–48)
E/A ratio	0.70 (0.60–0.90)	0.70 (0.50–0.90)
Inter-ventricular relaxation time (ms)	106 (85–120)	107 (80–120)
Deceleration time (ms)	206 (160–267)	210 (165–270)
Potassium (mmol/L)	4.4 (4.0–4.7)	4.4 (4.0–4.7)
Creatinine (μmol/L)	97 (84–111)	95 (81–110)
NTproBNP (pg/mL)	453 (206–1045) ($n = 184$)	335 (160–1014) ($n = 191$)
Aspirin (%)	280 (66%)	283 (67%)
Oral anti-coagulants (%)	65 (15%)	71 (17%)
Beta-blockers (%)	228 (54%)	235 (55%)
Nitrates (%)	208 (49%)	226 (53%)
Calcium channel blockers (%)	140 (33%)	135 (32%)
Lipid-lowering agents (%)	130 (31%)	151 (36%)
Oral hypoglycaemic (%)	47 (11%)	52 (12%)
Insulin (%)	20 (5%)	24 (6%)
Loop diuretics (%)	186 (44%)	198 (47%)
Thiazide diuretic (%)	236 (55%)	227 (54%)
Low-dose spironolactone (%)	48 (11%)	37 (9%)
Digoxin (%)	55 (13%)	45 (11%)

Secondary outcome

The rates for death and cardiovascular death among patients assigned to either treatment during the first or subsequent years of follow-up were similar. During the first year of follow-up, 53 patients (12.4%) assigned to placebo but only 34 (8.0%) assigned to perindopril had an unplanned hospitalization for heart failure (HR 0.63; CI 0.41–0.97; $P = 0.033$) (*Figure 3A* and *B*) but differences were not significant for the entire duration of follow-up. The rate of worsening heart failure requiring hospitalization or an increase in diuretic therapy was similar in patients assigned to placebo and perindopril. During the course of the study, of patients admitted to hospital, those assigned to perindopril spent a median of three less days in hospital for cardiovascular reasons ($P = 0.056$) and five less days in hospital for any reason ($P = 0.229$). At 1 year, patients assigned to perindopril were more likely to have improved NYHA class ($P < 0.030$) (*Tables 2* and *3*).

Other measures

Patients assigned to perindopril had a greater 6-min corridor walk distance at 52 weeks (*Table 3*). Plasma concentrations of NTproBNP tended to fall in patients assigned to perindopril but not on placebo, but this difference did not achieve statistical significance (mean difference in change −149 pg/mL 95% CI −353 to +56; $P = 0.153$).

The risk of cardiovascular death or unplanned heart failure related hospitalization, the primary outcome measure of CHARM preserved, was lower in patients assigned to perindopril (40 patients or 9.4%) compared with placebo (63 patients or 14.8%) (HR 0.62; CI 0.42–0.92 ; $P = 0.018$) over the first year. Slightly fewer patients experienced a stroke (11 vs. 19) or an acute coronary syndrome (41 patients with 66 events compared with 42 patients with 77 events) on perindopril.

Sitting systolic and diastolic blood pressure declined to a greater extent in patients assigned to perindopril and serum potassium and creatinine rose to a slightly greater extent.

