Effect of Intensive Versus Standard Blood Pressure Lowering on Diastolic Function in Patients With Uncontrolled Hypertension and Diastolic Dysfunction

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Abstract—Diastolic dysfunction may precede development of heart failure in hypertensive patients. We randomized 228 patients with uncontrolled hypertension, preserved ejection fraction, and diastolic dysfunction to 2 targeted treatment strategies: intensive, with a systolic blood pressure target of <130 mm Hg, or standard, with a systolic blood pressure target of <140 mm Hg, using a combination of valsartan, either 160 or 320 mg, plus amlodipine, either 5 or 10 mg, with other antihypertensive medications as needed. Echocardiographic assessment of diastolic function was performed at baseline and after 24 weeks in a prospective, open-label, blinded end point design. Blood pressure was reduced significantly in both groups, from 161.2±13.9/90.1±12.0 to 130.8±12.3/74.9±9.1 mm Hg (P<0.0001) in the intensive arm and from 162.1±13.2/93.7±12.2 to 137.0±12.9/79.6±11.0 mm Hg (P<0.0001) in the standard arm (P<0.003 for between-group comparisons). Myocardial relaxation velocity improved from 7.6±1.1 to 9.2±1.7 cm/s (Δ 1.54±1.4 cm/s; P<0.0001) in the intensive arm and from 7.5±1.3 to 9.0±1.9 cm/s (Δ 1.48±1.6 cm/s; P<0.0001) in the standard arm, with no difference between the 2 strategies in the achieved improvement (P=0.58). The degree of improvement in annular relaxation velocity was associated with the extent of systolic blood pressure reduction, and patients with the lowest achieved systolic blood pressure had the highest final diastolic relaxation velocities. *(Hypertension. 2010;55:241-248.)*

Key Words: hypertension ▪ diastolic dysfunction ▪ echocardiography ▪ arterial stiffness ▪ angiotensin receptor blocker

Many of the adverse sequelae of hypertension are the direct result of target-organ damage to the vasculature, the kidneys, and the heart. In the heart, long-standing hypertension serves as a stimulus for progressive fibrosis, ventricular hypertrophy,1–3 and diastolic dysfunction, which may be one of the earliest manifestations of cardiac target-organ damage.4 These changes may be accelerated by age and hypertension-related changes in central aortic stiffness, which may contribute to abnormal pulse wave reflection and enhanced pulsatile arterial load. Present in ≈50% of hypertensive patients, diastolic dysfunction likely represents an important intermediate in the development of heart failure, particularly in patients with preserved systolic function.5,6

We have demonstrated previously that blood pressure lowering in patients with stage 1 hypertension is associated with improvement in diastolic function, whether a renin-angiotensin-aldersterone system inhibitor or non–renin-angiotensin-aldersterone system blood pressure lowering was used.7 Because the degree of improvement in diastolic function appears to be closely tied to the degree of blood pressure lowering, we hypothesized that a strategy of aggressive blood pressure control (beyond the established Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure targets) would be more effective than a less intensive strategy in attenuating cardiac dysfunction. More aggressive targets have already been recommended in certain subgroups of patients, including those with diabetes mellitus, chronic kidney disease, and coronary artery disease.8 The Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction (EXCEED) Trial was designed to prospectively test the hypothesis that, among patients with uncontrolled hypertension, preserved ejection fraction, and diastolic dysfunction, lowering blood pressure to <130 mm Hg effectively improves diastolic function.
hypertension and diastolic dysfunction, blood pressure control with an angiotensin receptor blocker/calcium channel blocker drug combination targeted to an intensive goal of systolic blood pressure (SBP; <130 mm Hg) would be more effective in improving diastolic function than the same treatment targeted to a standard goal of <140 mm Hg.

Methods

Study Design and Subjects

Men and women ≥45 years of age with a history of uncontrolled systolic hypertension (mean of 3 sitting blood pressure measurements with SBP ≥150 mm Hg and ≤200 mm Hg) on no treatment or a maximum of 2 antihypertensive medications at randomization were screened for inclusion by assessing systolic and diastolic function by echocardiography. Subjects were eligible for inclusion if they were determined to have left ventricular (LV) ejection fraction ≥50% and echocardiographic evidence of diastolic dysfunction, as confirmed by a core laboratory. Exclusion criteria included severe hypertension, defined as SBP >200 mm Hg or diastolic BP >120 mm Hg; known secondary hypertension; history of stroke, transient ischemic attack, myocardial infarction, coronary artery bypass surgery, or unstable angina within 6 months of screening; history of heart failure or diabetes mellitus; renal impairment with serum creatinine >2.0 mg/dL; intolerance or contraindication to angiotensin receptor blocker or calcium channel blocker; and being pregnant or of childbearing age without birth control. Subjects were recruited from 28 centers in the United States and Canada, and the study protocol was approved by individual site and/or central institutional review boards before enrollment of any subjects.10

