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ORIGINAL RESEARCH ARTICLE

Efficacy and safety of supramaximal titrated inhibition of renin-angiotensin-aldosterone system in idiopathic dilated cardiomyopathy

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Abstract

Aims The optimal dosing strategies for blocking the renin-angiotensin-aldosterone system in idiopathic dilated cardiomyopathy (IDCM) are poorly known. We sought to determine the long-term efficacy and safety of supramaximal titration of benazepril and valsartan in patients with IDCM.

Methods and results 480 patients with IDCM in New York Heart Association functional class II–IV and with left ventricular ejection fraction ≤35% were randomly assigned to extended-release metoprolol (mean 152 mg/day, range 23.75–190), low-dose benazepril (20 mg/day), low-dose valsartan (160 mg/day), high-dose benazepril (mean 69 mg/day, range 40–80), and high-dose valsartan (mean 526 mg/day, range 320–640). After a median follow-up of 4.2 years, high-dose benazepril and valsartan, compared with their respective low dosages, resulted in 41% and 52% risk reduction in the primary endpoint of all-cause death or admission for heart failure ($P = 0.042$ and 0.002), promoted functional improvement, and reversed remodelling as assessed by New York Heart Association classes, quality-of-life scores, and echocardiographic recording of left ventricular ejection fraction, left ventricular end-diastolic volume, mitral regurgitation, and wall motion score index. Compared with metoprolol, high-dose valsartan reduced risk for the primary endpoint by 46% ($P = 0.006$), whereas high-dose benazepril and both low-dose groups showed no significant difference. Major adverse events involved hypotension and renal impairment but were largely tolerated.

Conclusions Supramaximal doses of benazepril and valsartan were well tolerated and produced extra benefit than their low dosages in clinical outcome and cardiac reverse remodelling in patients with IDCM and modest-severe heart failure. ClinicalTrials.gov identifier: NCT01917149.

Keywords Dilated cardiomyopathy; Angiotensin-converting enzyme inhibitor; Angiotensin II receptor blocker; Heart failure; Cardiac remodelling

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Introduction

Dilated cardiomyopathy, characterized by ventricular chamber enlargement and contractile dysfunction, is the third most common cause of heart failure and the most frequent reason for heart transplantation.[1] The majority of dilated cardiomyopathy was classified as idiopathic dilated cardiomyopathy (IDCM) with no identifiable causes. Anti-neuroendocrine medication that blocks the β-adrenergic and renin-angiotensin-aldosterone systems (RAAS), including β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), has been recognized as important therapeutic strategies for IDCM. However, patients with IDCM remain highly symptomatic and frequently progress to end-stage heart failure.

The currently used doses of ACEI/ARB are largely based on their anti-hypertensive effects.[2] Recently, higher doses of ACEI/ARB have shown extra benefits in high-risk patients

with HF, severe hypertension, diabetes, and chronic renal disease with proteinuria. For example, using large doses of enalapril (40 mg/day),[3] captopril (≥75 mg/day),[4] lisinopril (32.5–35 mg/day, ATLAS study),[5] and losartan (150 mg/day, HEAAL study),[6] earlier researches have documented increases in hemodynamic improvement and exercise tolerance, and reduced need for hospitalization compared with small doses in patients with chronic heart failure (CHF). These observations lend support to the hypothesis that supramaximal doses of ACEI/ARB beyond their maximal recommended anti-hypertensive dosage may provide more effective cardioprotection in HF.[2] However, supramaximal doses of ACEI/ARB may be of great concern to many physicians due to increased adverse events. It has also been suggested that low doses of ACEI/ARB could be as effective as high doses[7] but produced fewer side effects, especially the serious hypotensive effects that may compromise cerebral and renal functions.[8] Because the optimal doses of ACEI/ARB to prevent the progression of HF in IDCM patients are not known, titration of the ACEI/ARB doses to maximize the clinical benefits of RAAS inhibition may be warranted but not practical until more safety and tolerability data are available.

Angiotensin-converting enzyme inhibitors and ARBs are two distinct pharmacologic classes that both reduce the actions of angiotensin II, but each possesses unique pharmacologic effects that may be of therapeutic importance. Previous studies have reported that valsartan (up to160 mg bid) is equally effective as captopril (up to 50 mg tid) in reducing atherosclerotic events in post-myocardial infarction patients.[5] In addition, losartan (50 mg/day) has been suggested to be not superior to captopril (50 mg, tid) in reducing all-cause mortality, sudden death, or resuscitated arrest in patient with HF.[9] Thus, ARBs are commonly prescribed to ACEI-intolerant patients and assumed to be equivalent to ACEI. It is still not clear, however, whether ARBs at supramaximal doses possess a similar spectrum of cardiovascular benefits as ACEIs, such as reducing mortality and remodelling in IDCM-induced HF.

The primary purpose of this study was to compare in the IDCM patients the long-term outcome of supramaximal titrated ACEI/ARB with conventional regimens including low-dose ACEI/ARB and optimized metoprolol therapy. Additionally, we sought to evaluate the efficacy of an ACEI (benazepril) vs. an ARB (valsartan) at supramaximal dosages, and determine their adverse effects.

