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HYPERTENSION

Differential Effects of Antihypertensive Treatment on Left Ventricular Diastolic Function

An ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Substudy

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Objectives We hypothesized that an amlodipine-based regimen would have more favorable effects on left ventricular (LV) diastolic function.

Background Different antihypertensive therapies may vary in their effect on LV diastolic function.

Methods The HACVD (Hypertension Associated Cardiovascular Disease) substudy of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) collected detailed cardiovascular phenotypic data on a subset of 1,006 participants recruited from 2 centers (St. Mary's Hospital, London, and Beaumont Hospital, Dublin). Conventional and tissue Doppler echocardiography and measurement of plasma B-type natriuretic peptide (BNP) were performed approximately 1 year after randomization to atenolol-based or amlodipine-based antihypertensive treatment to assess LV diastolic function.

Results On-treatment blood pressure (BP) (mean ± SD) was similar in both groups: atenolol-based regimen, systolic BP of 137 ± 17 mm Hg, diastolic BP of 82 ± 9 mm Hg; amlodipine-based regimen, systolic BP of 136 ± 15 mm Hg, diastolic BP of 80 ± 9 mm Hg. Ejection fraction did not differ between groups, but early diastolic mitral annular velocity (E′), a measure of diastolic relaxation, was lower in patients on the atenolol-based regimen: atenolol-based regimen, 7.9 ± 1.8; amlodipine-based regimen, 8.8 ± 2.0. A measure of left ventricular filling pressure, E/E′, and BNP were significantly higher in patients on the atenolol-based regimen. Differences in E′, E/E′, and BNP remained significant after adjustment for age and sex. Further adjustment for systolic BP, LV mass index, and heart rate had no impact on differences in mean E′ or BNP. The difference in E/E′ was attenuated.

Conclusions Patients receiving treatment with an amlodipine-based regimen had better diastolic function than patients treated with the atenolol-based regimen. Treatment-related differences in diastolic function were independent of BP reduction and other factors that are known to affect diastolic function. (J Am Coll Cardiol 2010;55: 1875–81) © 2010 by the American College of Cardiology Foundation

Heart failure is a common consequence of hypertension (1), and in many patients is related to impaired left ventricular (LV) systolic function. However, heart failure is also commonly associated with diastolic dysfunction and apparently preserved systolic function. This accounts for approximately one-third to one-half of heart failure cases (2,3), and most of these patients have a history of hypertension (1), often with LV hypertrophy and remodeling (4–8).

While many studies have focused on the effectiveness of hypertension treatment in reducing cardiac hypertrophy, less is known about the impact of treatment on LV diastolic function (8,9). Previous studies addressing the impact of different antihypertensive agents on LV diastolic function have largely used conventional echocardiography assessing transmitral filling and isovolumic relaxation. These conventional assessments have limitations as measures of LV diastolic function are load dependent, which makes it

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide

BP = blood pressure

E′ = early diastolic mitral annular velocity

E/A ratio = early transmitral peak velocity

E/E′ = transmitral E-wave/E-wave velocity ratio

LV = left ventricular

LVMI = left ventricular mass index

SBP = systolic blood pressure

TDE = tissue Doppler echocardiography

difficult to separate alterations in loading conditions from intrinsic changes in LV diastolic function due to treatment. Second, the conventional parameters can undergo "pseudonormalization," where the ratio of the early to atrial transmitral peak velocity (E/A ratio) paradoxically increases with progressive diastolic impairment. Tissue Doppler echocardiography (TDE) offers improved assessment of diastolic function (10). TDE measurements of myocardial velocities are significantly less load dependent than conventional echocardiographic measurements; these measurements do not show pseudonormalization and independently predict cardiovascular events and mortality (11–13). Few studies to date have used TDE to assess diastolic function in relation to the effects of different antihypertensive agents.

The ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study was a large multicenter randomized clinical trial that compared the effects of a beta-blocker plus diuretic (atenolol and bendroflumethiazide-K) regimen with a calcium-antagonist plus angiotensin-converting enzyme (amlodipine and perindopril) regimen on nonfatal myocardial infarction and fatal coronary heart disease (14). The study showed the amlodipine-based regimen was superior to the atenolol-based regimen on all major cardiovascular end points and all-cause mortality. As part of this ASCOT substudy, extensive data on LV diastolic function were collected using both conventional echocardiography and TDE. This provides the ideal setting to determine the impact of different antihypertension treatment regimens on LV diastolic function. We hypothesized that the amlodipine-based regimen would have more favorable effects on LV diastolic function in this large group of well-controlled hypertensive subjects.

Methods

Patients. The population, methods, and response rate for the ASCOT study are described in detail elsewhere (15). In brief, the ASCOT study was a clinical trial of blood pressure (BP)-lowering regimens in 19,342 men and women, age 40 to 79 years, with hypertension. Patients eligible for inclusion had hypertension and ≥3 pre-specified cardiovascular risk factors. Risk factors included male sex, current smoking, age ≥55 years, microalbuminuria/proteinuria, type 2 diabetes mellitus, left ventricular hypertrophy (LVH), electrocardiographic abnormalities, a history of early coronary heart disease in a first-degree relative, ratio of plasma total cholesterol to high-density lipoprotein cholesterol of ≥6, peripheral vascular disease, and a history of cerebrovascular events. All participants were randomly assigned to either atenolol ± bendroflumethiazide-K (atenolol-based regimen) or amlodipine ± perindopril (amlodipine-based regimen). In addition, patients with a nonfasting cholesterol level of ≤6.5 mmol/l not already receiving lipid-lowering therapy were randomly assigned to either atorvastatin 10 mg or placebo. Participants had no history of heart failure, myocardial infarction, angina, uncontrolled arrhythmias, or cerebrovascular event within the past 3 months. They did not have fasting triglycerides >4.5 mmol/l or any important hematological or biochemical abnormality on routine screening.

Detailed cardiovascular phenotypic data were collected in the HACVD (Hypertension-Associated Cardiovascular Disease) substudy after approximately 1 year of treatment from a subset of 1,006 participants recruited from 2 centers (St. Mary's Hospital, London, and the Adapt Center, Beaumont Hospital, Dublin). Echocardiography was performed using an ATL HDI 5000 ultrasound machine equipped with a standard multifrequency transducer 12 months after initiation of treatment. All scans were performed by 3 experienced echocardiographers with the patient semirecumbent in the left lateral position. Interobserver reproducibility data were acquired and showed variations for all echocardiographic parameters between 3.5% and 7.5%. This is within acceptable limits as per previous studies (16). The LV measurements were performed using M-mode from the parasternal long-axis view according to the American Society of Echocardiography conventions (17), and LV mass was calculated according to the formula:

$$\text{LV mass} = 0.8\,[(\text{IVSd} + \text{LVIDd} + \text{PWTd})^3 - (\text{LVIDd})^3] + 0.6\ \text{g}$$

where IVSd = intraventricular septal thickness in diastole, LVIDd = left ventricular diameter in diastole, and PWTd = posterior wall thickness in diastole. This was then indexed for body surface area to give the left ventricular mass index (LVMI). Ejection fraction was calculated using the Teicholz formula from the parasternal long-axis view using M-mode, or if not technically possible, Simpson's rule was used.

Transmitral Doppler was assessed using a 5-mm sample volume placed at the tips of the mitral leaflets in passive end-expiration. A standardized loop of 10 cardiac cycles was downloaded to computer for off-line analysis of the early filling phase (E-wave) and the late filling phase (A-wave). The TDE was performed in the apical 4-, 2-, and 3-chamber views, with the 5-mm sample volume placed over the myocardium on the septal, lateral, and inferior walls at the level of the mitral annulus and the free wall of the right ventricle at the level of the tricuspid annulus. Using minimal gain settings, a series of 10 cardiac cycles were

recorded. These were then downloaded for off-line analysis, with measurements made of systolic velocity (S′-wave), early diastolic velocity (E′-wave), and late diastolic velocity (A′-wave) at each location, and these were averaged. Analysis was performed using the HDI Laboratory software (Philips, Surrey, United Kingdom) by a single researcher who was blinded to all patient details. Each value represents the mean of 3 measurements taken from 3 consecutive representative cardiac cycles.

