The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction

G W K Yip, M Wang, T Wang, S Chan, J W H Fung, L Yeung, T Yip, S-T Lau, C-P Lau, M-O Tang, C-M Yu, J E Sanderson

ABSTRACT

Background: Although heart failure with a preserved or normal ejection fraction (HFNEF or diastolic heart failure) is common, treatment outcomes on quality of life and cardiac function are lacking. The effect of renin–angiotensin blockade by irbesartan or ramipril in combination with diuretics on quality of life (QoL), regional and global systolic and diastolic function was assessed in HFNEF patients.

Methods: 150 patients with HFNEF (LVEF >45%) were randomised to (1) diuretics alone, (2) diuretics plus irbesartan, or (3) diuretics plus ramipril. QoL, 6-minute walk test (6MWT) and Doppler echocardiography were performed at baseline, 12, 24 and 52 weeks.

Results: The QoL score improved similarly in all three groups by 52 weeks (average +3–6%). Recurrent hospitalisation rates were equal in all groups (10–12% in 1 year). At 1 year, LV dimensions or LVEF had not changed in any group, though both systolic and diastolic blood pressures were lowered in all three groups from 4 weeks onwards. At baseline both mean peak systolic (Sm) and early diastolic (Em) mitral annulus velocities were reduced, and increased slightly in the diuretic plus irbesartan (Sm 4.5 (SEM 0.17) to 4.9 (SEM 0.16) cm/sec; Em 3.8 (SEM 0.25) to 4.2 (SEM 0.25) cm/sec) and ramipril (Sm 4.5 (SEM 0.24) to 4.9 (SEM 0.20) cm/sec; Em 3.3 (SEM 0.25) to 4.04 (SEM 0.25) cm/sec) groups (both p<0.05). NT-pro-BNP levels were raised at baseline (595 (SD 905) pg/ml; range 5–4748) and fell in the irbesartan (−124 (SD 302) pg/ml, p = 0.01) and ramipril (−173 (SD 415) pg/ml, p = 0.03) groups only.

Conclusions: In this typically elderly group of HF patients with normal LVEF, diuretic therapy significantly improved symptoms and neither irbesartan nor ramipril had a significant additional effect. However, diuretics in combination with irbesartan or ramipril marginally improved LV systolic and diastolic longitudinal LV function, and lowered NT-proBNP over 1 year.

METHODS

Study design and subjects

This trial was a prospective, multi-centred, randomised, open-label with blinded end point design (PROBE) to test the hypothesis that addition of ramipril or irbesartan to standard therapy with diuretics would be superior to diuretics alone in its effect on quality of life and ventricular function in patients with HFNEF. Patients admitted into hospital with a clinical diagnosis of heart failure were screened. The inclusion criteria were age >18 years, clinical history of heart failure within 2 months prior to screening including a chest x-ray demonstrating pulmonary congestion, NYHA functional class II–IV, left ventricular ejection fraction >45% by 2D-echocardiography or a
radionuclide technique, and therapy with diuretics with stable
dose >14 days prior to recruitment. Patients were randomly
allocated using computer-generated random numbers in blocks
of 10 (balanced stratification) to one of three treatments: (1)
continue with diuretics alone (either frusemide or thiazide
depending on the degree of fluid retention), (2) diuretics plus
irbesartan, (3) diuretics plus ramipril. The initial dose of
irbesartan was 18.75 mg daily which was titrated to 4 and
8 weeks to 75 mg daily. Ramipril was started at 2.5 mg daily
and similarly titrated to 10 mg daily. Exclusion criteria were:
NYHA functional class I, myocardial infarction within 3
months, unstable angina within 1 month, significant valvular
heart disease, uncontrolled hypertension, serious cardiac
arrhythmias, concurrent therapy with calcium channel antago-
nist, β-blockers (β-methyl dopa was used for treating hyperten-
sion if required), positive inotropic agents (except digoxin for
control of atrial fibrillation) and other angiotensin converting
enzyme inhibitors or receptor blockers. At baseline full Doppler
echocardiographic studies, electrocardiogram, chest x ray, 6-
minute Hall walk test (6MWT), QoL questionnaire, and routine
blood testing were carried out. These were repeated at 12 and
24 weeks, and all except the exercise test at 52 weeks after
randomisation.