Methods

This is a prospective, randomized, and controlled study conducted in a single centre. The study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Fourth Military Medical University. An independent data and safety monitoring board was informed of adverse events as they occurred. All participants provided written informed consent.

Patient eligibility

Patients diagnosed as IDCM were enrolled according to the following criteria: symptoms and signs of left or biventricular failure, global left ventricular hypokinesis with prominent left ventricular dilation, and left ventricular ejection fraction (LVEF) ≤35% by echocardiography. Additional inclusion criteria required ages between 18 and 70 years, New York Heart Association (NYHA) functional classes II–IV, and symptomatic but not rapidly deteriorating 1 month before enrollment. Exclusion criteria included the following: (1) contradictions and known intolerance to the study drugs, supine systolic blood pressure (SBP) < 90 mmHg, renal artery stenosis >50%, pregnancy or lactation, impaired renal function [estimated glomerular filtration rate (Cockcroft and Gault formula) < 30 mL/min/1.73 m^2], impaired liver function (total bilirubin >2 times upper limit of normal, serum aspartate or alanine aminotransferase >3 times the upper limit of normal), haemoglobin <8 mg/dL, hyperkalaemia (serum potassium >5.5 mmol/L), advanced atrioventricular block, and other comorbidities with impact on survival; (2) HF secondary to a known cause, coronary artery disease based on coronary angiography (≥50% stenosis in ≥1 of the major coronary arteries) and/or a history of myocardial infarction or angina pectoris, acute or subacute stage of myocarditis, primary valve disease, diabetes mellitus, and excessive use of alcohol or illicit drugs; and (3) expected or performed cardiac resynchronization therapy and heart transplantation. Known intolerance to the studies drugs was defined as previous discontinuation due to dry cough, allergy, symptomatic hypotension, azotaemia, hyperkalaemia, or angioedema. The indications for cardiac resynchronization therapy and heart transplantation were defined according to current guidelines.[10]

Study design

After baseline screen, eligible patients were randomly assigned to five groups (open labelled): metoprolol, low-dose benazepril, low-dose valsartan, high-dose benazepril, and high-dose valsartan. Patients in the metoprolol group were started on 11.875–23.75 mg of metoprolol succinate extended-release tablet once daily (11.875 mg was recommended for patients in NYHA III–IV), and then doses were doubled every 2 weeks to achieve asymptomatic bradycardia (55–60 bpm) over 4–6 weeks. Investigators were encouraged to up-titrate metoprolol to a maximum dose of 190 mg whenever possible. Patients in low-dose benazepril/valsartan groups received fixed dosages of benazepril (10 mg bid) or valsartan (80 mg bid) until study completion. Patients randomized to high-dose benazepril/

valsartan were started on benazepril 10 mg or valsartan 80 mg bid, and up-titrated to target doses within 7 days under in-hospital observation. The target doses were determined by the left ventricular end-diastolic diameter (LVEDD) (the larger value of the anteroposterior and lateral diameters) of the patient determined by echo at randomization. A target dose of benazepril 40, 60, and 80 mg or valsartan 320, 480, and 640 mg daily was assigned to patients with LVEDD of 50–59, 60–69, and ≥70 mm, respectively, according to our preliminary dose-effect analysis of benazepril/valsartan use in IDCM patients with varying LVEDD values. 11.875–47.5 mg of metoprolol was added to the last four groups whenever necessary. Other medications (diuretics, digoxin, long-acting nitrates, etc.) were added in accordance with current guidelines to achieve optimal control of heart failure (*Table 1*).

Patients were evaluated before each dose increase and observed for drug intolerance. Symptomatic medication and/or temporary decrease in study drug was adopted when worsening cardiac failure, symptomatic hypotension (palpitation, dizziness, syncope, and oliguria), bradycardia or elevations in serum creatinine and potassium occurs. The criteria for increasing the dose included a standing SBP ≥ 85 mmHg, absence of symptoms of hypotension, and a serum creatinine ≤177 μmol/L or ≤50% elevation of the baseline concentration. Patients with serum creatinine concentrations > twice the baseline value for two consecutive weeks or serum K^+ levels >6.0 mol/L were discontinued from the study.

Outcome measurements

The primary endpoint was all-cause death or admission for heart failure. The primary causes of death and hospital admission were determined by an endpoint classification