Blood pressure was measured after resting in a seated position for 5 min, using an Omron HEM 705-CP semiautomatic oscillometric recorder (Philips). Height and weight were measured in light clothing by a trained observer. Body mass index was calculated as weight (kg)/height (m^2). Information on history of diabetes was obtained by interview. Plasma glucose and serum total cholesterol were measured using standard enzymatic methods on a Roche/Hitachi 921 (Roche Diagnostics, Basel, Switzerland) automated analyzer.

B-type natriuretic peptide (BNP) was analyzed with the Bayer BNP assay (Bayer Diagnostics, Newbury, Great Britain) with standard quality control methods. Results quoted are in pg/ml. The ADVIA Centaur BNP assay (Bayer Diagnostics) is a fully automated 2-site sandwich immunoassay using 2 monoclonal antibodies, which measures only the physiologically active BNP (77-108) molecule. The assay has been well validated (18).

The study conformed to good clinical practice guidelines and was approved by the respective local hospital ethics committees (St. Mary's Hospital, London, and Beaumont Hospital, Dublin). Written informed consent for the study was obtained from all participants.

Statistical methods. Data analysis was performed with SPSS version 15.0.0 for Windows (SPSS Inc., Chicago, Illinois). Descriptive information for each of the variables was obtained and distributions assessed. The BNP and triglycerides values were skewed and were therefore log-transformed to permit subsequent parametric analysis. Data are presented as mean (SD), or median (interquartile range) for skewed data), and percentages. Statistical comparisons were made using a Student *t* test (or a Mann-Whitney *U* test as appropriate) for metric variables and a chi-square test for categorical variables. Multivariate analysis of variance was also used to assess the difference between treatments with covariate adjustment; because BNP data were skewed, they were log-transformed before multivariate analysis to permit subsequent parametric analysis. Geometric mean ± standard error are quoted for BNP. All p values <0.05 were considered statistically significant.

Results

Baseline demographic and clinical characteristics of the 2 treatment groups were similar (Table 1). After 12 months of treatment, systolic BP was reduced to a similar extent by both treatment regimens (Table 2), but, predictably, heart rate was significantly lower in the atenolol-based regimen. Ejection fraction did not differ between groups. The LVMI tended to be lower in patients treated with the amlodipine-based regimen, although this did not achieve statistical significance ($p = 0.089$). Treatment with the amlodipine-based regimen was associated with higher early diastolic mitral annular velocity (E′), lower plasma BNP, lower E/E′, a smaller atrial diameter, and a shorter E-wave deceleration time, whereas E/A ratio was higher in people randomly assigned to the atenolol-based regimen (Table 2).

After adjustment for age and sex, E′ remained significantly lower in patients treated with the atenolol-based regimen compared to patients randomly allocated to the amlodipine-based regimen ($p < 0.001$ adjusted for age and sex) (Table 3), and the intergroup difference remained

