Pulse pressure strongly predicts cardiovascular disease risk in patients with type 2 diabetes from the Swedish National Diabetes Register (NDR)

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Abstract

Objectives. – To analyze pulse pressure (PP) as a risk predictor for coronary heart disease (CHD), stroke and cardiovascular disease (CVD; CHD and/or stroke) in type 2 diabetic patients.

Methods. – A total of 11,128 female and male type 2 diabetic patients with known baseline PP values and no CVD, aged 50–74 years, were followed for a mean duration of 5.6 years (1998–2003). A subgroup of 5521 patients with known mean PP values (mean values at baseline and at the end of the study) was also included.

Results. – Hazard ratios (HRs) with 95% CI for fatal/nonfatal CHD with baseline or mean PP ≥ 75 mmHg, compared to < 75 mmHg, were 1.23 (1.07–1.40; \( P = 0.003 \)) and 1.32 (1.07–1.62; \( P = 0.009 \)), respectively, after adjusting for mean blood pressure (MBP), age, gender, diabetes duration, HbA1c, body mass index (BMI), lipid-reducing drugs, microalbuminuria > 20 mg/min, antihypertensive drugs and hypoglycaemic treatment, using Cox regression analyses. Fully-adjusted respective HRs for stroke were 1.17 (0.98–1.39) and 1.21 (1.05–1.61) and, for CVD, 1.23 (1.10–1.37; \( P < 0.001 \)) and 1.28 (1.07–1.52; \( P = 0.007 \)). Fully-adjusted HRs for baseline PP increased per quartile and, CHD, stroke or CVD, were 1.09 (1.03–1.16; \( P = 0.004 \)), 1.14 (1.05–1.23; \( P = 0.002 \)) and 1.11 (1.05–1.17; \( P < 0.001 \)), respectively. The data suggest that, if a mean PP ≥ 75 mmHg were to be avoided, then 15% and 17% of CHD and or CVD, cases, respectively, in such a cohort might be prevented after multivariable adjustments, with a further 10% of cases avoided if also adjusted for MBP and age. Increasing baseline MBP, age and microalbuminuria were independently and significantly associated (\( P < 0.001 \)) with increasing baseline or mean PP.

Conclusion. – Increased PP is a powerful independent risk predictor of CVD in type 2 diabetic patients, and lowering PP can lead to a marked reduction in risk.

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Keywords: Pulse pressure; Diabetes; Cardiovascular disease; Myocardial infarction; Epidemiology

Résumé

La pression pulsée est un indicateur puissant du risque d’événements cardiovasculaires chez des patients diabétiques de type 2 issus du Registre national suédois du diabète.

Objectifs. – Évaluer la valeur de la pression pulsée (PP) comme un facteur de risque d’événements coronaires (EC), d’accidents vasculaires cérébraux ischémiques (AVC) et d’événements cardiovasculaires (ECV : EC et/ou AVC) mortels et non mortels chez des diabétiques de type 2 (DT2).


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Résultats. – En analyse multivariée par régression de Cox, le risque relatif (RR) (intervalle de confiance à 95 %) d’événements coronaires chez les patients dont la PB ou la PPM était supérieure ou égale à 75 mmHg, comparés à ceux dont les valeurs étaient inférieure à 75 mmHg, était respectivement de 1,23 (1,07–1,40 ; P = 0,003) et 1,32 (1,07–1,62 ; P = 0,009), après ajustement pour la pression artérielle moyenne (PAM), l’âge, le sexe, la durée de diabète, l’HbA1c, l’IMC, la prise d’hypocholestérolémiants, d’antihypertenseurs, l’existence d’une micro-albuminurie supérieure à 20 μg/min et le traitement hypoglycémiant. Le RR multi-ajusté d’accident vasculaire cérébral était respectivement de 1,17 (0,98–1,39) et de 1,21 (0,90–1,61), et celui d’événement cardiovasculaire de 1,23 (1,10–1,37 ; P < 0,001) et 1,28 (1,07–1,52 ; P = 0,007). L’augmentation du RR multi-ajusté d’événements coronaires, d’accidents vasculaires cérébraux et d’événements cardiovasculaires totaux par quartile de la PB était respectivement de 1,09 (1,03–1,16 ; P = 0,004), 1,14 (1,05–1,23 ; P = 0,002) et 1,11 (1,05–1,17 ; P < 0,001). S’il avait été possible d’obtenir à l’inclusion une PB inférieure à 75 mmHg, après ajustement multivarié, 15 % des événements coronaires et 17 % des accidents vasculaires cérébraux de la cohorte auraient pu être évités (10 % des événements après ajustement supplémentaire pour la PAM et l’âge). L’augmentation de la PAM et de l’âge, ainsi que la micro-albuminurie basale étaient associées de manière indépendante (P < 0,001) à la PB et à la PPM.