Table 1 Baseline characteristics of patients

		Low-dose		High-dose	
	Metoprolol (n = 96)	Benazepril (n = 97)	Valsartan (n = 100)	Benazepril (n = 101)	Valsartan (n = 97)
General characteristics					
Age (years)	51 ± 14	47 ± 10	53 ± 13	49 ± 11	50 ± 13
Male	62 (65%)	67 (69%)	65 (65%)	60 (59%)	63 (65%)
Body mass index (kg/m^2)	22.3 ± 3.9	24.3 ± 3.5	21.8 ± 4.9	23.9 ± 3.3	22.0 ± 4.2
Symptomatic period (months)	13 ± 5	12 ± 5	14 ± 5	14 ± 6	12 ± 6
Heart rate (beats/min)	89 ± 14	91 ± 13	87 ± 15	86 ± 12	89 ± 12
Systolic/diastolic blood pressure (mmHg)	124 ± 15/80 ± 9	121 ± 15/79 ± 9	120 ± 15/75 ± 7	123 ± 12/78 ± 8	126 ± 17/80 ± 8
NYHA functional class					
II	13 (14%)	10 (10%)	12 (12%)	15 (14%)	13 (13%)
III	54 (56%)	53 (55%)	55 (55%)	51 (50%)	53 (55%)
IV	29 (30%)	34 (35%)	33 (33%)	35 (35%)	31 (32%)
Medical history					
Prior history of HF	73 (76%)	79 (81%)	80 (80%)	74 (74%)	78 (80%)
Hypertension	13 (14%)	12 (12%)	11 (11%)	13 (13)	15 (15%)
Peripartum cardiomyopathy	1 (1%)	0	1 (1%)	1 (1%)	2 (2%)
Atrial fibrillation	16 (17%)	12 (12%)	18 (18%)	15 (15%)	11 (11%)
Baseline echocardiographic data					
LVEDD (mm)	70 ± 6	69 ± 5	68 ± 6	67 ± 5	68 ± 5
LVEF (%)	27 ± 6	26 ± 6	26 ± 6	27 ± 6	26 ± 6
LVFS (%)	15 ± 3	16 ± 4	15 ± 3	17 ± 3	16 ± 2
WMSI	1.9 ± 0.3	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2
Mitral regurgitation	59 (61%)	53 (55%)	55 (55%)	57 (56%)	60 (63%)
Prior medications (on admission)					
Diuretics	70 (73%)	78 (80%)	78 (78%)	71 (71%)	72 (74%)
ACEIs	61 (64%)	58 (59%)	66 (66%)	62 (61%)	63 (65%)
ARBs	20 (21%)	24 (23%)	19 (19%)	25 (25%)	18 (19%)
β-Blockers	41 (42%)	45 (46%)	38 (38%)	41 (41%)	44 (45%)
Digoxin	30 (31%)	26 (27%)	24 (24%)	21 (21%)	27 (28%)
Dihydropyridine calcium antagonists	9 (9%)	7 (7%)	7 (7%)	11 (11%)	10 (10%)
Anticoagulants	16 (17%)	9 (9%)	11 (11%)	15 (15%)	13 (13%)
Statins	19 (20%)	14 (14%)	10 (10%)	16 (16%)	15 (15%)
Concomitant medications (on randomization)					
Metoprolol	96 (100%)	97 (100%)	98 (98%)	81 (81%)	84 (84%)
Diuretics (excluding aldosterone blockers)	90 (94%)	92 (95%)	96 (96%)	95 (94%)	91 (94%)
Digoxin	20 (21%)	17 (18%)	21 (21%)	16 (16%)	12 (12%)
Dihydropyridine calcium antagonists	7 (7%)	11 (11%)	14 (14%)	13 (13%)	9 (9%)
Anticoagulants	18 (19%)	16 (17%)	13 (13%)	19 (19%)	16 (17%)
Statins	20 (21%)	17 (18%)	10 (10%)	16 (16%)	17 (18%)

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; NYHA, New York Heart Association; WMSI, wall motion score index. Data presented as mean ± SD or number (%).

committee whose members were masked to treatment assignment. Admission for heart failure was defined as a minimum of 24 h inpatient admission to any healthcare facility, with the primary cause being treated for worsening heart failure and during which an additional diuretics, intravenous nitrate, or inotropic agent was given. Additional pre-specified outcomes included all-cause death, cardiovascular death, all-cause admission, and heart failure admission. Secondary cardiovascular outcomes included changes in NYHA functional class, quality-of-life scores from the Minnesota Living with Heart Failure Questionnaire, LVEF, LVEDD, left ventricular end-diastolic volume (LVEDV)/body surface area, peak instantaneous volume of mitral regurgitation, and wall motion score index (WMSI) assessed by echo. Patients at randomization visit were screened for blood biochemistry (serum electrolytes and renal and liver function test), chest X-ray, electrocardiogram, and echo. Patients returned for follow-up visits at 3, 6, and 12 months and every 6 months thereafter until study completion, and data were collected by blinded physicians. Compliance was ensured by careful questioning and tablet counts. Adverse events were reported during both in-hospital stay and follow-up visits.

Echocardiography

Left ventricular ejection fraction was calculated from measurements of left ventricular end-diastolic (LVEDV) and end systolic volumes in apical four and two chamber views by a Vivid 7 echocardiograph (GE healthcare, UK) using the modified Simpson's rule. The peak instantaneous volume of mitral regurgitation was selected by colour Doppler flow mapping from three separate cardiac cycles and calculated by computer algorithms. WMSI was analysed using an 11-segments model.[11] All recordings were processed by experienced ultrasound technicians unaware of treatment allocation.