The primary end points were (i) symptoms and quality of life
and (ii) Doppler echocardiographic measurement of ventricular
function. All outcomes were reviewed blind to treatment
allocation.

The study was conducted in accordance with the Declaration
of Helsinki and was approved by the local clinical research ethics
committee. All patients gave informed consent.

Quality of life
QoL was assessed using the Minnesota Heart Failure Symptom
Questionnaire, which has been previously validated in this
population.15 16

Exercise testing
Exercise capacity was measured using the 6MWT with two
baseline tests as recommended.17

Echocardiography
Echocardiograms were obtained using GE-VingMed System
FiVe or 7 with a 3.5 MHz transducer. Methods of acquiring 2-D
Doppler, TDI and their measurements were as previously
described.18 LVEF was measured by Simpson’s method as
recommended.19 All analyses of digitally stored recordings were
performed by one investigator (MW), who was “blinded” to
treatment. Mitral inflow velocities were recorded in the usual
manner to derive peak early diastolic (E) velocity and peak atrial
filling velocity (A). The LV mass was calculated using the
modified ASE cube formula proposed by Devereux et al.20 Colour
tissue Doppler derived myocardial velocities measured at basal
septal, lateral, inferior and anterior positions around the mitral
annulus were recorded, analysed off-line and averaged. Peak
velocities during systole (Sm), early diastole (Em) and late
diastole (Am) were measured and the ratio of E/Em was used as
an index of LV filling pressure as previously described.21
Measurements are a mean of three beats and for patients in
atrial fibrillation six beats were recorded and averaged.

N-terminal pro-brain natriuretic peptide (NT-proBNP)
Blood samples were collected for measurement of NT-proBNP on
study enrolment and at 12 and 52 weeks. Serum NT-pro-BNP was
quantified by electrochemiluminescence immunosassay on the
Roche Elecsys 2010 analyser (Roche Diagnostics Corporation,
Indianapolis, IN, USA) with an interassay coefficient of variation
(CV) of 2.6% at 1068 pg/ml and a measuring range from 5 to
35 000 pg/ml.

STATISTICS
With n = 50 in each group the study had a >90% power to
detect a 50% reduction of symptom score, a 20% improvement
in exercise time within each group, a 50% reduction in hospital
admissions, and a 20% improvement in peak systolic and early
diastolic basal myocardial velocities at a 5% significance level, all
of which would be considered to be clinically significant.

The statistical program SPSS version 11.0 (Chicago, IL, USA)
was used for all the analyses. Comparisons of the baseline
characteristics among the three groups were performed by
analysis of variance with repeated measures and with the χ2
test for categorical variables. Comparisons between baseline and
follow-up at different time points were by paired t test with
Bonferroni adjustment. Differences between groups at baseline,
12 or 52 weeks were tested by using the 1-way ANOVA and the
Kruskal–Wallis method for non-parametric data.

The results were expressed as mean (SE) (or mean (SD) where
indicated) and their differences considered significant if p<0.05.

RESULTS
Baseline clinical characteristics are shown in table 1. There were
no significant differences between the three treatment groups.
The majority of the patients had hypertension (82%) as the
main aetiology. Twenty per cent had a clinical diagnosis of
diabetes. Most (70%) were in NYHA class II. In the diuretic
group three patients died due to cerebrovascular haemorrhage,
cancer of the liver and cancer of the lung. In the diuretic group
one patient was withdrawn from the study at 4 weeks because
of uncontrolled high blood pressure, one defaulted and one
refused to continue. In the irbesartan group one patient died
due to heart failure and one was withdrawn due to onset of fast
atrial fibrillation. In the ramipril group four patients were
withdrawn because of persistent irritating cough and one
because of uncontrolled blood pressure, and one patient refused
to continue. No patient died.