Conclusion. – L’augmentation de la PP est un facteur de risque d’événements cardiovasculaires puissant et indépendant chez des diabétiques de type 2. Une réduction de la PP permettrait une réduction de ce risque.

Mots clés : Pression pulsée ; Diabète de type 2 ; Registre ; Étude longitudinale ; Maladies cardiovasculaires ; Infarctus du myocarde ; Accidents vasculaires cérébraux ; Épidémiologie

1. Introduction

Patients with type 2 diabetes have a two- to four-fold higher risk of cardiovascular disease (CVD) than do nondiabetic, healthy subjects [1,2]. The importance of systolic blood pressure (BP) as a risk factor for cardiovascular events has been verified by the United Kingdom Prospective Diabetes Study (UKPDS), and strict BP control has proved effective in reducing the risk of stroke and diabetes-related mortality [3]. Such patients are also thought to have increased arterial rigidity [4–8], and pulse pressure may be regarded as an indirect measure of arterial stiffness in middle-aged and older subjects [4,9–11]. However, only a few studies have investigated the predictive value of pulse pressure as a risk factor for CVD in patients with type 2 diabetes [12,13].

The aim of this observational prospective study was to analyze the association between pulse pressure, coronary heart disease (CHD), stroke and CVD (CHD and/or stroke) in a large sample of type 2 diabetic patients from the Swedish diabetes population registered at primary-care centers and hospital diabetes clinics nationwide.

2. Patients and methods

2.1. The Swedish National Diabetes Register (NDR)

The Swedish National Diabetes Register (NDR) was initiated in 1996 as a tool for local quality assurance in diabetes care. Annual reporting to the NDR is carried out by trained physicians and nurses via the Internet and through databases of clinical records, comprising information collected during patient visits at hospital outpatient clinics and primary healthcare centers across Sweden, from approximately 200 units participating in the present study. All included patients gave their informed consent to register before participating in the study. The study was approved by the regional ethics committee at the University of Gothenburg. In addition, reports on trends in risk factor control according to the NDR have been previously published [14–18].

2.2. Patients

This observational prospective study involved 11,128 female and male type 2 diabetic patients from the NDR who were free of CVD at baseline and aged 50–74 years, with data available for all of the analyzed variables. The patients were followed prospectively from 1998 to 2003 for analysis of baseline pulse pressure as a risk factor for first-incident fatal or nonfatal CHD, stroke and CVD. A subgroup of 5521 patients was also included with data available for estimation of mean pulse pressure during the study period, based on the mean values of pulse pressure at baseline and at the end of the study. Pulse pressure at the end of the study was defined as the value during the year prior to an event, whether fatal or nonfatal, or the value during 2003.

The definition of type 2 diabetes was treatment with diet only, treatment with oral hypoglycaemic agents only, or onset age of diabetes ≥40 years and treatment with insulin only or combined with oral agents. Only 1% had a diabetes-onset age <30 years, and 3% had an onset age <40 years.

2.3. Examinations at baseline

Clinical characteristics at baseline in 1997 and 1998 included type of hypoglycaemic treatment, age, diabetes duration, gender, systolic and diastolic BP, weight, height, smoking status, use of lipid-lowering drugs, cumulative microalbuminuria and use of antihypertensive drugs. Body mass index (BMI) was calculated as weight/height² (kg/m²). The Swedish standard for recording BP, used in the NDR, takes the mean value of two supine readings (Korotkoff: 1–5) with a cuff of appropriate size after at least five minutes of rest. Pulse pressure was defined as systolic BP minus diastolic BP. Mean BP (MBP) was defined as two-thirds of the diastolic BP plus one-third of the systolic BP. A smoker was defined as a patient who smoked one or more cigarettes a day, or smoked tobacco using a pipe, or who had stopped smoking within the past 3 months.

