Intensive Blood Pressure Control Reduces the Risk of Cardiovascular Events in Patients With Peripheral Arterial Disease and Type 2 Diabetes

Philip S. Mehler, MD; Joseph R. Coll, PhD; Raymond Estacio, MD; Anne Esler, PhD; Robert W. Schrier, MD; William R. Hiatt, MD

Background—Peripheral arterial disease (PAD) and diabetes are both associated with a high risk of ischemic events, but the role of intensive blood pressure control in PAD has not been established.

Methods and Results—The Appropriate Blood Pressure Control in Diabetes study followed 950 subjects with type 2 diabetes for 5 years; 480 of the subjects were normotensive (baseline diastolic blood pressure of 80 to 89 mm Hg). Patients randomized to placebo (moderate blood pressure control) had a mean blood pressure of 137±0.7/81±0.3 mm Hg over the last 4 years of treatment. In contrast, patients randomized to intensive treatment with enalapril or nisoldipine had a mean 4-year blood pressure of 128±0.8/75±0.3 mm Hg (P<0.0001 compared with moderate control). PAD, which is defined as an ankle-brachial index <0.90 at the baseline visit, was diagnosed in 53 patients. In patients with PAD, there were 3 cardiovascular events (13.6%) on intensive treatment compared with 12 events (38.7%) on moderate treatment (P=0.046). After adjustment for multiple cardiovascular risk factors, an inverse relationship between ankle-brachial index and cardiovascular events was observed with moderate treatment (P=0.009), but not with intensive treatment (P=0.91). Thus, with intensive blood pressure control, the risk of an event was not increased, even at the lowest ankle-brachial index values, and was the same as in a patient without PAD.

Conclusions—In PAD patients with diabetes, intensive blood pressure lowering to a mean of 128/75 mm Hg resulted in a marked reduction in cardiovascular events. (Circulation. 2003;107:753-756.)

Key Words: diabetes mellitus • hypertension • peripheral vascular disease

Peripheral arterial disease (PAD) is a manifestation of generalized atherosclerosis and, therefore, an independent predictor of cardiovascular ischemic events.1,2 Moreover, the severity of arterial occlusive disease in the leg correlates with the risk of ischemic systemic events such that a lower ankle-brachial index (ABI) portends a higher risk of a myocardial infarction, stroke, or vascular death.3 Key risk factors for PAD include diabetes and hypertension.4,5 Although the benefits of treating hypertension in diabetes are firmly established, data are not presently available to determine if treatment of hypertension will alter the natural history of PAD.6

The Appropriate Blood-Pressure Control in Diabetes (ABCD) trial is a prospective interventional study of patients with type 2 diabetes. The initial observations from this study documented that in the hypertensive cohort, intensive blood pressure lowering with an angiotensin-converting enzyme (ACE) inhibitor conferred significant protection against cardiovascular events compared with a calcium channel blocker.7 Recently, we demonstrated that aggressive blood pressure control in normotensive type 2 diabetic patients had a beneficial effect on albuminuria, retinopathy, and strokes, regardless of whether an ACE inhibitor or a calcium channel blocker was used as the initial antihypertensive agent.8

The purpose of the present study was to test the hypothesis that intensive lowering of blood pressure would be associated with a reduced risk of cardiovascular events in the normotensive cohort of patients with PAD and type 2 diabetes. An additional aim was to evaluate the interaction between blood pressure lowering and the ABI.

Methods

Study Design

The ABCD trial is a randomized, prospective, interventional study evaluating the effects of intensive versus moderate diastolic blood pressure control on diabetic microvascular and macrovascular complications.9 The study is composed of 2 cohorts: a normotensive group with a baseline diastolic blood pressure between 80 to
90 mm Hg and a hypertensive group with a baseline diastolic blood pressure ≥90 mm Hg.

Participants
All subjects in the ABCD trial were diagnosed with type 2 diabetes. There were 480 normotensive subjects with a baseline diastolic blood pressure between 80 and 89 mm Hg who were randomized to moderate versus intensive antihypertensive treatment. Those randomized to the intensive arm had a treatment goal of decreasing the diastolic blood pressure by 10 mm Hg from the mean baseline value, with further random assignment to receive either nisoldipine or enalapril. Those randomized to the moderate group had no intended change in their diastolic blood pressure and were thus randomly assigned to placebo. The average follow-up period was 5.3 years for the first phase of the study (described in this report), with a continuation for an additional 5 years that is ongoing.