QoL and exercise capacity
The changes in QoL units are shown in table 2 and fig 1. There
was a significant fall (improvement) in all three groups, which
was apparent by 12 weeks, and there was no difference between
groups. Distance walked in the 6MWT increased slightly in all
groups but this was not statistically significant. Readmission
rates were low (11–12%) in all groups and there was only one
death due to heart failure during the 1-year follow-up. The
mean dose of diuretics did not change significantly from
baseline to 1 year in any group (table 2).

Doppler echocardiography
In table 3 baseline echocardiographic variables for the whole
HFNEF group are compared with age-matched normal subjects.
Peak Sm and Em were significantly lower and LV mass and LA
size increased compared with normal subjects. Filling pressure
estimated by E/Em ratio was also increased in patients. The
impact of treatment on Doppler echocardiography variables is
shown in table 4. There was an increase (improvement) in the
peak early diastolic myocardial velocity (Em) in all groups but
this was more marked and statistically significant only for those

Heart failure and cardiomyopathy
Table 1  Baseline clinical characteristics of patients

<table>
<thead>
<tr>
<th>Patients' characteristics</th>
<th>Diuretic only n = 50</th>
<th>Diuretic + Irbesartan n = 56</th>
<th>Diuretic + Ramipril n = 45</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>73 (8.4)</td>
<td>75 (8.5)</td>
<td>74 (6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Female/male (%)</td>
<td>29(58)/21(42)</td>
<td>37/66)/19/54 (34)</td>
<td>27/60)/18/40 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (SD) (kg/m^2)</td>
<td>26.8 (4.2)</td>
<td>27.2 (4.1)</td>
<td>26.8 (3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>38 (76)</td>
<td>40 (71)</td>
<td>33 (73)</td>
<td>NS</td>
</tr>
<tr>
<td>Angina/Myocardial infarction (%)</td>
<td>9 (18)</td>
<td>12 (21)</td>
<td>7 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>3 (6)</td>
<td>6 (11)</td>
<td>4 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation (%)</td>
<td>10 (20)</td>
<td>10 (18)</td>
<td>10 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>4 (8)</td>
<td>7 (13)</td>
<td>3 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidaemia (%)</td>
<td>5 (10)</td>
<td>7 (13)</td>
<td>4 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>19 (38)</td>
<td>13 (23)</td>
<td>16 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>4 (8)</td>
<td>5 (9)</td>
<td>1 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology of heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart failure (%)</td>
<td>6 (12)</td>
<td>4 (7)</td>
<td>7 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>40 (80)</td>
<td>47 (84)</td>
<td>37 (82)</td>
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<tr>
<td>Signs and symptoms of CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>II 36 (72.0)</td>
<td>38 (67.9)</td>
<td>30 (66.7)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>III 14 (28.0)</td>
<td>17 (30.4)</td>
<td>15 (33.3)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>IV 0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SBP (mean (SD))</td>
<td>145 (23)</td>
<td>145 (19)</td>
<td>143 (22)</td>
</tr>
<tr>
<td></td>
<td>DBP (mean (SD))</td>
<td>80 (14)</td>
<td>82 (10)</td>
<td>79 (12)</td>
</tr>
<tr>
<td></td>
<td>Pulse</td>
<td>76 (14)</td>
<td>77 (9)</td>
<td>79 (13)</td>
</tr>
<tr>
<td></td>
<td>JVP &gt;6 cm (%)</td>
<td>4 (8.0)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td></td>
<td>Oedema (%)</td>
<td>14 (28.0)</td>
<td>9 (16.1)</td>
<td>7 (15.9)</td>
</tr>
<tr>
<td></td>
<td>Third heart sound (%)</td>
<td>3 (6.0)</td>
<td>1 (1.8)</td>
<td>4 (8.9)</td>
</tr>
<tr>
<td>Chest x ray (on admission)</td>
<td>Upper lobe vein prominent (%)</td>
<td>41 (83.7)</td>
<td>48 (88.9)</td>
<td>38 (88.4)</td>
</tr>
<tr>
<td></td>
<td>Kerley lines (%)</td>
<td>9 (18.4)</td>
<td>11 (20.4)</td>
<td>5 (11.6)</td>
</tr>
<tr>
<td></td>
<td>Interstitial oedema (%)</td>
<td>21 (42.9)</td>
<td>16 (29.6)</td>
<td>12 (27.9)</td>
</tr>
<tr>
<td>Medical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide (%)</td>
<td>34 (68.0)</td>
<td>45 (80.4)</td>
<td>36 (80.0)</td>
<td>NS</td>
</tr>
<tr>
<td>mean dosage (SD) (mg)</td>
<td>44.0 (19)</td>
<td>33.3 (14)</td>
<td>33.3 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Hydrochlorothiazide (%)</td>
<td>3 (6.0)</td>
<td>6 (10.7)</td>
<td>4 (8.9)</td>
<td>NS</td>
</tr>
<tr>
<td>mean dosage (SD) (mg)</td>
<td>25 (0)</td>
<td>29 (10)</td>
<td>38 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Indapamide (%)</td>
<td>3 (6.0)</td>
<td>3 (5.4)</td>
<td>2 (4.4)</td>
<td>NS</td>
</tr>
<tr>
<td>mean dosage (SD) (mg)</td>
<td>1.8 (0.6)</td>
<td>2.5 (0)</td>
<td>2.0 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyazide (%)</td>
<td>6 (12.0)</td>
<td>1 (1.8)</td>
<td>1 (2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>α-methyldopa (%)</td>
<td>9 (18.8)</td>
<td>7 (13.0)</td>
<td>10 (23.3)</td>
<td>NS</td>
</tr>
<tr>
<td>mean dosage (SD) (mg)</td>
<td>151 (346)</td>
<td>93 (258)</td>
<td>157 (327)</td>
<td>NS</td>
</tr>
</tbody>
</table>