Table 1 Characteristics of the Population at Baseline

	Atenolol-Based Regimen (n = 411)	Amlodipine-Based Regimen (n = 413)	p Value
Eligibility risk factors			
Age ≥55 yrs	349 (85)	349 (85)	0.870
Male	332 (81)	325 (79)	0.456
Peripheral arterial disease	25 (6)	25 (6)	0.986
Prior known ECG or echocardiogram LVH	16 (4)	13 (3)	0.557
Diabetes mellitus	82 (20)	90 (22)	0.516
Smoker	85 (21)	99 (24)	0.257
Baseline characteristics			
Age, yrs	62.1 ± 7.9	62.4 ± 7.8	0.542
Systolic blood pressure, mm Hg	159.9 ± 17.5	159.9 ± 18.7	0.965
Diastolic blood pressure, mm Hg	92.9 ± 9.7	92.3 ± 9.6	0.349
Heart rate, beats/min	71.1 ± 12.0	70.9 ± 12.5	0.766
Body surface area, m^2	2.0 ± 0.2	1.9 ± 0.2	0.720
BMI, kg/m^2	28.2 ± 4.5	28.8 ± 4.6	0.971
Total cholesterol, mmol/l	5.8 ± 1.0	5.8 ± 1.0	0.932
Triglycerides, mmol/l*	1.6 (1.1–2.1)	1.5 (1.1–2.1)	0.714

Values are n (%) or mean ± SD. *Data are median and interquartile range.
BMI = body mass index; ECG = electrocardiogram; LVH = left ventricular hypertrophy.

Table 2 Characteristics of the Population at Year 1

	Atenolol-Based Regimen (n = 411)	Amlodipine-Based Regimen (n = 413)	p Value
Blood pressure and heart rate			
Systolic blood pressure, mm Hg	137.8 ± 17.4	136.2 ± 14.6	0.167
Diastolic blood pressure, mm Hg	81.6 ± 9.3	80.1 ± 8.6	0.012
Heart rate, beats/min	57.8 ± 10.0	72.8 ± 11.4	<0.001
2nd-line antihypertensive, %	40	43	0.386
Cardiac structural and functional measures			
LV structural measures			
Interventricular septum, diastole, cm	1.27 ± 0.23	1.26 ± 0.23	0.170
LV internal dimension, diastole, cm	4.92 ± 0.55	4.84 ± 0.60	0.046
Posterior wall thickness, diastole, cm	1.17 ± 0.18	1.18 ± 0.18	0.761
Interventricular septum, systole, cm	1.65 ± 0.25	1.63 ± 0.27	0.352
LV internal dimension, systole, cm	3.27 ± 0.55	3.22 ± 0.56	0.180
Posterior wall thickness, systole, cm	1.58 ± 0.25	1.59 ± 0.23	0.510
LV ejection fraction, %	69.48 ± 11.32	69.21 ± 12.19	0.759
LVMI, g/m^2	122.66 ± 30.92	118.80 ± 31.56	0.089
Relative wall thickness	0.51 ± 0.10	0.51 ± 0.10	0.412
Left atrial size, cm*	4.25 ± 0.59	4.14 ± 0.64	0.022
Transmitral Doppler			
E wave, cm/s	60.08 ± 14.87	63.41 ± 15.01	0.001
A wave, cm/s	68.25 ± 14.63	75.08 ± 15.76	<0.001
E/A ratio	0.91 ± 0.29	0.86 ± 0.22	0.004
E-wave deceleration time, ms	0.20 ± 0.05	0.18 ± 0.05	<0.001
Tissue Doppler			
Systolic velocity (S′), cm/s	8.2 ± 1.75	9.5 ± 2.21	<0.001
Early diastolic velocity (E′), cm/s	7.91 ± 1.84	8.76 ± 2.04	<0.001
Late diastolic velocity (A′), cm/s	10.76 ± 2.15	12.34 ± 2.31	<0.001
Mean E/E′ ratio	8.14 ± 2.38	7.76 ± 2.05	0.013
BNP, pg/ml†	37 (20–56)	19 (10–34)	<0.001

Values are mean ± SD unless otherwise indicated. *Data available for only 661 patients for left atrial size. †Data are median and interquartile range.
BNP = B-type natriuretic peptide; LV = left ventricular; LVMI = left ventricular mass index.

highly significant ($p < 0.001$) after further adjustment for systolic BP and LVMI. Further adjustment for heart rate, a factor directly related to hypertension treatment, had no impact on difference in E′ ($p < 0.001$). Differences in E/E′ and E/A ratio remained significant after adjustment for age, sex, systolic BP, and LVMI (Table 3). Further adjustment for heart rate attenuated the difference in E/E′ and E/A between the treatment regimens ($p = 0.703$ and $p = 0.139$, respectively). Similar associations were observed for BNP comparing the treatment regimens (Table 3). No significant differences in LVMI between treatment groups were observed in unadjusted or adjusted data (Table 3).