Laboratory analyses of HbA1c were carried out at local laboratories and were quality-assured across the country by regular calibration, using the high-performance liquid chromatography (HPLC) Mono-S method. In the present study, all HbA1c values...
were converted to the Diabetes Control and Complications Trial (DCCT) standard values using the formula HbA1c (DCCT) = 0.923 × HbA1c (Mono-S) + 1.345; $R^2 = 0.998$ [19]. Microalbuminuria was defined as cumulative, with urine albumin excretion > 20 μg/min in two out of three consecutive tests.

2.4. Follow-up and definition of endpoints

All patients were followed from the baseline examination until the first incidence of a cardiovascular event or death, or until censor date 31 December 2003. The mean follow-up duration was 5.6 years. All patients were free of CHD, stroke and heart failure at baseline. Three major endpoints were used in this study:

- first-incident fatal or nonfatal CHD;
- first-incident fatal or nonfatal stroke;
- first-incident fatal or nonfatal CVD (defined as CHD or stroke, whichever came first).

A fatal CHD event was defined as fatal ischemic heart disease (ICD-10 codes I20–I25; www.who.int/classifications/icd/en/) or sudden cardiac death (ICD-10 codes R96.0–1). A nonfatal CHD event was defined as nonfatal myocardial infarction (ICD-10 code I21), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention and/or coronary artery bypass grafting (CABG). In patients with multiple CHD events, only the first event was considered in our study. A stroke event was defined as fatal or nonfatal intracerebral haemorrhage, cerebral infarction or unspecified stroke (ICD-10 codes I61, I63, I64, I67.9). Heart failure was defined as ICD-10 code I50.

All endpoint events were retrieved by data linkage with the Swedish Cause of Death and Hospital Discharge Registers (National Board of Health and Welfare, Sweden), a reliable, validated alternative to revised hospital discharge and death certificates [20,21]. In total, 1175 first-incident fatal/nonfatal CHD events, 699 stroke events and 1728 CVD events occurred, based on 55,016 person/years, while 460 CHD events, 237 stroke events and 635 CVD events were seen in the subgroup of 5521 patients, based on 27,356 person/years.

2.5. Statistical methods

Absolute risk was expressed as events per 1000 person/years. Cox regression analysis was used to estimate hazard ratios (HRs) with 95% confidence intervals (95% CI) for pulse pressure and CHD, stroke or CVD, adjusted for several covariates in three models (Tables 1 and 2). Patients were subdivided into two groups with pulse pressure either ≥ 75 mm Hg or < 75 mm Hg, as 75 mm Hg was found to be the 75th percentile in the distribution of both baseline and mean pulse pressures. Pulse pressure was also applied as a continuous variable that increased in quartiles. A test of linear trend using the difference in the Wald χ² statistic of global fit from two models, with pulse pressure applied as either a continuous or a nominal variable, showed that the former model produced a better fit. The proportional-hazards assumption was confirmed for all covariates with the Kolmogorov-type supremum test, using resampling, and with a test of all time-dependent covariates simultaneously. Maximum likelihood estimation was used to evaluate interactions between all analyzed variables, and significant interactions were added as covariates.

### Table 1

<table>
<thead>
<tr>
<th>Fatal/Nonfatal coronary heart disease</th>
<th>Patients (n)</th>
<th>Events (n)</th>
<th>Absolute risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP ≥ 75 vs &lt; 75 mm Hg (Model 1&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>3255/7873</td>
<td>447/728</td>
<td>27.6/18.2</td>
<td>1.51 (1.35–1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP ≥ 75 vs &lt; 75 mm Hg (Model 2&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>3255/7873</td>
<td>447/728</td>
<td>27.6/18.2</td>
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<td>PP ≥ 75 vs &lt; 75 mm Hg (Model 3&lt;sup&gt;d&lt;/sup&gt;)</td>
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<td>1.51 (1.35–1.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP per quartile (Model 3&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>11,128</td>
<td>1175</td>
<td>20.9</td>
<td>1.09 (1.03–1.16)</td>
<td>0.004</td>
</tr>
<tr>
<td>Fatal/Nonfatal stroke</td>
<td></td>
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<td></td>
</tr>
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<td>PP ≥ 75 vs &lt; 75 mm Hg (Model 1&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>3255/7873</td>
<td>289/410</td>
<td>17.7/10.2</td>
<td>1.75 (1.50–2.03)</td>
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<td>PP per quartile (Model 3&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>11,128</td>
<td>699</td>
<td>12.3</td>
<td>1.14 (1.05–1.23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal/Nonfatal cardiovascular disease</td>
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<td></td>
</tr>
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<td>PP ≥ 75 vs &lt; 75 mm Hg (Model 1&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>3255/7873</td>
<td>681/1047</td>
<td>43.3/26.6</td>
<td>1.63 (1.48–1.79)</td>
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<td>PP per quartile (Model 3&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>11,128</td>
<td>1728</td>
<td>31.4</td>
<td>1.11 (1.05–1.17)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NB: 75 mm Hg corresponded to the 75th percentile in the distribution of PP, and the PP increase per quartile corresponded to an increase per 10 mm Hg; CI: confidence interval.