D, diuretic; DBP, diastolic blood pressure; NS, not significant; SD, standard deviation; SBP, systolic blood pressure.

Figure 1  Quality of life scores (QoL) in the three treatment groups over 1 year. *p<0.01, significant differences between baseline and follow-up at 12 weeks, 24 weeks or 1 year.
receiving irbesartan or ramipril (fig 2). E/Em tended to fall more in the diuretic plus ramipril group. There was a significant fall in LV mass in the group receiving irbesartan (fig 2). However, after one year, there were no statistically significant differences in the percentile changes in Em, E/Em and LV mass among the three groups (table 5). There were no significant changes in LV, LA dimensions, or LV ejection fraction, although peak systolic myocardial velocity increased in all groups.

Reproducibility

The intraclass correlations for various mitral annular variables by the same observer were between 0.8 and 0.9. The interobserver correlations for the same variables were between 0.7 and 0.9. With the Bland–Altman method, the mean difference between observations was less than 5% of the mean value of the observations for measurements of velocity.

Figure 2 Effect of treatment on peak early diastolic mitral annular velocities (Em), peak systolic velocity (Sm), E/Em (an index of LV filling pressures) and LV mass in the three treatment groups. *p < 0.05; **p < 0.01; ***p < 0.001 vs baseline.

Table 2 Main clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Diuretic alone</th>
<th>Diuretic + Irbesartan</th>
<th>Diuretic + Ramipril</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmission for HF (%)</td>
<td>6 (12.2)</td>
<td>6 (11.1)</td>
<td>5 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death (weeks)</td>
<td>1 (38)</td>
<td>1 (51)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other cause of death</td>
<td>2 (liver and lung cancer)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Withdrawn (%)</td>
<td>3 (6.0)</td>
<td>3 (5.3)</td>
<td>6 (13.3)</td>
<td></td>
</tr>
<tr>
<td>QoL score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20 (1.8)</td>
<td>19 (2.1)</td>
<td>23 (2.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>12 weeks</td>
<td>12.9 (1.5)**</td>
<td>10.8 (1.6)**</td>
<td>12.7 (1.4)**</td>
<td>0.9</td>
</tr>
<tr>
<td>24 weeks</td>
<td>10.9 (1.3)**</td>
<td>9.6 (1.2)**</td>
<td>12.9 (1.7)**</td>
<td>0.8</td>
</tr>
<tr>
<td>52 weeks</td>
<td>10.9 (1.3)**</td>
<td>9.4 (1.3)**</td>
<td>11.4 (1.4)**</td>
<td>0.7</td>
</tr>
<tr>
<td>6MWT (feet/6 mins)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1011 (37)</td>