Measurements and Definitions
During the 7 to 11-week single-blind placebo run-in period, all baseline studies were performed, including measurement of the ABI. Descriptions of procedures and definitions of myocardial infarction, albuminuria, retinopathy, neuropathy, and left ventricular hypertrophy have been reported previously.15 Cardiovascular outcomes that were reviewed by an independent end point committee included: (1) death due to cardiovascular events (sudden death, progressive heart failure, fatal myocardial infarction, fatal arrhythmias, cerebral vascular accidents, and ruptured aortic aneurysm), (2) nonfatal myocardial infarction, (3) nonfatal cerebral vascular accidents, (4) heart failure requiring hospital admission, and (5) pulmonary infarction. PAD was defined by an ABI <0.90, and calcified vessels were defined as an ABI >1.30, as previously described.16 These noninvasive measurements have previously been validated in patients with diabetes, where medial calcification has been observed in 5% of the population.11,12

Data Analysis
Of the 480 subjects in the normotensive cohort, 33 subjects were excluded (14 had a baseline ABI >1.30, indicating calcified vessels, and 19 were missing a baseline ABI), leaving 447 subjects and 56 cardiovascular events for analysis. A χ² test was used to compare the unadjusted differences in event rates between treatment groups in the 53 patients with PAD. Next, logistic regression was employed to determine the univariate relationship between baseline ABI and treatment level was tested to evaluate whether the treatment effect depended on the baseline ABI. Model sensitivity was assessed by performing similar adjusted logistic models in the PAD population only.

Results
The baseline characteristics, clinical complications, and comorbidities of the normotensive diabetic patients randomized to intensive or moderate treatment were similar (Table 1). The mean blood pressure after randomization for the last 4 years of follow-up was 128 ± 0.8/75 ± 0.3 mm Hg for the intensive group and 137 ± 0.7/81 ± 0.3 mm Hg for the moderate group (P = 0.0001).

There were a total of 56 cardiovascular events (myocardial infarction, stroke, or cardiovascular death) in the entire cohort. Overall, there was a similar number of events in the intensive (n = 26) versus moderate group (n = 30). However, in patients with PAD, intensive blood pressure treatment was associated with 3 cardiovascular events in 22 patients (13.6%) versus 12 events in 31 patients (38.7%) in the moderate blood pressure treatment arm (P = 0.046). A further analysis of the PAD patients revealed an inverse relationship between the ABI and the risk of cardiovascular events (P = 0.009), as shown in the Figure. However, this relationship was abolished in the intensive treatment group, such that even at the lowest ABI, intensively treated subjects had no increased risk of events (P = 0.91) (Figure). This protective effect of intensive blood pressure control was independent of drug class. In addition, the difference in slopes for the intensive and moderate treatment group curves depicted in the Figure was due to a significant interaction term of ABI and treatment level (P = 0.04). At an ABI of 0.50, the adjusted odds ratio of a cardiovascular event in the intensively treated group compared with the moderate group was 0.108 (95% confidence interval, 0.012 to 0.999). At an ABI of 0.30, the adjusted odds ratio decreased to 0.046 (95% confidence interval, 0.002 to 0.948; Table 2).

Discussion
PAD affects an estimated 8 million Americans and is strongly associated with substantial risks of adverse cardiovascular events.14 Moreover, the severity of peripheral arterial occlu-
patients with coronary artery disease. The recent PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program demonstrated an overall prevalence of PAD of 29% in persons at risk who were evaluated in 320 primary care practices. Further, this study demonstrated that patients with PAD were significantly less likely than those with coronary artery disease to be treated for hypertension and hyperlipidemia or to receive antiplatelet medications.