All of the subjects who fulfilled inclusion and exclusion criteria and signed informed consent underwent echocardiographic screening for systolic and diastolic function (n=444). Diastolic function was assessed by Doppler imaging of lateral mitral annular relaxation velocity (E'). For the purposes of study entry, diastolic dysfunction was defined as E’<10 cm/s for subjects between age 45 and 55 years, <9 cm/s for subjects between age 55 and 65 years, and <8 cm/s for subjects >65 years of age.2,11 We excluded 215 subjects during screening. One subject was randomized in error and never received study drug and was, therefore, excluded from analyses. Of the 228 subjects enrolled, follow-up data were available in 196 patients (Figure 1). Eligible patients discontinued previous antihypertensive medication and were randomly assigned to 1 of 2 treatment targets: an intensive arm with an SBP target of <130 mm Hg or a standard arm with an SBP target of <140 mm Hg. Randomization was stratified by age group (45 to 54 years, 55 to 65 years, and >65 years). Treatment randomization was assigned by an interactive voice response system. Titration of study medication is illustrated in Figure 2. The dose of study medication could be down-titrated to the previous level in the event of hypotension, dizziness, or intolerance. Patients in the standard treatment arm (SBP target <140 mm Hg) had their study medication up-titrated if their SBP had not reached the target, and, once they reached target SBP, they were maintained on the dose of study drugs at which the target was reached for the study duration. If patients in either group had not reached their respective SBP treatment targets by week 8 or the patient SBP was >140 mm Hg at any study visit thereafter, additional antihypertensive medications were added in the following order: hydrochlorothiazide (HCTZ) 12.5 mg, HCTZ 25.0 mg, HCTZ 25.0 mg+atenolol 50.0 mg, and HCTZ 25.0 mg+atenolol 100.0 mg. Off-protocol use of other antihypertensive agents was not allowed during the study.
EXCEED was a multicenter, prospective, randomized open-label study with blinded outcome evaluation. Study visits were conducted over 24 weeks of follow-up (Figure 2). Subjects underwent radial applanation tonometry (HEM 9000AL, Omron Healthcare Co, Ltd) at every study visit and a complete echocardiographic examination at baseline and end of follow-up. Blood pressure and heart rate were measured at each visit using an automated oscillometric device contained within the tonometry system and recorded as the average of 3 separate seated readings.

**Echocardiographic Analysis**

At visits 1 (baseline) and 9 (24 weeks), patients underwent a standard echocardiographic examination, which included Doppler tissue imaging. All of the sonographers participating in the trial were trained in the technique of Doppler tissue imaging using a combination of in-person training and video-based training material and were required to submit a qualifying study for certification before enrolling patients. Echocardiograms were stripped of identifying personal health information and transferred either digitally or on videotape to the core laboratory for further analysis. The primary echocardiographic efficacy analyses were performed in the core laboratory on an offline analysis workstation by a single experienced investigator blinded to treatment allocation and previous individual patient measures. Each secondary efficacy measure was also performed in the core laboratory. Echocardiographic analyses were performed at baseline and at 24 weeks. Eight patients underwent echocardiographic analyses earlier than 24 weeks and were included in the final results. Sixteen patients in each arm did not have the final echocardiographic assessment for a variety of reasons, including withdrawal because of adverse events, protocol violations, withdrawal of consent, loss to follow-up, or uncontrolled hypertension.

Spectral pulsed-wave Doppler tissue interrogation of longitudinal mitral annular velocities was recorded throughout the cardiac cycle at the lateral annulus in the apical 4-chamber view. Early diastolic myocardial velocity (E') from the lateral mitral annulus was measured using the modal spectral velocity. Additional Doppler echocardiographic assessments included were the peak velocities of the E and A waves on transmitral pulse wave Doppler, mitral (E wave) deceleration time, and isovolumic relaxation time (IVRT). The ratio of mitral inflow velocity:annular relaxation velocity (E/E') was calculated. Left atrial size was assessed by tracing left atrial contours in the apical 4- and 2-chamber views, and volume was calculated using the modified Simpson rule method. LV endocardial borders were manually traced at end diastole and end systole at the mitral and papillary short axis levels and at the apical 4- and 2-chamber views from 3 separate cardiac cycles. LV volumes were derived according to the modified biplane Simpson rule in the apical 4-chamber and 2-chamber views, and ejection fraction was calculated in the standard fashion from LV end diastolic volume and LV end systolic volume.