<td>950 (37)</td>
<td>962 (42)</td>
<td>0.4</td>
</tr>
<tr>
<td>12 weeks</td>
<td>1055 (38)</td>
<td>968 (37)</td>
<td>1011 (43)</td>
<td>0.2</td>
</tr>
<tr>
<td>24 weeks</td>
<td>1048 (43)</td>
<td>1007 (33)</td>
<td>1028 (37)</td>
<td>0.8</td>
</tr>
<tr>
<td>Blood pressure (mean (SD)) (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>145 (23)/80 (12)</td>
<td>144 (19)/82 (10)</td>
<td>143 (22)/82 (10)</td>
<td>0.9</td>
</tr>
<tr>
<td>4 weeks</td>
<td>139 (21)/77 (10)**</td>
<td>134 (18)/76 (11)**</td>
<td>138 (21)/77 (12)**</td>
<td>0.3</td>
</tr>
<tr>
<td>8 weeks</td>
<td>134 (21)/75 (12)**</td>
<td>135 (18)/76 (11)**</td>
<td>139 (20)/76 (11)**</td>
<td>0.6</td>
</tr>
<tr>
<td>12 weeks</td>
<td>134 (21)/75 (12)**</td>
<td>136 (20)/76 (10)**</td>
<td>136 (18)/77 (10)**</td>
<td>0.9</td>
</tr>
<tr>
<td>24 weeks</td>
<td>138 (21)/75 (9)**</td>
<td>136 (20)/76 (12)**</td>
<td>137 (21)/76 (11)</td>
<td>0.5</td>
</tr>
<tr>
<td>52 weeks</td>
<td>138 (24)/78 (10)</td>
<td>137 (21)/73 (10)</td>
<td>141 (23)/76 (13)</td>
<td>0.7</td>
</tr>
<tr>
<td>NT-proBNP (mean (SD)) (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>566 (944)</td>
<td>568 (757)</td>
<td>488 (701)</td>
<td>0.7</td>
</tr>
<tr>
<td>12 weeks</td>
<td>390 (625)</td>
<td>394 (641)</td>
<td>282 (376)</td>
<td>1.0</td>
</tr>
<tr>
<td>52 weeks</td>
<td>334 (414)</td>
<td>443 (603)**</td>
<td>314 (422)**</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Results expressed as mean (SEM) unless otherwise stated. *p < 0.05; **p < 0.01; ***p < 0.001 vs baseline.

NT-proBNP, N-terminal pro-brain natriuretic peptide; QoL, quality of life score; 6MWT, 6-minute corridor walk test.
as effective as diuretics combined with irbesartan or ramipril. This had occurred by 12 weeks (table 2). There was a trend towards quicker progress with the addition of irbesartan or ramipril. The symptomatic improvement was quite rapid and 70–90% of this had occurred by 12 weeks (table 2). There was a trend towards quicker progress with the addition of irbesartan or ramipril.

**DISCUSSION**

In this study we found, first, that in HFNEF diuretics alone appeared to be effective in reducing symptoms and improving quality of life, and the addition of ramipril or irbesartan was not obviously more efficacious; second, that all therapies had only a slight effect on exercise capacity as assessed by the 6-minute walk test; and third, that ventricular annular or basal peak velocities are reduced in both systole and diastole and that these improve slightly after diuretics with ramipril or irbesartan.