Statistical analysis

The sample size was estimated based on our previous pilot study, which showed 40% and 28% rate of primary endpoint among DCM patients treated with 160 and 400 mg valsartan, respectively. We expected that supramaximal titrated dose of valsartan would reduce this rate to 20%. Because no data on long-term effect of supramaximal dose of ACEI in DCM were available at the start of the study, we assumed that treatment with supramaximal dose of benazepril would also reduce the rate of primary endpoint to 20% vs. its low dose 40%. Therefore, it was estimated that a minimum of 96 patients in each group should be enrolled to ensure an alpha of 0.05, power of 80%, a desired detectable 20% difference in primary endpoint between low-dose and high-dose benazepril/valsartan groups and allow 20% dropout rate.

The primary and secondary endpoints were analysed according to the intention-to-treat principle. Missing data were treated using last observation carried forward method. The primary endpoint was also analysed by using the per-protocol principle. Cox proportional hazards regression models were used to estimate hazard ratios and two-sided 95% confidence interval. Risk reduction was calculated as $100\% \times (1 - \text{hazard ratio})$. Event curves were based on Kaplan–Meier analysis, and significance was assessed by log-rank test. Changes in NYHA functional class, quality-of-life scores, and echo data were assessed by analysis of variance. Multiple comparisons were conducted with Bonferroni's *t*-test when analysis of variance was significant. Longitudinal comparison of continuous variables was performed by the paired *t*-test or Wilcoxon test. Categorical parameters were presented as number and proportion, and differences between groups were assessed with χ^2 test. Normally distributed continuous variables are reported as means ± SD. Two-sided tests have been used throughout, and *P*-values <0.05 were considered statistically significant. SPSS software version 14.0 (SPSS, Chicago, IL, USA) was used for data analysis.

Results

Patient characteristics

Figure 1 shows the trial profile. A total of 491 consecutive patients were enrolled from March 2005 through October 2010. Follow-up was concluded in July 2014. The median duration of follow-up was 4.2 years. All treatment groups were well balanced at baseline in age, body mass index, heart rate, blood pressure, and NYHA functional class (*Table 1*). Seventy-nine percent of participants were in NYHA class III–IV, indicating modest-severe heart failure at randomization. All patient groups revealed comparable clinical history and echo measurements and followed similar medication regimens except the study drugs.

During follow-up visits, 63 patients were discontinued from the study due to adverse effects; the major three were dry cough (29, 46%), hypotension (13, 20%), and renal dysfunction (10, 15%) (*Figure 1*). Sixteen patients were lost to follow-up, of which six had poor compliance and 10 refused to continue the treatment (*Figure 1*). The mean dosages at the end of the up-titration phase in the metoprolol group and high-dose benazepril/valsartan groups were 152, 69, and 526 mg daily, respectively. The compliance assessed by pill counting was $>95\%$ in all groups.

Primary outcomes

A total of 176 patients experienced the primary endpoint of all-cause death or hospital admission for heart failure (*Table 2*).

Figure 1 Trial profile.

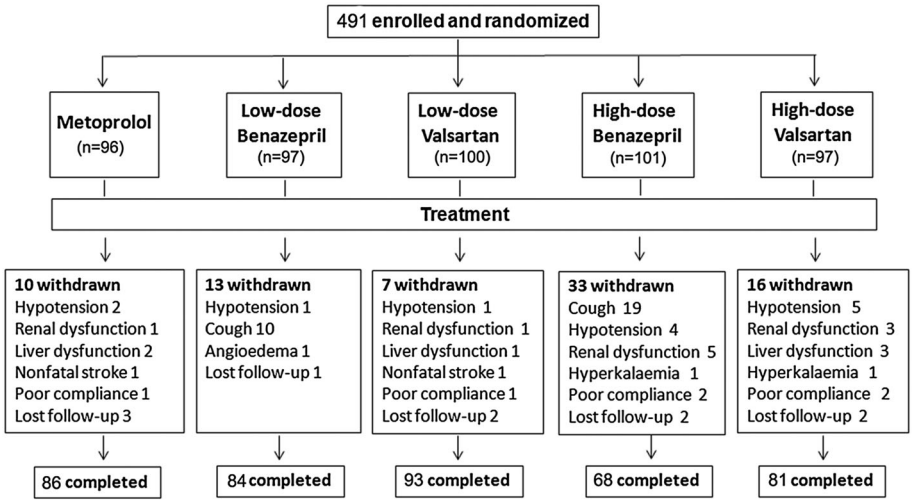


Table 2 Primary endpoints and components

	Metoprolol ($n = 96$)	Low-dose		High-dose	
		Benazepril ($n = 97$)	Valsartan ($n = 100$)	Benazepril ($n = 101$)	Valsartan ($n = 97$)
All-cause death or heart failure admission	39	38	44	25	30
All-cause death	14	11	13	8	8
Cardiovascular death	10	8	11	7	5
Heart failure admission	31	33	37	25	27
All-cause hospital admission	57	52	54	42	46

Treatment with high-dose benazepril or valsartan, compared with their low-dose arms, resulted in overall reduction in the risk for primary endpoint by 41% in the benazepril arm (95% CI 0.36–0.98, $P = 0.042$) and 52% in the valsartan arm (95% CI 0.30–0.77, $P = 0.002$) (*Figure 2A*). Compared with metoprolol group, both low-dose groups receiving either benazepril or valsartan showed no significant difference in rates of primary endpoint. However, high-dose valsartan resulted in significantly reduced risk for primary endpoint by 46% (95% CI 0.33–0.88, $P = 0.013$), while high-dose benazepril group showed a 30% risk reduction (95% CI 0.43–1.15) but failed to achieve statistical difference by log-rank test ($P = 0.16$). The per-protocol analyses of the primary endpoint showed similar results, except that the high-dose benazepril regimen turned to show significant difference vs. metoprolol with a 36% reduction in risk for primary endpoint (95% CI 0.26–0.96, $P = 0.044$) (*Figure 2B*). There was no statistical difference between benazepril and valsartan in the overall relative risk reduction at their respective maximal titrated dose or at low dosages.