**Radial Artery Tonometry**

Arterial waveforms were obtained at each visit from the radial artery using a proprietary automated applanation tonometry device that uses a self-centering, multiaxial sensor to obtain semiautomatic radial tonometry measurements and an automated blood pressure cuff for simultaneous brachial blood pressure measurements (HEM9000AI, Omron Healthcare Co, Ltd). All of the tonometry data were stored and uploaded via a file transfer protocol mechanism to a central server and reviewed by a single core laboratory member to ensure adequate waveform quality for analysis. Augmentation index was calculated as the ratio of the second and first radial systolic pressure peaks. Central aortic pressure was estimated post hoc from the height of a second radial systolic pressure peak using a previously validated regression. All of the end point evaluations were assessed in a core laboratory without knowledge of the patient’s treatment assignment. The primary efficacy measure was change in diastolic myocardial relaxation velocity of the lateral mitral annulus (E') from baseline to follow-up (24 weeks). Secondary efficacy measures included differ-
Echocardiographic and vascular measures

- Tissue Doppler E'/E' change from baseline in the ratio of mitral inflow velocity:annular relaxation velocity (E'/E'), change from baseline in radial augmentation index, and estimated central aortic pressure.

- Mean age (SD), y: 60.2 (10.0) vs. 58.9 (9.5)
- Percentage with age ≥65 y, n (%): 28 (24.6) vs. 27 (23.7)
- Women, n (%): 61 (53.5) vs. 54 (47.4)
- Mean SBP (SD), mm Hg: 161.3 (13.6) vs. 162.1 (13.7)
- Mean DBP (SD), mm Hg: 90.9 (12.7) vs. 93.5 (12.7)
- Mean pulse (SD), bpm: 70.8 (11.4) vs. 72.5 (11.2)
- Race/ethnicity, n (%):
  - White: 79 (69.3) vs. 79 (69.3)
  - Black: 28 (24.6) vs. 29 (25.4)
  - Hispanic: 7 (6.1) vs. 3 (2.6)
  - Other: 0 (0) vs. 2 (1.8)
  - Missing: 0 (0) vs. 0 (0)
- BMI, kg/m²: 31.5 (7.2) vs. 31.1 (5.3)
- eGFR, mL/min: 84.0 (20.3) vs. 83.7 (20.0)
- Antihypertensive medication, n (%):
  - Any previous antihypertensive treatment: 80 (70.2) vs. 80 (70.2)
  - ACEi: 32 (28.2) vs. 26 (22.8)
  - ARB: 29 (25.4) vs. 31 (27.2)
  - CCB: 21 (18.4) vs. 28 (24.6)
  - β-Blocker: 17 (14.9) vs. 16 (14.0)
  - Diuretic: 45 (39.5) vs. 39 (34.2)
  - Other: 8 (7.0) vs. 13 (11.4)
  - Treatment naïve: 34 (29.8) vs. 34 (29.8)

**Table 1. Baseline Demographics for Each Treatment Group**

**Table 2. Study and Add-On Medications During the Trial**

**Statistical Analyses**

We calculated that a sample size of ~214 randomized patients would be necessary to detect a 0.75-cm/s difference in the primary end point, E', with 90% power on the basis of SDs of 1.4 cm/s, allowing for a drop out rate of ~30%. Reproducibility of the primary measurement was assessed by repeating this measure in 50 randomly chosen patients. The coefficient of variability of this measure was 4.2%.

Continuous variables were summarized by mean±SD. Between-group comparisons of the primary efficacy variable were performed using ANCOVA, adjusting for baseline assessment of E' and SBP, treatment regimen, and stratum. A similar ANCOVA model was used for the between-group comparisons of secondary variables.

