Complex Relationship Between Blood Pressure and Mortality in Type 2 Diabetic Patients
A Follow-Up of the Botnia Study

Mats Rönnback, Bo Isomaa, Johan Fagerudd, Carol Forsblom, Per-Henrik Groop, Tiinamaija Tuomi, Leif Groop; for the Botnia Study Group

Abstract—The presence of hypertension aggravates the high cardiovascular risk in type 2 diabetic patients. Pulse pressure is a marker of arterial stiffness and constitutes a risk factor for cardiovascular mortality. This study examines the relationship between different blood pressure indices and mortality in a cohort of type 2 diabetic patients. A total of 1294 type 2 diabetic patients with a median age of 69.1 years participated in the Botnia Study from 1990 to 1997. In 2004, after a median follow-up of 9.5 years, data on mortality was collected from the national population registry and hospital records. Systolic and diastolic blood pressure correlated negatively with mortality after adjustment for other risk factors. The association between low systolic and diastolic blood pressure and mortality was pronounced in patients with previous cardiovascular disease. A U-shaped association between pulse pressure and mortality was observed in elderly patients. These observations could be linked to arterial stiffness and heart failure. Low blood pressure in high-risk patients is likely to be a marker of poor health rather than the cause of mortality. The results suggest that the role of blood pressure as a risk marker in elderly type 2 diabetic patients with cardiovascular disease needs to be reevaluated.

Key Words: diabetes mellitus ■ blood pressure ■ cardiovascular diseases ■ elderly ■ mortality ■ risk factors

Patients with type 2 diabetes have a 2- to 4-fold increased risk of dying from cardiovascular disease (CVD). Type 2 diabetes is frequently accompanied by hypertension, which additionally increases the cardiovascular risk. The beneficial effect of effective blood pressure (BP)–lowering therapy on cardiovascular mortality in type 2 diabetic patients has been established in several large studies.

Arterial stiffness and its clinical manifestation, pulse pressure (PP), have quite recently been recognized as important risk factors for cardiovascular mortality, particularly in elderly individuals. Although some studies have shown evidence that PP is the most powerful BP index in predicting cardiovascular end points in elderly persons, the results of other studies challenge this view.

Both type 1 and type 2 diabetes are characterized by premature arterial stiffening, and increased PP has been found to predict cardiovascular mortality and progression of renal failure in type 2 diabetes. Whether PP is more useful than systolic (SBP) or diastolic BP (DBP) for predicting mortality in type 2 diabetic patients remains to be clarified.

Despite hypertension being an established risk factor for CVD, evidence of an inverse relationship between BP and mortality among elderly individuals exists. No such association has, to our knowledge, been reported in type 2 diabetic patients. This study investigated the relationship between different BP indices and all-cause and cardiovascular mortality in a follow-up of a cohort of type 2 diabetic patients.

Methods

Subjects
The Botnia Study was initiated in 1990 with the aim to identify risk factors for type 2 diabetes. Patients with type 2 diabetes from 5 primary healthcare centers in Finland were invited to participate together with their family members. Diagnosis of diabetes was based on existing World Health Organization criteria. The current study represents 1294 consecutive type 2 diabetic patients examined between 1990 and 1997. Subjects with a diagnosis of type 2 diabetes (n=1173) and previously nondiagnosed family members whose results from an oral glucose tolerance test (OGTT) met the most recent WHO diabetes criteria (n=121) were included. Patients with glutamic acid decarboxylase antibodies or maturity onset diabetes of the young were excluded.

The study was carried out in accordance with the Declaration of Helsinki and was approved by all of the local ethics committees. All of the subjects gave informed consent before participation.
Baseline Examination
A standard OGTT was performed on all of the noninsulin-treated subjects with fasting plasma glucose <11 mmol/L (n = 698). Urine was collected during the OGTT or overnight, and albumin excretion rate (AER) was measured (n = 666). Fasting blood samples were drawn for the measurement of serum lipids. BP was measured by trained nurses using mercury sphygmomanometers. SBP was recorded at phase I and DBP at phase V of Korotkoff sounds. Two BP recordings were obtained from the right arm of a sitting patient after 30 minutes of rest at 5-minute intervals, and the mean value was calculated.

A standardized health questionnaire covering the subjects’ medical history was completed by trained nurses. Additional information on the medical history was obtained from medical records. Coronary heart disease was defined as the use of nitroglycerine, typical chest pain, or a history of myocardial infarction. Stroke, including both ischemic and hemorrhagic stroke, were defined as clinically or radiologically diagnosed events requiring hospitalization. Previous CVD was defined as a history of coronary heart disease or stroke.