Discussion

This is one of the first large randomized clinical trials to compare the effect of antihypertensive medications on LV diastolic function assessed using TDE. In the present study, after approximately 12 months of intensive therapy, patients treated with the amlodipine-based regimen had evidence of better LV diastolic function compared with patients treated with the atenolol-based regimen (i.e., higher E′, lower plasma BNP, lower E/E′, smaller atrial diameter, and shorter E-wave deceleration time). These effects were independent of other factors associated with diastolic dysfunction including the BP-lowering effect of the drug and LVMI. Differences in E/E′ between the 2 treatment regimens could be accounted for by differences in heart rate, but this did not explain the differences in E′ or BNP. The difference in E/A ratio, a widely used indicator of diastolic function, was discordant with other more sensitive measures of diastolic function, in that unadjusted E/A was higher in the atenolol-based regimen. This difference was also accounted for by differences in heart rate. A previous study also observed an improvement in the E/A ratio after 48 weeks of treatment with atenolol, which was highly correlated with the reduction in heart rate (8). We, therefore, suggest that E/A ratio is not a particularly useful indicator of diastolic function when heart rate differs between treatments. Differences in diastolic function seen in this study could be a consequence of differences in mechanisms of action of the drugs: amlodipine, perindopril, and bendroflumethiazide reduce blood pressure principally by reducing peripheral resistance, whereas atenolol has negative cardiac inotropic and chronotropic effects (19).

Table 3 Multivariate Analysis, Echocardiographic Measures by Treatment Group

	Atenolol-Based Regimen	Amlodipine-Based Regimen	p Value
Left ventricular mass index			
Model 1 adjusted for age and sex	121.02 ± 1.81	117.25 ± 1.80	0.096
Model 2 adjusted for model 1 and SBP	119.92 ± 1.78	116.77 ± 1.80	0.155
Model 3 adjusted for model 1, SBP, HR	118.26 ± 1.92	118.67 ± 1.94	0.879
E/A ratio			
Model 1 adjusted for age and sex	0.90 ± 0.02	0.85 ± 0.02	0.007
Model 2 adjusted for model 1 and LVMI	0.90 ± 0.02	0.85 ± 0.02	0.004
Model 3 adjusted for model 1 and SBP	0.91 ± 0.02	0.85 ± 0.02	0.004
Model 4 adjusted for model 1, LVMI, SBP, HR	0.87 ± 0.02	0.90 ± 0.02	0.139
Mean early diastolic velocity (E′) cm/s			
Model 1 adjusted for age and sex	7.76 ± 0.11	8.59 ± 0.10	<0.001
Model 2 adjusted for model 1 and LVMI	7.78 ± 0.11	8.54 ± 0.11	<0.001
Model 3 adjusted for model 1 and SBP	7.80 ± 0.11	8.62 ± 0.11	<0.001
Model 4 adjusted for model 1, LVMI, SBP, HR	7.72 ± 0.12	8.64 ± 0.12	<0.001
Mean E/E′ ratio			
Model 1 adjusted for age and sex	8.32 ± 0.13	8.00 ± 0.13	0.043
Model 2 adjusted for model 1 and LVMI	8.32 ± 0.13	8.03 ± 0.13	0.060
Model 3 adjusted for model 1 and SBP	8.31 ± 0.13	8.00 ± 0.13	0.031
Model 4 adjusted for model 1, LVMI, SBP, HR	8.20 ± 0.14	8.12 ± 0.14	0.703
BNP pg/ml			
Model 1 adjusted for age and sex	35.80 ± 1.05	19.26 ± 1.05	<0.001
Model 2 adjusted for model 1 and LVMI	35.69 ± 1.05	19.57 ± 1.05	<0.001
Model 3 adjusted for model 1 and SBP	35.87 ± 1.05	19.36 ± 1.05	<0.001
Model 4 adjusted for model 1, LVMI, SBP, HR	32.52 ± 1.05	22.02 ± 1.05	<0.001