Although hypertension is a major risk factor for PAD, to date, no prospective studies have been performed to assess whether intensive blood pressure control improves cardiovascular outcomes in diabetic patients with PAD. It the ABCD study, intensive blood pressure lowering was effective in reducing the risk of cardiovascular events in PAD patients with the use of either a calcium channel blocker or an ACE inhibitor. The Systolic Hypertension in Europe (Syst-Eur) study and the Hypertension Optimal Treatment (HOT) study recently showed that calcium channel blockers reduced cardiovascular events in diabetic hypertensive patients. These results are all consistent with the emerging theme that aggressive blood pressure control is especially advantageous in the diabetic population.

There are limitations to our study. First, it was based on a post hoc analysis of the ABCD trial data. Second, the number of defined cardiovascular events was few. However, the rigorous definitions of primary end points and the fact that cardiovascular events were a prospective end point and other variables were kept consistent throughout the study add credence to the overall findings. Although there were relatively few events in patients with the lowest ABI, the regression coefficients were estimated from all 56 cardiac events observed in all 427 subjects. Model sensitivity was assessed by performing a logistic model in the PAD population only, excluding patients with an ABI >0.90. This analysis yielded similar significant results with ABI as a continuous variable to those that were observed in the entire population (data not shown). From this analysis, we can conclude that the larger number of patients without PAD did not substantially influence the results in the PAD subgroup.

In summary, PAD is a common presentation of atherosclerosis and is also a strong independent predictor of future cardiovascular ischemic events. Our results suggest that blood pressure lowering in normotensive type 2 diabetic patients with PAD is particularly effective in preventing adverse cardiovascular events. Intensified efforts to treat hypertension aggressively in patients with PAD therefore seem justified, particularly because diabetes is a strong predictor of a worse natural history for PAD, with more patients progressing to ischemic ulceration. Additional longitudinal studies of intensive blood pressure control in patients with PAD should be conducted to clarify this association further.

Acknowledgment

Supported by a grant from the Bayer Pharmaceutical Company and a grant (DK50298-02) from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

### TABLE 2. Odds Ratios of Cardiovascular Events by ABI

<table>
<thead>
<tr>
<th>Baseline ABI</th>
<th>Adjusted Odds of Cardiovascular Events</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.020</td>
<td>0.000</td>
<td>0.909</td>
</tr>
<tr>
<td>0.20</td>
<td>0.030</td>
<td>0.001</td>
<td>0.928</td>
</tr>
<tr>
<td>0.30</td>
<td>0.046</td>
<td>0.002</td>
<td>0.948</td>
</tr>
<tr>
<td>0.40</td>
<td>0.071</td>
<td>0.005</td>
<td>0.971</td>
</tr>
<tr>
<td>0.50</td>
<td>0.108</td>
<td>0.012</td>
<td>0.999</td>
</tr>
<tr>
<td>0.60</td>
<td>0.166</td>
<td>0.026</td>
<td>1.034</td>
</tr>
<tr>
<td>0.70</td>
<td>0.253</td>
<td>0.059</td>
<td>1.083</td>
</tr>
<tr>
<td>0.80</td>
<td>0.386</td>
<td>0.128</td>
<td>1.161</td>
</tr>
<tr>
<td>0.90</td>
<td>0.589</td>
<td>0.264</td>
<td>1.314</td>
</tr>
<tr>
<td>1.00</td>
<td>0.900</td>
<td>0.474</td>
<td>1.707</td>
</tr>
<tr>
<td>1.10</td>
<td>1.374</td>
<td>0.672</td>
<td>2.809</td>
</tr>
<tr>
<td>1.20</td>
<td>2.098</td>
<td>0.792</td>
<td>5.557</td>
</tr>
<tr>
<td>1.30</td>
<td>3.203</td>
<td>0.862</td>
<td>11.897</td>
</tr>
</tbody>
</table>

A cardiovascular event was defined as a vascular death, nonfatal myocardial infarction, or ischemic stroke. CI indicates confidence interval.
References
Intensive Blood Pressure Control Reduces the Risk of Cardiovascular Events in Patients With Peripheral Arterial Disease and Type 2 Diabetes
Philip S. Mehler, Joseph R. Coll, Raymond Estacio, Anne Esler, Robert W. Schrier and William R. Hiatt

*Circulation*. 2003;107:753-756; originally published online January 20, 2003;
doi: 10.1161/01.CIR.0000049640.46039.52

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/5/753

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org/subscriptions/