Clinical and echocardiographic evaluation of ventricular function

The average reduction in NYHA class in benazepril arm over the 4-year follow-up was 34% in high-dose group, and 21% in low-dose group ($P < 0.001$), while a 19% decrease of average NYHA class was observed in low-dose valsartan arm, and 43% decrease in high-dose valsartan arm ($P < 0.001$) (*Figure 3A*). Both high-dose benazepril/valsartan groups showed significantly higher improvement than the metoprolol group in percentage of NYHA classes (*Figure 3B*), and the Minnesota Living with Heart Failure Questionnaire score (*Figure 3C*). Both high-doses groups showed marked increase in LVEF improvement, as evidenced by 15.0 ± 2.2% increase from baseline to 4-year follow-up with benazepril and 18.5 ± 2.5% with valsartan, compared with 9.9 ± 1.8% increase with metoprolol ($P < 0.01$) (*Figure 3D* and *E*). The LVEF increases in both high-doses groups were also significantly higher than the low-dose groups (6.8 ± 2.4% and 6.6 ± 1.9%, both $P < 0.01$). When comparison was performed between benazepril and valsartan at high doses (not low doses), a slight but significant higher increase was observed in the valsartan arm ($P < 0.05$, *Figure 3E*).

Echocardiographic analysis of cardiac remoulding

Significant reduction in LVEDD was observed in both benazepril and valsartan arms at high doses as early as 6-month follow-up ($P < 0.001$, *Figure 4A*), and achieved 7.8 ± 0.8/12.4 ± 1.2 mm reduction at 4-year follow-up, in contrast

Figure 2 Kaplan–Meier cumulative event curves for primary endpoint of all-cause death or admission for heart failure, according to (A) intention-to-treat or (B) per-protocol principal.

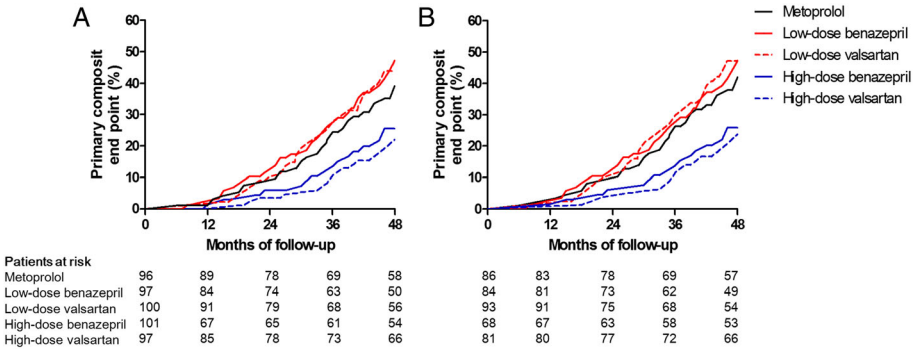
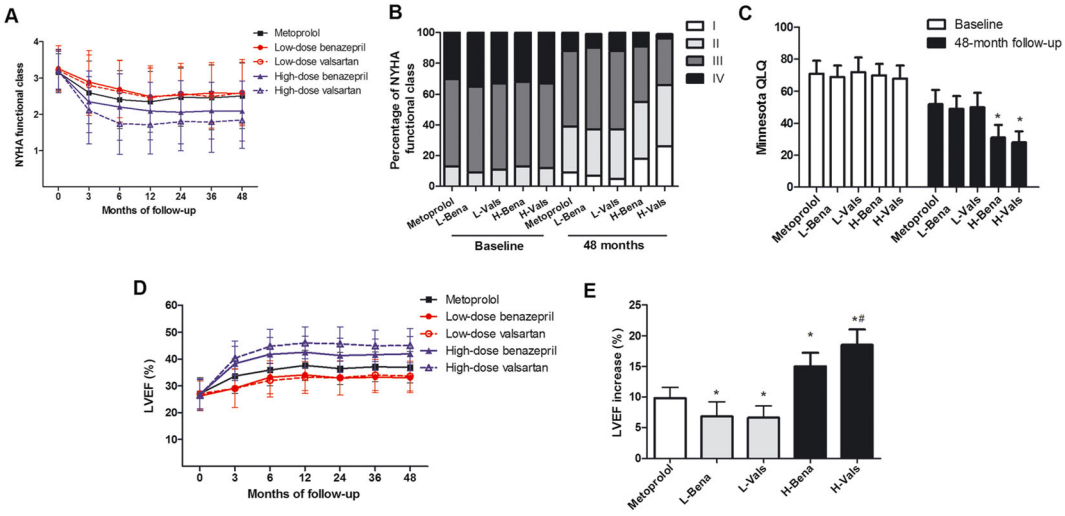