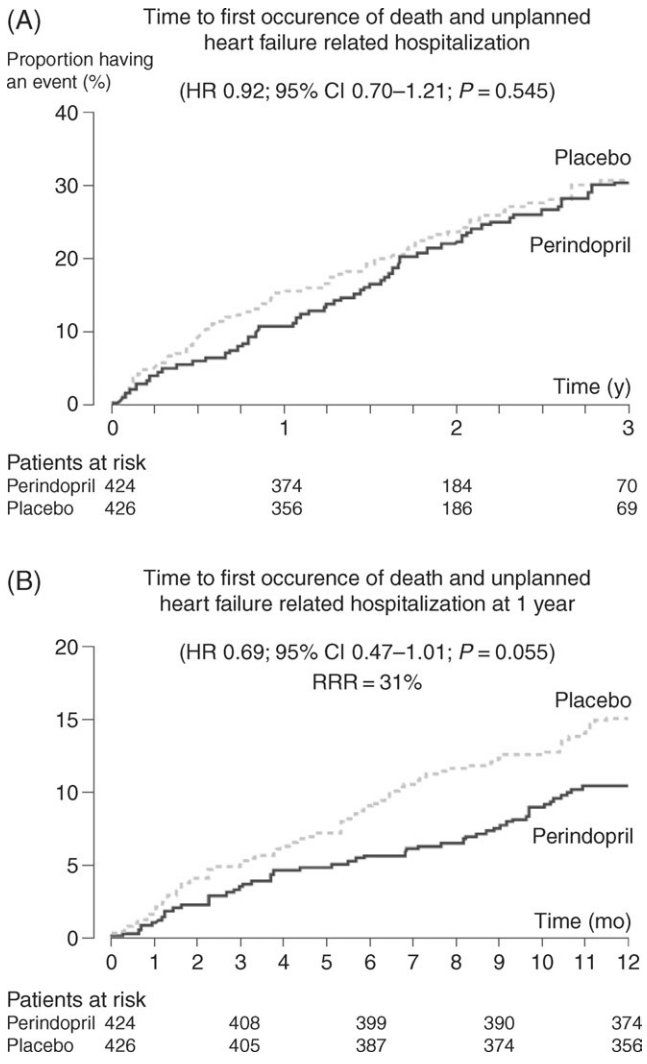

Figure 2 (*A*) Kaplan–Meier curves showing time to first occurrence of the primary endpoint, all-cause mortality or unplanned heart failure related hospitalization, for the entire duration of the study. (*B*) Kaplan–Meier curves showing time to first occurrence of primary endpoint events during the first year of follow-up during which most patients remained on their assigned therapy.

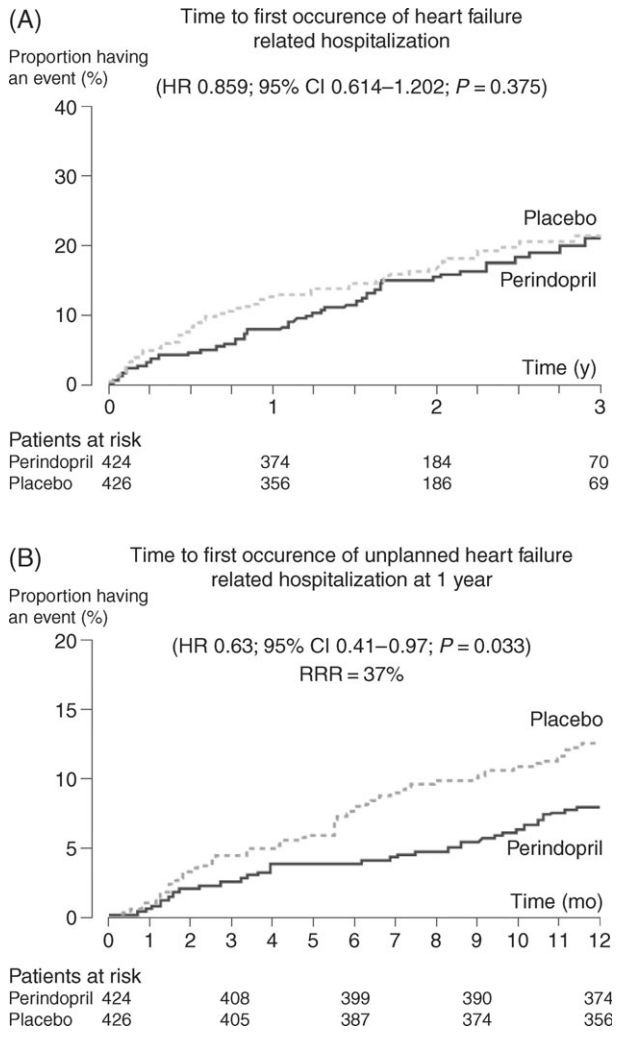

Figure 3 (*A*) Kaplan–Meier curves showing time to first occurrence of the pre-specified secondary endpoint, unplanned heart failure related hospitalization, for the entire duration of the study. (*B*) Kaplan–Meier curves showing time to first occurrence of the pre-specified secondary endpoint, unplanned heart failure related hospitalization, during the first year of follow-up during which most patients remained on their assigned therapy.