Sensitivity of the primary results was also tested using a nonparametric test (Wilcoxon rank-sum test) for comparing the change in annular velocity (E') between the 2 treatment groups. Differences in baseline characteristics between groups were assessed by independent-sample t tests for continuous variables and χ² statistics or Fisher exact test for categorical variables. The safety and demographic analysis was summarized for both treated patients and patients who had valid postbaseline diastolic dysfunction assessment. In contrast, efficacy analysis was based on patients who had valid postbaseline diastolic dysfunction assessment.

Multiple linear regression analysis using continuous data was used to investigate the linear association between echocardiographic changes in E' and blood pressure obtained at the time of echocardiography, as well as the relationship between final achieved blood pressure and final measures of diastolic function in a prespecified exploratory analysis. Nonparametric tests were used to explore further this association. All of the P values were 2 sided; P<0.05 was used to determine statistical significance. Statistical analyses were performed using Stata software (Stata Corp) and SAS software (SAS Institute Inc).

**Role of the Funding Source**

The EXCEED Study was funded by Novartis Pharmaceuticals. The EXCEED was designed by the academic steering committee in consultation with the sponsor. The sponsor was involved in site management, data collection, site monitoring, data management, and data analysis. At the completion of the study and after unblinding, all of the data and randomization codes were transferred to the academic principal investigator for confirmatory and additional analysis.

**Results**

We screened 444 patients and randomized and treated 228 patients who fulfilled criteria for diastolic dysfunction and all of the other inclusion criteria. Baseline characteristics of enrolled patients are shown in Table 1. The mean age was 59.6±9.7 years, and 24% of patients were >65 years. Approximately 50% of patients were women, 69% were white, and 25% were black. Mean SBP/diastolic blood pressure was 162±14/92±13 mm Hg. Mean body mass index was 31.3±6.3 kg/m², and estimated glomerular filtration rate was 83.9±20.1 mL/min.
per 1.73 m². By design, all of the patients had evidence of diastolic dysfunction, with mean lateral mitral annular relaxation (E') of 7.6±1.2 cm/s. Mean baseline radial augmentation index was 87.3±13.0%, and estimated central aortic systolic pressure was 151.0±16.7 mm Hg. There were no differences in any baseline characteristics between treatment groups in either patients enrolled or in the patients who underwent the final evaluation.

Seventy percent of patients were on antihypertensive medication at baseline. The maximum dose of study medication (valsartan 320 mg/amlodipine 10 mg) was used in 90% of patients in the intensive arm and 63% of patients in the standard arm, with an average maximum dose of valsartan/amlodipine of 305.0/9.7 mg in the intensive arm and 261.0/9.2 mg in the standard arm (Table 2). Protocol-based add-on antihypertensive medications were used in 62% of patients in the intensive arm and 53% of patients in the standard arm.

SBP and diastolic blood pressure decreased significantly from baseline in both treatment groups (P<0.0001; Table 3 and Figure 3), dropping from 161±14/90±12 to 131±12/75±9 mm Hg in the intensive arm and from 162±13/94±12 to 137±13/80±11 mm Hg in the standard arm (P<0.003 for both systolic and diastolic between-group comparisons). Sixty percent of patients in the standard arm and 46% of patients in the intensive arm achieved their respective blood pressure targets by 24 weeks, and 82% of patients in the intensive arm achieved a SBP of <140 mm Hg by 24 weeks.

Ninety-eight patients in each arm had valid postbaseline diastolic dysfunction assessment. Primary and secondary efficacy measures at baseline and follow-up are shown in Table 3. Mitral annular relaxation velocity (E'), the primary efficacy assessment, increased significantly from 7.6±1.1 to 9.2±1.7 cm/s in the intensive arm and from 7.5±1.3 to