Follow-Up
Data on the subjects’ vital status were obtained from the national population registry on May 31, 2004. In order to classify the cause of mortality, death certificates of the diseased subjects were obtained from the central death-certificate registry. Additionally, medical records were acquired if the cause of death was unclear. Cardiovascular mortality was classified using the 9th revision of the International Classification of Disease (codes 399 to 459) before 1997 and the 10th revision (codes I 10 to 99) thereafter. The reliability of cause-of-death data obtained from the national population registry has been established previously. It has also been demonstrated that the Finnish hospital discharge register give a correct picture on the occurrence of CVD.

Statistical Analysis
Statistical analyses were performed with SPSS 12.0.1 (SPSS Inc). Results are expressed as the mean±SD for normally distributed variables and as the median (interquartile range) for nonnormally distributed variables. Comparisons of variables were performed using t test or Mann-Whitney U test, as appropriate. Relevant clinical variables were entered into a forward stepwise Cox regression model. AER was not included in the model because of missing data on a large number of patients. Variables that contributed significantly to the model were added to the model in order of significance, except gender, which was forced into the model. Hazard ratios were calculated by merging the results of separate analyses for medicated and nonmedicated patients to reduce the confounding effects caused by antihypertensive medication.

Results
The baseline characteristics of the cohort are described in Table 1. Patients had a median age of 69.1 (range, 24.5 to 96.9; interquartile range, 61.1 to 75.7) years and a median duration of diabetes of 6.3 years. Their mean BP was 149/83 mm Hg. Of the entire sample, 39% did not use any hypoglycemic medication, 28% were on oral agents, 11% on antihypertensive medication, 5% were on oral antihypertensive medication, and 22% were on combination therapy.

Table 1. Baseline Characteristics According to Outcome

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Entire Group</th>
<th>Survivors</th>
<th>Cardiovascular Death</th>
<th>Other Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1294</td>
<td>742</td>
<td>332</td>
<td>220</td>
</tr>
<tr>
<td>Sex, % males</td>
<td>46</td>
<td>45</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Age, y</td>
<td>66.1 (61.1–75.7)</td>
<td>64.0 (56.7–71.4)</td>
<td>75.7 (70.5–80.9)*</td>
<td>74.8 (69.4–80.2)*</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>6.3 (2.4 to 11.6)</td>
<td>4.6 (1.4 to 9.8)</td>
<td>8.2 (4.4 to 13.9)*</td>
<td>7.7 (3.1 to 13.2)*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>149±21</td>
<td>148±20</td>
<td>151±21†</td>
<td>150±20</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>83±11</td>
<td>85±11</td>
<td>80±11*</td>
<td>82±10*</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>66±18</td>
<td>63±18</td>
<td>71±19*</td>
<td>69±18*</td>
</tr>
<tr>
<td>Mean arterial BP, mm Hg</td>
<td>105±10</td>
<td>106±12</td>
<td>104±12</td>
<td>104±12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.3±4.7</td>
<td>28.8±4.7</td>
<td>27.5±4.5*</td>
<td>27.5±4.6*</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.93±0.08</td>
<td>0.93±0.08</td>
<td>0.93±0.09</td>
<td>0.93±0.07</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>8.4 (7.1 to 11.0)</td>
<td>8.1 (7.0 to 10.7)</td>
<td>9.1 (7.2 to 11.6)*</td>
<td>8.3 (6.9 to 10.7)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.5±1.5</td>
<td>7.4±1.6</td>
<td>7.7±1.4</td>
<td>7.4±1.5</td>
</tr>
<tr>
<td>AER, μg/min</td>
<td>5.5 (2.8 to 11.7)</td>
<td>4.7 (2.5 to 9.3)</td>
<td>6.8 (3.7 to 22.2)*</td>
<td>7.1 (3.1 to 13.7)*</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.85±1.20</td>
<td>5.84±1.13</td>
<td>5.96±1.26</td>
<td>5.72±1.30</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.80±1.05</td>
<td>3.75±1.01</td>
<td>3.89±1.05</td>
<td>3.70±1.15</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.18±0.31</td>
<td>1.19±0.30</td>
<td>1.12±0.29*</td>
<td>1.23±0.35</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.70 (1.25 to 2.38)</td>
<td>1.55 (1.26 to 2.27)</td>
<td>1.83 (1.32 to 2.54)*</td>
<td>1.58 (1.15 to 2.45)</td>
</tr>
<tr>
<td>Diabetes treatment, diet/oral agents/insulin/combination, %</td>
<td>39/28/11/22</td>
<td>41/31/11/18</td>
<td>38/25/12/27†</td>
<td>37/24/10/29†</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>51</td>
<td>46</td>
<td>62*</td>
<td>52</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>8</td>
<td>4</td>
<td>16*</td>
<td>7†</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>29</td>
<td>21</td>
<td>48*</td>
<td>28†</td>
</tr>
<tr>
<td>Total CVD, %</td>
<td>32</td>
<td>23</td>
<td>55*</td>
<td>30†</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>8</td>
<td>10</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Normally distributed values are presented as mean±SD, nonnormally distributed values as median (interquartile range). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