Subgroup analyses on primary endpoint at 1 year

Younger patients and those with a history of MI or hypertension tended to obtain greater benefit from perindopril (*Figure 4*). Hazard ratios for men and women and for those with serum creatinine above or below median were similar. Only 7.8% of patients with plasma concentrations of NTproBNP below median reached the primary endpoint by 1 year compared with 19.1% in patients with above median values.

Serious adverse events

Nine serious adverse events, assessed by investigators as possibly study drug related, were reported in nine patients in the perindopril group (one tongue oedema and one eyelid oedema, three increase in serum creatinine, one hypotension, and three events linked to the musculoskeletal disorders or chronic obstructive airways disease) and four events in four patients in the placebo group (one cough, one hypotension, one hypertensive encephalopathy, and one renal dysfunction).

Discussion

This is the first randomized controlled trial to investigate the effects of ACE-inhibitors on morbidity and mortality in patients with a clinical diagnosis of diastolic heart failure. The study did not achieve its primary endpoint for several reasons. The event rate was much lower than expected. Despite a much longer follow-up than originally intended, only 46% of the expected events occurred and consequently the study only had a power of 35% to show a difference in the primary endpoint. Also, a large number of these older patients stopped their assigned treatment after 1 year, most of whom subsequently started taking open-label ACE-inhibitors. Extending the duration of follow-up of patients who were not taking their assigned therapy would have been likely to diminish rather than enhance the power of the study to show a difference. However, the reduction in hospitalizations for heart failure reached and the reduction in the primary endpoint approached conventional levels of statistical significance over the first year of follow-up (in patients assigned to perindopril). Also,

Table 2 Occurrence of primary and secondary endpoints

	1 Year			Entire follow-up		
	Placebo	Perindopril	HR (*P*-value)	Placebo	Perindopril	HR (*P*-value)
Primary outcome						
Death or hospitalization	65	46	0.69 [0.47; 1.01] (0.055)	107	100	0.92 [0.70; 1.21] (0.545)
Secondary outcomes						
Death	19	17	0.90 [0.47; 1.73] (0.747)	53	56	1.09 [0.75; 1.58] (0.665)
Cardiovascular death	17	10	0.59 [0.27; 1.29] (0.181)	40	38	0.98 [0.63; 1.53] (0.928)
Hospitalization for heart failure	53	34	0.63 [0.41; 0.97] (0.033)	73	64	0.86 [0.61; 1.20] (0.375)
Worsening heart failure events	71	59	0.81 [0.58; 1.15] (0.239)	106	97	0.89 [0.68; 1.18] (0.413)
Hospital days among patients admitted [median days (IQR)]						
Cardiovascular reasons	NA	NA	NA	15 (7–35)	12 (7–26)	(0.056)
All-cause	NA	NA	NA	19 (9–40)	14 (8–35)	(0.229)

NA, not analysed.

Table 3 Symptoms, exercise capacity, blood pressure, and renal function at 1 year

	Placebo	Perindopril	
NYHA I	47 (12.4%)	75 (20.3%)	
NYHA II	268 (70.5%)	235 (63.7%)	$P = 0.030$*
NYHA III/IV	65 (17.1%)	59 (16%)	
Six-min walk distance (m)	$n = 324$	$n = 318$	Mean difference in change [95% CI]
Mean (SD)	309 (132)	328 (126)	14 m [3 to 25] $P = 0.011$**
Systolic blood pressure (mmHg)			Mean difference in change [95% CI]
Mean (SD)	138 (18)	135 (18)	−3 mmHg [−5 to 0] $P = 0.03$**
Serum creatinine (μmol/L)			Mean difference in change [95% CI]
Mean (SD)	95.1 (24)	104.9 (38)	4 μmol [−1 to 9] $P = 0.096$**