Symptoms are an important part of the heart failure syndrome and quality of life is often severely impaired. Many patients with HFNEF are elderly and often frail, and for them therapy which improves symptoms or exercise capacity immediately may be more important than an uncertain possibility of a small reduction in mortality in the future. Relief of symptoms is, therefore, an important target of therapy but, being subjective, this is difficult to evaluate. A number of health-related quality of life instruments have evolved in order to assess the impact of disease, effect of treatment and other variables affecting people’s lives. In this study we used a disease-specific instrument – the Minnesota Living with Heart Failure (MLHF) questionnaire. A recent review has compared the MLHF with two other questionnaires and shown that the MLHF was more sensitive than the Chronic Heart Failure questionnaire and the generic abbreviated short form health survey. In this study we used a Chinese version of the MLHF which has been validated in previous studies. It is likely, therefore, that the marked reduction in the MLHF score does truly represent an improvement in quality of life. Interestingly, we found that diuretics alone were almost equally as effective as diuretics combined with irbesartan or ramipril.

### NT-pro-BNP

The mean NT-pro-BNP level of all patients in the study was raised at baseline (595 (SD 904) pg/ml) although there was a wide scatter from 5–4748 pg/ml (table 2). The levels tended to fall in all treatment groups by 12 months although this reached statistical significance only in the irbesartan and ramipril groups.

### DISCUSSION

In this study we found, first, that in HFNEF diuretics alone appeared to be effective in reducing symptoms and improving quality of life, and the addition of ramipril or irbesartan was not obviously more efficacious; second, that all therapies had only a slight effect on exercise capacity as assessed by the 6-minute walk test; and third, that ventricular annular or basal peak velocities are reduced in both systole and diastole and that these improve slightly after diuretics with ramipril or irbesartan.

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### NT-pro-BNP

The mean NT-pro-BNP level of all patients in the study was raised at baseline (595 (SD 904) pg/ml) although there was a wide scatter from 5–4748 pg/ml (table 2). The levels tended to fall in all treatment groups by 12 months although this reached statistical significance only in the irbesartan and ramipril groups.

### DISCUSSION

In this study we found, first, that in HFNEF diuretics alone appeared to be effective in reducing symptoms and improving quality of life, and the addition of ramipril or irbesartan was not obviously more efficacious; second, that all therapies had only a slight effect on exercise capacity as assessed by the 6-minute walk test; and third, that ventricular annular or basal peak velocities are reduced in both systole and diastole and that these improve slightly after diuretics with ramipril or irbesartan.

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increased volumes consistent with a mild volume overload state rather than the typical DHF paradigm. A combination of cardiac and many extra cardiac factors such as renal function and venous tone, amongst others, may cause the rapid rise in LV filling pressures and pulmonary oedema.

Despite the significant improvement in quality of life scores in this study, the changes in exercise capacity were relatively modest. The 6-minute walk test is commonly used in heart failure clinical trials. Intuitively, walking on level ground would seem to be a more suitable test for elderly patients. However, the ability of the 6-minute walk test (MWT) to distinguish between effective and ineffective treatments has been questioned. In a systematic review of trials that have used the 6MWT, Olsson et al concluded that the test has not yet been proven to be robust enough for the identification of effective pharmacological intervention. However, Olsson et al did find that the results of the 6MWT are usually concordant with changes in symptoms. In our study the directional change, if not the magnitude, in 6MWT was compatible with the symptoms score. However, in this group of elderly patients many other factors limit mobility and any improvement of cardiac function alone may not be sufficient to impact significantly on exercise capacity.