Figure 3 Clinical and echocardiographic evaluation of cardiac function over 4 years of follow-up. Changes from baseline to 4 years of follow-up in (A) New York Heart Association (NYHA) functional classes, (B) distribution of patients in each of the four NYHA classes, (C) score of the Minnesota Living with Heart Failure Questionnaire, (D) left ventricular ejection fraction (LVEF), and (E) total LVEF increase. $^{*}P < 0.001$ vs. metoprolol, $^{\#}P < 0.001$ vs. high-dose benazepril.

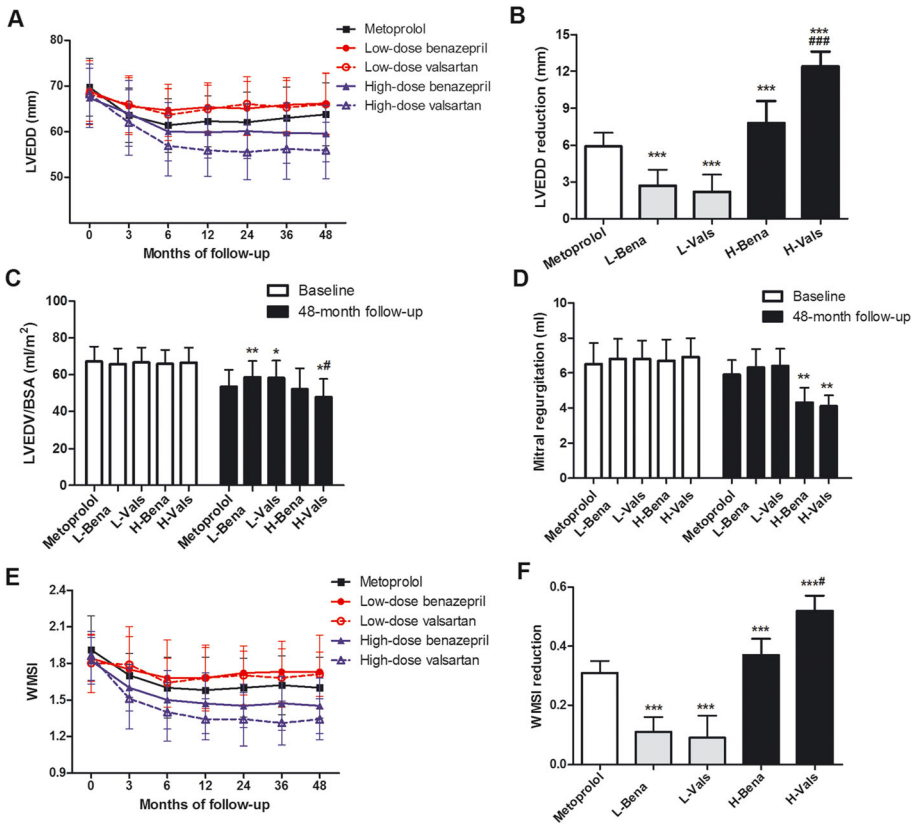


to their respective low doses (2.7 ± 1.3/2.2 ± 1.4 mm, $P < 0.001$) and metoprolol therapy (5.9 ± 1.1 mm, $P < 0.001$) (*Figures 4B* and *5*). LVEDV showed a similar trend during follow-up (*Figure 4C*). Compared with metoprolol, reduction in mitral regurgitation was observed in the high-dose benazepril/valsartan groups but not low-dose groups (*Figure 4D*). The motion of individual LV segments as evaluated by WMSI showed the highest level of WMSI reduction in high-dose groups during follow-up (*Figure 4E* and *F*).

Safety

Patients receiving metoprolol experienced increased frequencies of weakness, fatigue, and worsening heart failure during the dose-adjustment phase but usually responded favourably to prolongation of the dosing interval or addition of diuretics (*Table 3*). There was dose-related increase in rate of cough in patients receiving benazepril, and cough largely appeared after the rapid up-titration period. In high-dose groups, hypotension occurred in 25 patients treated with benazepril and in 29 patients with valsartan. Of these patients, 42 were successfully treated with intravenous dopamine, oral Chinese herb medications with a pressor effect, and/or adjustment of titration doses; only nine patients withdrew from the study because of continued hypotension. By the end of the study, high-dose benazepril/valsartan was associated with 15 ± 9 mmHg decline of SBP and 11 ± 7 mmHg decline of diastolic blood pressure (DBP). Elevation in serum creatinine was also prominent in both high-dose groups, and the use of α-ketoacid, diuretics, and dopamine was effective in the majority of patients presented with varied degrees of renal

Figure 4 Left ventricular remoulding evaluated by echocardiography. Changes from baseline to 4 years of follow-up in (A) left ventricular end-diastolic diameter (LVEDD), (B) total LVEDD reduction, (C) left ventricular end-diastolic volume (LVEDV)/body surface area (BSA), (D) peak instantaneous volume of mitral regurgitation, (E) wall motion score index (WMSI), and (F) total WMSI reduction. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. metoprolol, $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$ vs. high-dose benazepril.



impairment. Although 21 patients presented bilirubin increase and 10 patients with aminotransferase elevation, 25 of them completed the entire study after titration adjustment or treatment with polyene phosphatidylcholine.