*P<0.01 vs survivors.
†P<0.05 vs survivors.
insulin, and 22% were treated with a combination of oral agents and insulin. In all of the patients using oral medication, the frequency of the specific agents was as follows: metformin 30%, glibenclamide 67%, glipizide 21%, and guar gum 10%. Glitazones were not in clinical use at the time of baseline examinations. During a median follow-up time of 9.5 years (range, 6.5 to 14.4 years), 192 patients (35% of deaths) died of coronary heart disease, 68 (12%) of cerebrovascular disease, 72 (13%) of other CVD, 102 (18%) of neoplasms, 100 (18%) of other disease, and 12 (2%) of accidents or suicide. Six (1%) of the total 552 deaths could not be classified because of lack of information. Survivors had lower age, shorter duration of diabetes, lower PP, and lower AER but higher DBP and body mass index than the patients that died. In addition, patients who died of CVD had higher SBP, fasting plasma glucose, and triglycerides but lower HDL cholesterol compared with the survivors.

The Cox regression analyses (Table 2) showed that the unadjusted relationship with all-cause and cardiovascular mortality was negative for DBP but positive for PP. When adjusting for other risk factors, SBP and DBP correlated negatively with both all-cause and cardiovascular mortality, whereas no association between PP and mortality was observed.

In a subgroup of patients below the median age of 69.1 years at baseline (n=647), the all-cause mortality hazard ratio in a corresponding risk factor–adjusted model (not shown) for SBP was 1.01 (95% CI, 0.92 to 1.11); DBP was 0.93 (95% CI, 0.78 to 1.11); and PP was 1.05 (95% CI, 0.93 to 1.19). In the same subgroup, the cardiovascular mortality hazard ratio for SBP was 1.00 (95% CI, 0.87 to 1.14); DBP was 0.78 (95% CI, 0.61 to 1.00); and PP was 1.12 (95% CI, 0.95 to 1.32).

To exclude that the observed effects were because of admixture of individuals with microalbuminuria, we also performed a Cox regression analysis including only patients with available AER measurements (n=666; data not shown). Adding AER to the model lowered the hazard ratio for all of the BP indices by 0.01 to 0.03.

Cardiovascular mortality rates in relation to the age- and gender-adjusted BP indices are shown in Figures 1, 2, and 3. The relationships between all-cause mortality and BP (data not shown) were similar to those shown in the figures.

### No Previous CVD
In patients without a history of CVD, a DBP of 90 to 99 mm Hg was predictive of low mortality. The association between PP and mortality was U-shaped with the highest risk found in the lowest and highest PP categories.

### Previous CVD
A negative association between SBP and mortality was observed in patients with a positive history of CVD, and SBP levels <140 mm Hg were associated with increased mortality in this group. Both all-cause and cardiovascular mortality correlated negatively with DBP in these patients. The association between PP and mortality was U-shaped, with the lowest mortality observed in the intermediate categories.

### Effect of Age
In patients older than the median age of 69.1 years, SBP and PP correlated with mortality in a U-shaped fashion, whereas no such relationship in patients below the median age was observed.