Ventricular long axis function is an important component of overall ventricular function. Recent studies using MRI have shown that longitudinal atrioventricular plane displacement accounts for 60% of stroke volume even in those with depressed systolic function due to dilated cardiomyopathy. Loss of longitudinal function may be compensated for by increased radial motion in the early stages. Previous studies have shown that both the peak systolic myocardial velocity (Sm) and the peak early diastolic myocardial velocity (Em) are reduced in HFNEF, despite a normal LVEF, challenging the concept that HFNEF/DHF is a distinct entity due to isolated diastolic dysfunction, and therefore in many patients systolic function cannot be considered to be truly normal in HFNEF/DHF. Not unexpectedly, given the fundamental role of mitral annular motion in ventricular function, both Sm and Em are powerful predictors of prognosis in a variety of cardiac conditions, including heart failure. Furthermore, in a study of suspected heart failure, the echocardiographic parameter which best correlated with NT-proBNP was LV longitudinal peak systolic velocity. In an experimental model of heart failure, Em declined early and before radial derived early diastolic velocities. This may be because motion of the ventricular base during early diastole is in effect reflecting both systolic and diastolic ventricular function. Em correlates well with tau, which is a measure of LV relaxation, but the mitral ring motion starts at the same time as mitral inflow, that is, when the pressure has already fallen. The early diastolic annular velocity (Em) is therefore primarily a measure of recoil or ventricular restoring forces, which depend to some extent on the nature of the previous systolic contraction, the degree of twist and untwist, incoordination and dys synchrony.

How therapy with diuretics plus either irbesartan or ramipril improved long axis ventricular function without any appreciable change of LV ejection fraction cannot be exactly deduced from this study. There are a number of possible reasons including a reduction of LV mass, myocardial fibrosis, subendocardial ischaemia and afterload. It is known that arterial load affects both systolic and diastolic LV performance, prolonging contraction and relaxation (an effect seen early in the progression of systolic dysfunction), and shortening the diastolic filling period. Arterial compliance is also an independent predictor of diastolic dysfunction in patients with hypertensive heart disease. The effect of increased afterload or raised BP would be particularly troublesome for diastolic filling when heart rates are higher, such as with exercise and in those with atrial fibrillation. Thus, part of the improvement in peak myocardial systolic and diastolic velocities could be due to a reduction in arterial BP, which was observed in all treatment groups.

There was a trend for irbesartan and ramipril therapy in combination with diuretics to reduce LV mass, which became statistically significant only for irbesartan at 24 weeks, although by 1 year there was no difference between the three groups. Systolic blood pressure was lowered to a similar extent by all treatments, although diastolic blood pressure was reduced slightly more by irbesartan. In the Losartan intervention for End-point Reduction in Hypertension (LIFE) trial, losartan induced greater reduction in LV mass index from baseline than the β-blocker atenolol measured by echocardiography. ACE inhibitors also reduced LV mass in the Treatment Of Mild Hypertension study (TOMHS). In the VALIHD study antihypertensive therapy reduced blood pressure and improved diastolic relaxation velocity, but there was no significant difference between those receiving the angiotensin receptor blocker valsartan and those receiving a matching placebo. There have been no direct head-to-head comparisons of an angiotensin receptor antagonist with ACE inhibitors regarding their effect on LVH. However, LVH regression may be a clinically important end point, since regression of hypertensive LVH is associated with improved prognosis.

LV fibrosis is increased with LVH and hypertension and this is associated with reduced peak myocardial velocities. Shan et al found that both Sm and Em were inversely related to the percentage of interstitial fibrosis in endomyocardial biopsy specimens. ACE inhibitors and ARBs can block the fibrogenic action of angiotensin experimentally and have been shown to reduce fibrosis in patients with hypertension. Fibrosis and altered collagen in LVH may have a profound effect on overall myocardial architecture, and in particular ventricular twist and torsion, which is reflected in reduced longitudinal velocities, and this will impact directly on diastolic filling. Reducing fibrosis may, therefore, be an important therapeutic target in patients with LVH and heart failure or HFNEF.