Discussion

This is the first study to demonstrate that use of supramaximal dose of an ACEI/ARB is effective and well tolerated in patients with IDCM and modest-severe HF. The superior outcomes associated with high-dose benazepril/valsartan, vs. their low-dose regimens, suggest that the recommended dosages of ACEI/ARB in current practice might be inadequate to halt maladaptive remodelling and HF progression, and titrating ACEI/ARB beyond approved doses is critical to maximize the cardioprotective effects of RAAS inhibition in IDCM patients with HF. Additionally, valsartan compared favourably with metoprolols both at maximally titrated doses, highlighting the advantage of aggressive RAAS inhibition over β-adrenergic blockage in modest-severe HF. Lastly, our study identified valsartan as a preferred option over benazepril at supramaximal doses, which added to our understanding of the ARBs usage, which is commonly prescribed when ACEI intolerance occurs and assumed to be equivalent to ACEIs.

Evidence from pioneer studies in 1970s showed that long-term therapy with β-blockers, including metoprolol, improved hemodynamics and survival in patients with CHF.[12] Although recent large clinical trials have documented decreases in mortality and clinical deterioration in response to several different β-blockers, few evidence addressed the long-term efficacy of metoprolol at maximally tolerated doses in HF secondary to IDCM, as well as its comparative data with ACEI/ARB therapy.[13–15] Data from the present study indicated that metoprolol at optimized doses exhibited no significant difference from conventional low-dose benazepril/valsartan in primary endpoint over 4-year follow-up, although it appeared to be more potent in reversing adverse remodelling. However, metoprolol is remarkably inferior to benazepril/valsartan both at maximal doses, indicating less protection afforded by aggressive blockade of β-adrenergic vs. RAAS system, hence the predominant role of

Figure 5 Significant improvement in left ventricular function and remodelling in a representative patient with idiopathic dilated cardiomyopathy and heart failure under high-dose valsartan treatment. Left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) were evaluated via apical four chamber view and M-mode estimation of left ventricular wall motion was recorded from 1 month to 3 years of follow-up.

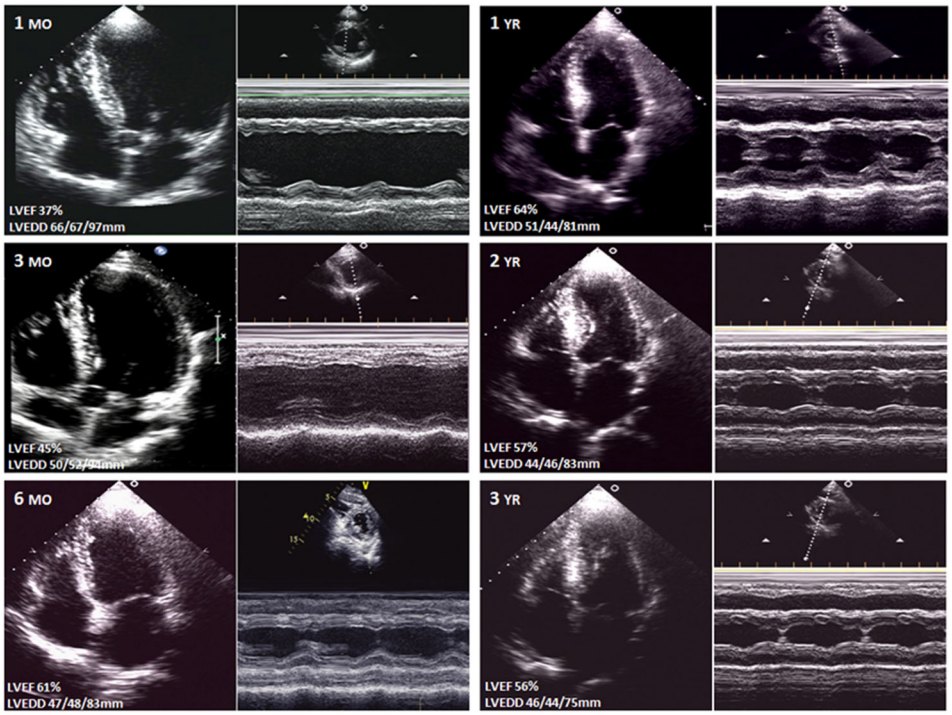


Table 3 Adverse events after randomization

	Adverse events					Adverse events with discontinuation				
		Low-dose		High-dose			Low-dose		High-dose	
	Metoprolol ($n = 96$)	Benazepril ($n = 97$)	Valsartan ($n = 100$)	Benazepril ($n = 101$)	Valsartan ($n = 97$)	Metoprolol ($n = 96$)	Benazepril ($n = 97$)	Valsartan ($n = 100$)	Benazepril ($n = 101$)	Valsartan ($n = 97$)
Hypotension	19	2	4	25	29	2	1	1	4	5
Renal impairment	5	2	3	21	13	1	0	1	5	3
Dry cough	0	14	0	22	0	0	10	0	19	0
Liver dysfunction	10	2	2	6	11	2	0	1	0	3
Hyperkalaemia	1	1	0	4	5	0	0	0	1	1
Non-fatal stroke	1	0	1	1	0	1	0	1	0	0
Angioedema	0	1	0	0	0	0	1	0	0	0