Table 3. SBP, Diastolic Blood Pressure, Heart Rate, and Echocardiographic Measures at Baseline and 38 Weeks and Changes Between Treatment Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>24 wk</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>161±14</td>
<td>162±13</td>
<td>131±12</td>
</tr>
<tr>
<td></td>
<td>162±13</td>
<td>137±13</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>90±12</td>
<td>94±12</td>
<td>75±9</td>
</tr>
<tr>
<td></td>
<td>94±12</td>
<td>80±11</td>
<td></td>
</tr>
<tr>
<td>E', cm/s</td>
<td>7.6±1.1</td>
<td>7.5±1.3</td>
<td>9.2±1.7</td>
</tr>
<tr>
<td></td>
<td>7.5±1.3</td>
<td>9.0±1.9</td>
<td></td>
</tr>
<tr>
<td>Peak E, cm/s</td>
<td>67.4±16.7</td>
<td>64.9±1.4</td>
<td>71.4±16.4</td>
</tr>
<tr>
<td></td>
<td>64.9±1.4</td>
<td>70.0±14.8</td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.97±0.24</td>
<td>0.92±0.23</td>
<td>1.06±0.29</td>
</tr>
<tr>
<td></td>
<td>0.92±0.23</td>
<td>1.00±0.27</td>
<td></td>
</tr>
<tr>
<td>E/E'</td>
<td>8.97±2.4</td>
<td>8.79±2.1</td>
<td>8.02±2.4</td>
</tr>
<tr>
<td></td>
<td>8.79±2.1</td>
<td>8.11±2.3</td>
<td></td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>245.1±29.2</td>
<td>242.0±30.6</td>
<td>221.1±30.0</td>
</tr>
<tr>
<td></td>
<td>242.0±30.6</td>
<td>222.9±26.5</td>
<td></td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>110.4±15.8</td>
<td>110.7±18.6</td>
<td>88.8±15.1</td>
</tr>
<tr>
<td></td>
<td>110.7±18.6</td>
<td>94.5±15.7</td>
<td></td>
</tr>
<tr>
<td>IVRT normalized</td>
<td>3.7±0.06</td>
<td>3.8±0.07</td>
<td>3.0±0.5</td>
</tr>
<tr>
<td></td>
<td>3.8±0.07</td>
<td>3.2±0.6</td>
<td></td>
</tr>
<tr>
<td>Left atrial volume index</td>
<td>25.8±3.5</td>
<td>25.2±3.4</td>
<td>24.3±3.6</td>
</tr>
<tr>
<td></td>
<td>25.2±3.4</td>
<td>23.9±3.9</td>
<td></td>
</tr>
<tr>
<td>Augmentation index</td>
<td>89.0±13.4</td>
<td>86.1±10.8</td>
<td>82.9±13.2</td>
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<tr>
<td></td>
<td>86.1±10.8</td>
<td>80.5±12.1</td>
<td></td>
</tr>
<tr>
<td>Estimated central aortic pressure</td>
<td>151.2±16.2</td>
<td>151.9±15.6</td>
<td>120.1±13.5</td>
</tr>
<tr>
<td></td>
<td>151.9±15.6</td>
<td>124.9±12.3</td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>106.2±22.2</td>
<td>105.0±20.5</td>
<td>102.2±22.3</td>
</tr>
<tr>
<td></td>
<td>105.0±20.5</td>
<td>102.5±21.3</td>
<td></td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>48.1±11.7</td>
<td>47.7±10.8</td>
<td>42.3±11.4</td>
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<tr>
<td></td>
<td>47.7±10.8</td>
<td>43.4±11.5</td>
<td></td>
</tr>
<tr>
<td>LV mass index</td>
<td>71.0±13.5</td>
<td>72.5±15.8</td>
<td>64.8±9.7</td>
</tr>
<tr>
<td></td>
<td>72.5±15.8</td>
<td>66.1±11.5</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>55.0±2.8</td>
<td>54.7±2.8</td>
<td>58.9±3.9</td>
</tr>
<tr>
<td></td>
<td>54.7±2.8</td>
<td>58.0±4.2</td>
<td></td>
</tr>
</tbody>
</table>

P values underneath changes reflect within-group differences. E’ indicates early diastolic lateral mitral annular relaxation velocity; A’, late-diastolic lateral mitral annular relaxation velocity; E, standard early diastolic mitral inflow velocity; A, standard late-diastolic mitral inflow velocity.
9.0±1.9 cm/s in the standard arm (P<0.0001 for both intragroup comparisons). The change from baseline to week 24 was 1.54±1.4 cm/s in the intensive arm and 1.48±1.6 cm/s in the standard arm and was not significantly different between groups (P=0.58). This result was similar for patients who were on previous antihypertensive medications and those who were treatment naive (P for interaction=0.80). Similarly, other direct and indirect measures of diastolic function, including the ratio of mitral inflow velocity:mitral annular relaxation velocity (E/E’), IVRT, deceleration time, and left atrial size improved over 24 weeks in both arms. Of these, only IVRT was different between groups (P=0.04). Radial augmentation index and estimated central aortic pressure decreased in both treatment arms significantly from baseline to week 24 (Table 3; P=0.0001), but the changes in these measures were not different between groups. In pre-specified exploratory analyses, changes in E’, IVRT, and deceleration time were all related to the degree of reduction in blood pressure (Table 4). The primary outcome measure, mitral annular relaxation velocity (E’), was significantly associated with the extent of SBP reduction adjusting for age, sex, baseline SBP, and E’ and treatment group (P=0.025). Similarly, achieved final blood pressure was associated with improvement in this measure of diastolic function (Figure 4).