All values are mean ± standard error; BNP data were log transformed for use in multivariate analysis of variance.
HR = heart rate; SBP = systolic blood pressure; other abbreviations as in Table 2.

Among patients 65 years of age and more with evidence of diastolic dysfunction, approximately 15% will have heart failure within 5 years (20). Effective treatment could potentially delay or reduce the number of people having LV diastolic dysfunction and later progression to heart failure. Previous research has suggested that antihypertensive medications vary in their ability to maintain or improve LV diastolic function and filling pressure (8,21,22). In particular, many studies have focused on effectiveness of hypertension treatments on LV mass; however, because of serious limitations of the study designs and methodologies, conclusions from these studies have been viewed with great caution (23). In general, studies have used small samples sizes (8,21,24–26) and have been underpowered to detect a difference between therapies. The majority of study durations have ranged from just a few weeks to 6 months (21,25,26), and very few studies have extended to a year of follow-up (8,24,27). Moreover, conventional echocardiography alone, which has been used in the majority of published studies, has limitations as a means of assessing LV diastolic function (28,29).

As far as we are aware, no previous large randomized clinical trials have evaluated the effect of antihypertensive treatment on LV diastolic function using TDE. Two small studies that have used TDE to compare the effectiveness of antihypertensive treatments on LV diastolic function have yielded conflicting results (8,30). In a recent study of 134 subjects, irbesartan, an angiotensin AT_1-receptor blocker, produced greater improvement in E/E′ compared with atenolol among subjects with and without hypertensive LV hypertrophy (8). In contrast, in a study of 186 subjects with evidence of diastolic dysfunction, valsartan, an AT_1-receptor blocker, was shown to be no more effective than standard treatment in improving LV diastolic function over 38 weeks (30). Our findings, based on a large number of participants, demonstrate clear benefits in terms of diastolic function in those randomized to the amlodipine-based regimen compared with those randomized to the atenolol-based regimen. This finding is of interest since TDE measures of diastolic function have been reported to predict cardiovascular events and mortality (11,12). Similarly, although the BNP values were largely within the normal range, data from the Framingham study indicate a significantly increased cardiovascular event rate is associated with small increases in BNP levels, even at levels thought to be within the normal range (31).

Study limitations. The majority of participants were male, elderly, and of white European ethnicity, and so our observations may not necessarily be extrapolated to other hypertensive patients. Additionally, patients were required to have at least 3 other cardiovascular disease risk factors; however, these included age ≥55 years and male sex. Overall in the ASCOT study, the total primary event rate (i.e., nonfatal myocardial infarction, including silent, plus fatal coronary heart disease) was 8.5 per 1,000 patient years (14), so the participants should not be regarded as a

particularly high risk group. Measures of LV diastolic function were not recorded at baseline, and therefore we cannot comment on how treatment changed diastolic function from the pre-treatment state. However, this limitation does not extend to the comparison of treatment regimens, because randomization is likely to balance time effects of unmeasured covariates (32). Finally, approximately 40% of participants in both treatment groups received 2 antihypertensive agent as part of the treatment regimen, so differences cannot be attributed to any individual drug in each regimen.

Conclusions

This prospective randomized study in hypertensive patients showed that those receiving treatment with the amlodipine-based regimen have better diastolic function than those treated with the atenolol-based regimen. Treatment-related differences in diastolic function were independent of BP reduction and other factors that are known to affect diastolic function.

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