*Fisher's exact test.
**Analysis of covariance.

cardiovascular death and heart failure related hospitalization, the primary endpoint of CHARM-preserved, was significantly reduced by perindopril over 1 year. These effects were of similar magnitude to those observed with enalapril in patients with LV systolic dysfunction in SOLVD[17,23] over a similar time-frame. This is also the first substantial study to confirm that a treatment can improve symptoms and functional capacity in patients with diastolic heart failure.[11]

The clinical diagnosis of heart failure was only partially corroborated by the patient characteristics. In general, patients had mild symptoms and these could have reflected conditions other than heart failure in some patients. Left atrial dilatation and LV hypertrophy were present in >75% of patients but plasma concentrations of NTproBNP were not generally grossly elevated, suggesting that many patients had well-treated heart failure or did not have important cardiac dysfunction. The rate of the primary endpoint was three-fold higher in patients with values of NTproBNP above median. It appears that natriuretic peptides are not only powerful prognostic markers in patients with heart failure and LV systolic dysfunction but also in patients with diastolic dysfunction.[24] Indeed, it is possible that natriuretic peptides rather than echocardiographic criteria should be used as objective evidence of cardiac dysfunction in this setting and as a key criterion for selecting patients in future clinical trials.

The event rate, which was based on reports of the outcome of heart failure with preserved LV function in elderly people available during the planning phase, was much lower than anticipated.[5] This was despite the requirement for multiple subjective and objective criteria to support a diagnosis of heart failure. However, this relatively low event rate is consistent with most contemporary randomized controlled trials now reported in this population. Indeed, the rate of cardiovascular death and hospitalization was higher than in either the CHARM-preserved study[17] or patients with preserved LV systolic dysfunction in the DIG study.[14] This suggests either that the prognosis of this syndrome is more benign than suggested by observational studies or that clinical trials selectively enrol lower risk patients, who are perhaps younger, less frail, and with fewer co-morbidities such as renal dysfunction. Patients with a serum creatinine >200 μmol/L were excluded from PEP-CHF and only 25% had a serum creatinine >110 μmol/L. The risk of death or re-hospitalization is highest in the first few weeks after hospitalization for heart failure[7,8] but it is likely that the PEP-CHF, CHARM-preserved, and DIG-