### Table 5 Comparison between three groups at 52 weeks (percentile change from baseline)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LVmass</th>
<th>Sm</th>
<th>Em</th>
<th>E/Em</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>−11 (−22 to 10)</td>
<td>−8 (−25 to 11)</td>
<td>−7 (−21 to 18)</td>
<td>−5 (−31 to 17)</td>
<td>0.67</td>
</tr>
<tr>
<td>Diuretic + Irbesartan</td>
<td>−6.4 (−6 to 26)</td>
<td>12.5 (0.2 to 31.28)</td>
<td>5.5 (−8.8 to 29)</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Diuretic + Ramipril</td>
<td>4.4 (−10 to 49)</td>
<td>19 (−7 to 33)</td>
<td>27 (−1 to 63)</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

Results expressed as median (interquartile range).

Comparison using Kruskal–Wallis test.
Limitations
This study has some limitations. Recruitment was slow as many potential patients were ineligible because of significant comorbidities, particularly renal dysfunction, valvular heart disease (which is common in this age group), anaemia, already frailty and dementia. These are typical for this age group. In addition, the strict entry criteria in this study, which required chest x-ray evidence of pulmonary oedema, were also a hurdle. Our experience does highlight the difficulty in performing clinical trials in this group of patients if the criteria for heart failure are strict. However, this study does have strengths: the study population is a representative sample with respect to age and aetiology, the diagnosis required x-ray confirmation of pulmonary oedema on admission, and other treatments that may have interfered, such as β-blockers and calcium antagonists, were not allowed; confirmation of the diagnosis comes from raised NT-proBNP levels in the majority despite earlier treatment with diuretics (to levels above those recommended in the recent revision of the European Society of Cardiology guidelines[8]); E/Em ratios were increased, which is another diagnostic criterion in the new guidelines[23]. Using colour tissue velocity imaging (which produces the mean velocity rather than peak as with pulsed tissue Doppler imaging) the ratio E/Em is higher but a ratio >1.5 is still considered diagnostic.[24] Using averaged velocity measurements from two or more sites is also recommended, as was done in this study.

In summary, this study is the first comparison of an ACE inhibitor and an angiotensin receptor blocker in patients with heart failure and normal ejection fraction. In addition, we have compared both of these drugs with diuretics alone. We have shown that diuretics alone can improve quality of life and symptoms in this group of patients and there was little further symptomatic benefit with the addition of irbesartan or ramipril. In addition, we have confirmed in a group of patients with HFNEF (DHF) that ventricular long axis function is reduced in both systole and diastole and that this was improved slightly by treatment with irbesartan or ramipril in combination with a diuretic.

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Competing interests: None.

REFERENCES


Failed endothelialisation of a percutaneous atrial septal defect closure device

A 77-year-old woman with severe myxomatous mitral regurgitation underwent mitral valve replacement. Twenty-six months previously, she had undergone percutaneous closure of an atrial septal defect (ASD) with an Amplatzer device. At the time of surgery inspection of both sides of the septal occluder device revealed bare Nitinol wires suggesting failed endothelialisation (Panel A).

The use of percutaneous closure devices for the treatment of atrial septal defects is increasing. However, our current knowledge regarding the long-term safety and efficacy of these devices is limited. This case illustrates that endothelialisation of such devices may be significantly delayed or even absent following implantation, raising the possibility of late thromboembolic complications. Presently there is no consensus of opinion regarding antiplatelet therapy following device implantation. In the United Kingdom, general guidelines issued in 2004 regarding the percutaneous implantation of ASD closure devices estimated the incidence of device-associated thrombus formation at 0.4–3%, based on data from large non-randomised studies. However, these studies differed in the type of device implanted and the antiplatelet agent regimens employed. We routinely perform transoesophageal echocardiography 6 months postprocedure prior to stopping dual antiplatelet therapy, which is continued thereafter only if there has been a neurological event.

Non-endothelialised devices present potent substrates for thrombus formation and the potential for cerebrovascular accidents. This case illustrates a previously unrecognised and potentially serious problem, highlighting the unresolved issue of the appropriate type and duration of antiplatelet therapy, and the need for strategies to accelerate endothelial coverage of such occluder devices.

Panel A. Intraoperative image of the atrial septal defect closure device, viewed from the left atrium, showing the bare Nitinol mesh.

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