### Antihypertensive Medication
In patients with antihypertensive medication, SBP and DBP correlated with mortality in an inverse manner. The association with PP in these patients was U-shaped. Patients without antihypertensive medication demonstrated an inverse corre-

<table>
<thead>
<tr>
<th>Variable Added</th>
<th>Hazard Ratio*</th>
<th>SBP</th>
<th>DBP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure per 10 mm Hg</td>
<td>1.00 (0.96 to 1.05)</td>
<td>0.70 (0.64 to 0.76)</td>
<td>1.12 (1.07 to 1.18)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.11 (1.09 to 1.12)</td>
<td>0.92 (0.88 to 0.97)</td>
<td>0.86 (0.78 to 0.94)</td>
<td>0.95 (0.91 to 1.00)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.51 (1.24 to 1.83)</td>
<td>0.92 (0.88 to 0.97)</td>
<td>0.82 (0.75 to 0.90)</td>
<td>0.96 (0.92 to 1.01)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.40 (1.62 to 3.52)</td>
<td>0.92 (0.88 to 0.96)</td>
<td>0.82 (0.75 to 0.90)</td>
<td>0.96 (0.91 to 1.01)</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>1.02 (1.01 to 1.04)</td>
<td>0.92 (0.88 to 0.97)</td>
<td>0.83 (0.76 to 0.91)</td>
<td>0.96 (0.91 to 1.01)</td>
</tr>
<tr>
<td>Previous CVD</td>
<td>1.39 (1.15 to 1.69)</td>
<td>0.93 (0.89 to 0.97)</td>
<td>0.85 (0.77 to 0.93)</td>
<td>0.96 (0.91 to 1.01)</td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure per 10 mm Hg</td>
<td>1.00 (0.96 to 1.05)</td>
<td>0.65 (0.58 to 0.72)</td>
<td>1.14 (1.07 to 1.20)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.12 (1.10 to 1.14)</td>
<td>0.92 (0.87 to 0.98)</td>
<td>0.80 (0.71 to 0.90)</td>
<td>0.96 (0.91 to 1.03)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.49 (1.13 to 1.97)</td>
<td>0.92 (0.88 to 0.97)</td>
<td>0.77 (0.68 to 0.86)</td>
<td>0.98 (0.91 to 1.04)</td>
</tr>
<tr>
<td>Previous CVD</td>
<td>1.82 (1.38 to 2.40)</td>
<td>0.93 (0.88 to 0.99)</td>
<td>0.81 (0.72 to 0.91)</td>
<td>0.97 (0.91 to 1.04)</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>1.03 (1.01 to 1.04)</td>
<td>0.93 (0.87 to 0.98)</td>
<td>0.82 (0.73 to 0.93)</td>
<td>0.96 (0.90 to 1.03)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.19 (1.25 to 3.81)</td>
<td>0.93 (0.88 to 0.99)</td>
<td>0.81 (0.72 to 0.91)</td>
<td>0.97 (0.91 to 1.04)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.55 (0.33 to 0.89)</td>
<td>0.92 (0.87 to 0.98)</td>
<td>0.82 (0.73 to 0.92)</td>
<td>0.96 (0.90 to 1.03)</td>
</tr>
</tbody>
</table>

Hazard ratios refer to a pressure increase of 10 mm Hg. Analyses were performed with antihypertensive medication as strata variable. Values in parenthesis are 95% CIs. HDL indicates high-density lipoprotein.

*Hazard ratio in final model not including BP indices.
lation between mortality and SBP, but no significant associations with DBP or PP were observed.

Figure 4 shows all-cause mortality stratified by SBP and DBP levels. Mortality increases toward the upper right corner, where the combination of a high SBP (>160 mm Hg) and a low DBP (<75 mm Hg) results in a high PP. A similar peak in mortality can be observed in the lower left corner, where a low SBP (<135 mm Hg) and a high DBP (>90 mm Hg) result in a low PP. A corresponding analysis for cardiovascular mortality displayed a very similar pattern (data not shown).

Discussion
This study shows that a U-shaped association between PP and mortality exists in elderly type 2 diabetic patients. In addition, low BP is associated with poor survival in type 2 diabetic patients with a history of previous CVD.

The finding that high, not low, BP is predictive of favorable survival in type 2 diabetic patients may seem controversial in view of the vast evidence of the detrimental effects of hypertension and the established benefit of treating hypertension in type 2 diabetes. However, many major trials, such as the UK Prospective Diabetes Study Group, have focused on younger hypertensive patients without previous CVD. The present study examines mortality in a cohort recruited with type 2 diabetes as the only selection criteria and is, therefore, likely to represent a more typical type 2 diabetic population. The difference between the populations is illustrated by the fact that, of the 1294 Botnia patients, only 401 (31%) would have fulfilled the UK Prospective Diabetes Study Group inclusion criteria.

This study did not assess the cardiac function or vascular properties of the patients. Thus, one can only speculate about the mechanisms underlying the finding that patients with discordant SBP and DBP levels (high or low PP) had a strikingly elevated mortality compared with patients with concordant SBP and DBP levels (intermediate PP).