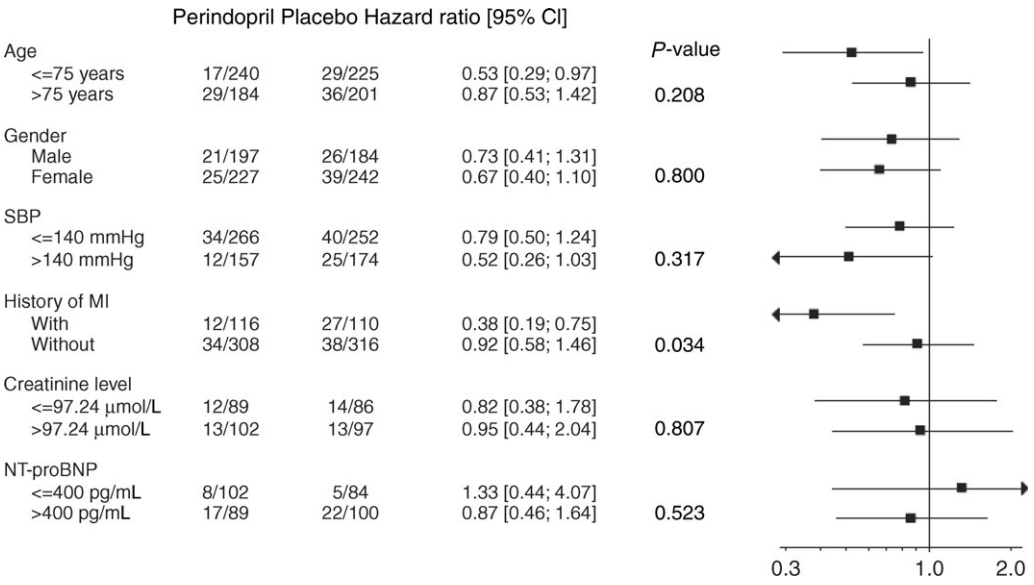

Figure 4 Analysis of outcome in subgroups. Age and sex were pre-specified subgroups; subgroups according to prior history of MI, systolic blood pressure, median serum creatinine, and median plasma concentration of NTproBNP were not pre-specified. *P*-values reflect results of a Wald χ^2 test for interaction.

preserved studies did not recruit many patients in this high-risk period. It is also possible that patients in clinical trials are managed better than is usual in standard clinical practice.

Patients who had a previous MI or with elevated systolic blood pressure were at increased risk of events and appeared to benefit from perindopril, at least during the first year of follow-up. This was not a pre-specified subgroup analysis and therefore should be interpreted with caution. However, there is a wealth of data showing that ACE-inhibitors reduce morbidity and mortality in patients with LV systolic dysfunction after an MI.[25] More recently, perindopril was shown to influence cardiac remodelling favourably in patients who had post-infarction heart failure but without LV systolic dysfunction.[26] The PEP-CHF trial provides evidence to support the hypothesis that patients who exhibit features of heart failure after an MI should receive an ACE-inhibitor whether or not the LVEF is $<$40%. The apparently greater benefit in patients with a systolic blood pressure $>$140 mmHg is consistent with the anti-hypertensive effects of perindopril. Perindopril has also been shown to reduce cardiovascular events in patients without LV systolic dysfunction or heart failure.[27]

The only other agents that have been the subject of substantial studies in patients with heart failure and preserved LV systolic dysfunction are digoxin[12,14] and candesartan.[17] The DIG-preserved study suggested that digoxin reduced hospitalization for heart failure over the first 2 years of treatment but that it had no overall effect on hospitalization or mortality.[14] The study did not provide information on the effect on symptoms or functional capacity. The CHARM-preserved study also suggested that candesartan reduced hospitalization for heart failure, with no effect on death, and equivocal effects on symptoms.[28,29] The study provided no information on functional capacity. Although the PEP-CHF study also does not provide conclusive evidence that perindopril is of benefit in this population, the observed favourable trends on hospitalization and days in hospital for heart failure, combined with improvements in symptoms and functional capacity provide arguments for its use. There is no evidence that any other treatment is more effective for patients already receiving diuretics for the control of symptoms and fluid retention in this setting. Indeed, diuretic-induced neuro-endocrine activation will occur whether or not LV systolic dysfunction is present, providing a substrate for the action of ACE-inhibitors. Finally, there is a wealth of evidence that ACE-inhibitors improve symptoms and reduce cardiovascular morbidity in other settings, which lend circumstantial support for their use in this clinical setting. Two other substantial, placebo-controlled trials in similar patients populations should report within the next few years, one investigating the effects of irbesartan[30] and the other spironolactone. Objective markers of cardiac dysfunction are required for enrolment in the I-PRESERVE study, which appears to have a similar rate of events to PEP-CHF. As the study includes substantially more patients and will have many more patient-years of follow-up, it should be adequately powered to identify or exclude an important effect of irbesartan in this clinical setting.

In conclusion, the PEP-CHF trial did not show a statistical benefit of perindopril compared with placebo on long-term morbidity and mortality in patients with diastolic heart failure but this may reflect inadequate power compounded by many of these elderly patients withdrawing from assigned therapy to start open-label ACE-inhibitors. In contrast, perindopril does appear to improve symptoms and exercise capacity, and possibly heart failure related hospitalizations, which may be considered valuable treatment objectives in this population.

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Appendix

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