Both the intensive and standard regimens were well tolerated. There were 3 patients (2.6%) with 5 serious adverse events in the intensive group and 3 patients with 6 adverse events in the standard arm. Comparing intensive versus standard arms, peripheral edema was observed in 24 (20.1%) versus 20 (17.5%) patients; dizziness was observed in 17 (15%) versus 9 (7.9%) patients; and hypotension or orthostatic hypotension was observed in 2 patients (1.8%) in each arm.

Discussion
The EXCEED Trial was designed to test the hypothesis that intensive blood pressure lowering to levels beyond the currently recommended targets for management of uncontrolled hypertension would be associated with significant improvement in diastolic and vascular function relative to treatment to standard targets. We observed that treatment with the combination of an angiotensin receptor blocker/calcium channel blocker was associated with substantial blood pressure reduction in both the intensive and standard treatment arms, with improvements in both measures of diastolic function and vascular function in both

Table 4. Relationship Between Reduction in SBP (by Quartiles) and Change in Measures of Diastolic Function

<table>
<thead>
<tr>
<th>Blood Pressure Reduction, mm Hg</th>
<th>Less than −38</th>
<th>−38 to −28</th>
<th>−28 to −17</th>
<th>More than −17</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage change in E’</td>
<td>25.4</td>
<td>24.7</td>
<td>19.8</td>
<td>13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage change in IVRT</td>
<td>−19.9</td>
<td>−14.7</td>
<td>−16.7</td>
<td>−11.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Percentage change in DT</td>
<td>−11</td>
<td>−8.2</td>
<td>−7.4</td>
<td>−5.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Percentage change in E/E’</td>
<td>−10.1</td>
<td>−4.8</td>
<td>−7.1</td>
<td>−5.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Percentage change in E mitral</td>
<td>−2.9</td>
<td>3</td>
<td>−4.9</td>
<td>−0.63</td>
<td>0.9</td>
</tr>
<tr>
<td>Percentage change in E/A</td>
<td>13.3</td>
<td>14.1</td>
<td>15.2</td>
<td>7.2</td>
<td>0.53</td>
</tr>
</tbody>
</table>

DT indicates deceleration time; E’, early diastolic lateral mitral annular relaxation velocity; A’, late-diastolic lateral mitral annular relaxation velocity; E, standard early diastolic mitral inflow velocity; A, standard late-diastolic mitral inflow velocity.
groups. No difference was observed in annular relaxation velocity (E’) or measures of arterial stiffness between the intensive and standard treatment targets groups, although we achieved only a 5-mm Hg separation in SBP between the groups at 24 weeks. Nevertheless, regardless of group assignment, patients who achieved the lowest SBP demonstrated the highest E’ in exploratory analyses, independent of starting blood pressure. Patients assigned to the intensive treatment strategy were substantially more likely (82% versus 60%) to achieve the recommended Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure treatment targets than those randomized to the standard group.

The epidemiological relationship between hypertension and diastolic dysfunction has been well established in a number of recent studies.4,18 Up to 50% of patients with hypertension have evidence of diastolic dysfunction, which has been associated with an 8- to 10-fold increased risk of mortality.4 Hypertension has been associated with increased collagen deposition and cross-linking, increased interstitial fibrosis, and disturbance of calcium homeostasis in the myocardium,19,20 all of which may contribute to worsening diastolic function. Similar mechanisms likely contribute to increased vascular stiffness and worsening of vascular function in patients with hypertension.21 Both diastolic dysfunction and abnormalities of vascular function likely play a role in the pathogenesis of heart failure with preserved ejection fraction, and abnormalities of both have been observed in these patients, although diastolic dysfunction likely precedes the overt manifestations of heart failure by many years.