RAAS activation in HF progression. In addition, worsening heart failure was frequently seen either upon initiation or during the up-titration period of metoprolol treatment; thus, a small starting dose and slow titration procedure are required to avoid abrupt withdrawal of the homeostatic support provided by the sympathetic nervous system.

Chronic therapy with ACEI/ARB has been demonstrated to enhance cardiac function, reduce hospitalization, and increase survival in CHF.[16–19] However, a large percentage of patients with IDCM still progress to end-stage HF despite the use of an ACEI/ARB. It is proposed that one possible reason is that the currently approved doses of ACEI/ARB are unable to block tissue-based RAAS which is activated in HF and participates in myocardial hypertrophy, fibrosis, cytokine activation, and ultimately remodelling.[2] No data are available so far regarding the relative risk–benefit profile of higher doses of ACEI/ARB in a patient population of IDCM. In this study, when the dose of valsartan was extended beyond the maximally approved 320 mg/day, there were remarkable reductions, compared with both 160 mg/day valsartan and optimized doses of metoprolol, in primary composite endpoint and LV dilation, and greater improvement in cardiac function and life quality. High-dose benazepril, compared with metoprolol, exhibited a trend towards further reduction in death and HF

reoccurrence when the dropout patients were excluded, although the current study is not adequately powered to evaluate this efficacy according to the intention-to-treat principle, likely attributive to high frequency of dry cough associated early discontinuation. Additional data also revealed reduced efficacy of benazepril in reversing contractile dysfunction and adverse remodelling, suggesting that valsartan is preferred vs. benazepril when supramaximal doses are used in the treatment of IDCM with modest-severe HF. However, this notion warrants further cost-effectiveness analysis, and the question why valsartan was superior to benazepril at high doses remains to be evaluated. Factors such as increased tissue penetration due to lipophicidity[20] and prevention of the 'ACE escape' phenomenon via blockage at angiotensin II receptor level may be included in consideration.[21]

Underdosing of ACEI/ARB in CHF continued to be common in clinical practice.[22] Reasons that preclude the use of higher doses of ACEI/ARB in IDCM patients with CHF may include low pre-treatment blood pressure or pre-existing renal insufficiency, side effects including hypotension, renal dysfunction, and hyperkalaemia, and clinical manifestations considered not severe enough for higher dose regimen. In addition, published guidelines recommend 1–2 weeks intervals during up-titration of ACEI/ARB, which contributes to increased length of hospital stay, underdosing at discharge, and increased outpatient visits for titration.[23] Our study indicated that dosages of benazepril and valsartan at 40–80 mg and 320–640 mg daily were well tolerated, and rapid titration to target doses within 7 days was feasible and safe under in-hospital supervision and with proper management. Bedtime administration was recommended to prevent hypotension-related symptoms. It is noteworthy that Chinese herbal medicine, with scutellarin and ginsenoside as the main active ingredients, helped to treat high dose-associated hypotension in this study. Hyperkalemia, a potential concern for supramaximal doses of ACEI/ARB treatment, was unexpectedly unusual, probably due to the fact that the study population was essentially free of significant renal impairment, and thiazide adding to the ACEI/ARB regimen helped in the prevention of hyperkalaemia. The safety data from the present study were in line with previous trials, wherein titration of valsartan up to 640 mg/day in patients with type 2 diabetes and hypertension, or candesartan up to 128 mg/day in patients with persistent proteinuria were safe and well tolerated.[24,25]

Limitations

Our study was limited by the lack of blinding both the participants and investigators, which may allow non-specific drug effects and biased supplemental treatment to be expressed as a fraction of the overall clinical benefits. Also, our experience from a single tertiary care facility may differ from other sites in patterns of care and disease. Our results that optimized dosages of β-blockers was inferior to supramaximal titration of valsartan should be limited to metoprolol and cannot be extrapolated to other β_1-blocking agents with varying degrees of β_2-blockade, β_1-agonist, and α_1-antagonist properties. In addition, the mechanisms underlying the extra clinical benefits from supramaximal titrated ACEI/ARB need to be addressed by a larger, multicenter study designed to explore the cardiovascular RAAS response to long-term supramaximal blockade of RAAS, as well as the dose–response relationship with efficacy–safety score in patients with IDCM.

Conclusions

Supramaximal doses of an ACEI/ARB are well tolerated and superior to low doses as well as the conventional maximal titrated metoprolol as a strategy for reducing mortality and HF reoccurrence, and reversing adverse remodelling in a patient population with IDCM and modest-severe HF.

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Conflict of interest

All authors declare that they have no conflict of interest.

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