Arterial stiffness causing elevated PP constitutes a risk factor for CVD, as well as all-cause and cardiovascular mortality, in both diabetic and nondiabetic individuals. Considering the accelerated arterial stiffening in type 2 diabetes, it seems plausible that the elevated mortality observed in the highest PP categories would be linked to increased arterial stiffness and, thus, reflect arterial ageing. In addition to being a marker of poor vascular health, arterial stiffness increases the cardiac afterload by augmenting the SBP and reduces coronary perfusion by decreasing the DBP, thereby lowering the ischemic threshold of the myocardium.

The favorable prognosis associated with a high BP in patients with previous CVD (Figure 1) is presumably related to preserved cardiac function. This is supported by recent evidence that suggests a markedly increased prevalence of heart failure in type 2 diabetes. Low SBP and DBP have been associated previously with congestive heart failure in type 2 diabetic patients. Another factor that could contribute to this association is diabetic cardiomyopathy, which could lower BP by impairing cardiac output. Thus, low BP in these patients is likely to be a marker of disease rather than the cause of it. Cardiac output failure could also explain the high mortality associated with low PP in patients without previously known CVD.

Although this is the first evidence of a negative association between BP and mortality in a type 2 diabetic population, similar associations have been observed in elderly nondiabetic populations. These studies have generally included only subjects >75 years of age, whereas the median age of

Figure 1. Cardiovascular mortality in patients with (●), dotted line) previous cardiovascular disease in relation to age- and gender-adjusted blood pressure indices. Bars, 95% CIs.

Figure 2. Cardiovascular mortality in patients older (●, solid line) than and younger (●, solid line) than the baseline median age (69.1 years) in relation to age- and gender-adjusted blood pressure indices. Bars, 95% CIs.
the Botnia cohort was 69 years. Nevertheless, because the negative associations between BP and mortality were confined to patients with older age or previous CVD, this study supports the view that the positive association between BP and survival is limited to the elderly patient population.

Some limitations of this study should be noted. No conclusions on the benefit of antihypertensive treatment of type 2 diabetic patients can be drawn on the basis of this observational study. Given the previously reported U-shaped relationship between SBP and diabetes-related end points in BP-medicated elderly diabetic patients,28 our observations clearly underline the need to additionally clarify the impact of BP treatment in the older diabetic population. This study evaluated survival after a median follow-up of 9.5 years in a relatively elderly population. Considering the weak associations between BP and mortality in subjects <69 years of age, one cannot make assumptions on the effects of BP on long-term survival in younger diabetic individuals.

Considering the substantial mortality in the type 2 diabetic population and the relatively high age of the cohort, this study may be subject to survival bias. Thus, high-risk patients are likely to be somewhat underrepresented in this cohort. Because elevated urinary AER is an important risk factor for mortality in type 2 diabetes,29,30 the insufficient data on this issue constitutes a limitation. This is likely to cause an underestimation of the observed relationships, because adjusting for AER in the subgroup with available data on AER lowered the hazard ratio for all of the BP indices and additionally strengthened the inverse association between BP and mortality in patients with previous CVD.

The fact that a substantial proportion of the studied subjects were taking antihypertensive medication at the time of the baseline visit would certainly have influenced the results. High-risk patients with previous CVD and diabetic complications are more likely to use medication. An artificially low BP in high-risk patients could, therefore, seriously confound the results. On the other hand, any effects of BP on the circulatory system would be mediated by the actual BP rather than a theoretical naive BP. Given that the main findings of this study can be observed when analyzing medicated and nonmedicated patients separately (Figure 3), a major confounding effect caused by antihypertensive medication seems unlikely. Additionally, the Cox regression analyses were performed in a manner that eliminates confounding effects that could result from differences between the groups.

It should be noted that the impact of the various BP indices on mortality in the entire cohort was quite moderate, with hazard ratios for a 10 mm Hg increase ranging from 0.85 to 1.14. Despite this, because of the complex nonlinear relationship, BP appears to be an important risk factor for mortality in elderly type 2 diabetic patients and in diabetic patients with previous CVD.

Perspectives
Both low and high PP are risk factors for mortality in elderly type 2 diabetic patients. Low SBP and DBP are predictive of elevated all-cause and cardiovascular mortality in type 2 diabetic patients with previous CVD. In contrast, no BP index contributed significantly to mortality in young type 2 diabetic patients without CVD. The results suggest that there might be a need to reevaluate the role of BP as a risk marker in certain high-risk subgroups of type 2 diabetic patients.

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