In the current study, we directly tested the hypothesis that intensive blood pressure lowering would improve diastolic function in patients with at least moderate hypertension to a greater extent than standard blood pressure lowering. This hypothesis was generated from our previous comparison of renin-angiotensin-aldosterone system–inhibiting and non–renin-angiotensin-aldosterone system–inhibiting approaches to improving diastolic function in the Valsartan in Diastolic Dysfunction Trial, in which neither strategy proved superior, yet improvement in diastolic function was related to blood pressure reduction.7 In EXCEED, we did not find a difference in our primary measure of diastolic function in patients randomized to the intensive versus standard targets, although another measure of diastolic function, IVRT, was improved in the intensive arm. In a prespecified exploratory hypothesis-generating analysis, patients who achieved the lowest blood pressure, regardless of which arm they were randomly assigned to, achieved the best improvement in diastolic function. These somewhat paradoxical findings may be best explained by the fact that within-group reductions in blood pressure and, hence, improvement in diastolic function overwhelmed between-group differences. Indeed, the final SBP difference between groups, −5 mm Hg, was less than we had expected on the basis of the prescribed targets, and, thus, the intrinsic heterogeneity in the blood pressure–lowering response and improvement in diastolic function were greater than the intended between-group effect.

Nevertheless, these data suggest that the degree of blood pressure reduction observed may be the most important determinant of the degree of improvement in diastolic function (Figure 4). Interestingly, we observed substantial individual variability in the degree of blood pressure lowering, with target blood pressure achieved in only 60% of patients in the standard arm and 46% of patients in the intensive arm and could be accounted for by differences in conduit vessel stiffness or target organ involvement. Still, using a more aggressive strategy allowed as many as 82% of patients in that arm to achieve Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure–recommended blood pressure levels.

We observed similar improvements in 2 measures of vascular function in parallel with improvement in diastolic function. These results are not surprising given that similar mechanisms are likely to contribute to both abnormalities of myocardial relaxation and vascular stiffness.21 Central aortic pressure has been identified previously as an important correlate of outcomes in patients with hypertension and appears to correlate with measures of LV structure and function.22 Although we observed important improvement in these measures of vascular function in tandem with improvements in diastolic function, the extent to which reduction in pulsatile load might contribute to improvements in myocardial relaxation remains unknown. These measures of vascular load would be expected to contribute to increased end-systolic wall stress, which may also relate to changes in diastolic function.

Some limitations of the current study should be noted. Patients with diabetes mellitus and chronic kidney disease were excluded from EXCEED, because current guidelines recommend achieving SBP <130 mm Hg in this group. Thus, the effect of blood pressure lowering on diastolic function in these populations remains unknown. Nevertheless, our previous data suggest that diabetic patients would not have behaved differently with respect to improvement of diastolic function with blood pressure reduction.7 Measurements of arterial function in this study were limited to those obtainable from radial artery tonometry; this may have limited our

Figure 4. Relationship between final achieved blood pressure and final diastolic relaxation velocity (E’). P<0.004 adjusting for age, baseline blood pressure, and treatment group.
ability to accurately gauge variations in central aortic parameters that may more accurately reflect pulsatile ventricular load. In addition, follow-up in EXCEED was relatively short in patients without extensive hypertrophy. It is conceivable that strategies aimed at addressing myocardial fibrosis and hypertrophy directly may be more effective over a longer follow-up period. In addition, because many patients were on antihypertensive medication at baseline, we do not know whether our results would have been different had we started with untreated patients. However, we did not see any heterogeneity in the primary results on the basis of whether patients were on antihypertensive therapy at baseline. Finally, whether the specific regimen used in EXCEED contributed to the benefit observed on diastolic function or whether this benefit would have been observed with this degree of blood pressure lowering by any method remains unknown.

**Perspectives**

We found that a strategy of aggressive blood pressure lowering with a combination of an angiotensin receptor blocker, valsartan; a calcium channel blocker, amlodipine; and potential additional therapy with diuretics or β-blockers was associated with improved annular relaxation velocity ($E'$), a measure of diastolic function, in patients with hypertension and diastolic dysfunction. Although we did not directly observe improvement in diastolic function in patients randomized to the intensive arm compared with those randomized to the standard arm, this may be explained by the much greater within-group differences than the observed between-group differences. Nevertheless, those patients who achieved the greatest blood pressure reduction had the best improvement in diastolic function. These data provide further support that achieving lower blood pressures may be an effective means to improve this measure of myocardial target-organ damage in hypertension but also highlight the extreme variability in the degree of blood pressure lowering despite clearly defined treatment targets.

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Effect of Intensive Versus Standard Blood Pressure Lowering on Diastolic Function in Patients With Uncontrolled Hypertension and Diastolic Dysfunction
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