-<sup>a</sup> Events per 1000 patient-years.
-<sup>b</sup> Unadjusted crude hazard ratios.
-<sup>c</sup> Adjusted for gender, diabetes duration, HbA1c, body mass index, smoking status, lipid-lowering drugs, microalbuminuria, antihypertensive drugs, type of hypoglycaemic treatment and significant interactions.
-<sup>d</sup> Adjustment as in Model 2, and also for age and mean blood pressure.
Table 2  
Hazard ratios (95% CI) for higher vs lower values of mean pulse pressure (PP) and first-incident cardiovascular events, using Cox regression analysis in 5521 type 2 diabetic patients, aged 50–74 years, followed for 6 years.

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<th>P value</th>
</tr>
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<td>PP ≥ 75 mmHg vs &lt; 75 mmHg (Model 1&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>1501/4020</td>
<td>169/291</td>
<td>22.8/14.3</td>
<td>1.59 (1.31–1.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PP ≥ 75 vs &lt; 75 mmHg (Model 2&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>1505/4016</td>
<td>93/144</td>
<td>12.4/7.0</td>
<td>1.76 (1.36–2.29)</td>
<td>&lt;0.001</td>
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<tr>
<td>PP ≥ 75 mmHg, (Model 3&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>1515/4006</td>
<td>239/396</td>
<td>32.6/19.8</td>
<td>1.64 (1.40–1.93)</td>
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<table>
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<tr>
<th>Fatal/Nonfatal stroke</th>
<th>Patients (n)</th>
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<tr>
<th>Fatal/Nonfatal cardiovascular disease</th>
<th>Patients (n)</th>
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NB: 75 mmHg corresponded to the 75th percentile in the distribution of PP.
CI: confidence interval.
<sup>a</sup> Events per 1000 patient-years.
<sup>b</sup> Unadjusted crude hazard ratios.
<sup>c</sup> Adjusted for gender, diabetes duration, HbA<sub>1c</sub>, body mass index, smoking status, lipid-lowering drugs, microalbuminuria, antihypertensive drugs, type of hypoglycaemic treatment and significant interactions.
<sup>d</sup> Adjustment as in Model 2, and also for age and mean blood pressure.

- antihypertensives × microalbuminuria;
- age × smoking;
- MBP × antihypertensives.

The Hosmer-Lemeshow test demonstrated a nonsignificant χ² statistic, indicating excellent goodness-of-fit of the models.

The homogeneity of the effect of pulse pressure on CHD, stroke and CVD outcomes across the subgroups of each covariable was tested by adding interaction terms to the relevant Cox models. In addition, the percent partial population-attributable risk with 95% CI was calculated [22], estimating the percent cases of fatal/nonfatal CHD, stroke and CVD in the cohort that might have been prevented if a pulse pressure ≥ 75 mmHg had been avoided.

The association between age vs pulse pressure and baseline MBP vs pulse pressure were analyzed by univariate regression. Multiple regression was used to analyze baseline MBP, age and microalbuminuria as independent variables vs pulse pressure as a dependent variable, with MBP and age increased per standard deviation (SD) to allow for comparisons of the power of the estimated regression coefficients (± standard error [SE]) of the continuous variables, while microalbuminuria was included as a dichotomous variable.

All statistical analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC, USA). A P value < 0.05 was considered statistically significant.

3. Results

Table 3 shows the baseline characteristics of the study sample of 11,128 men and women with type 2 diabetes, aged 50–74 years and free of CVD at baseline, divided into subgroups according to baseline pulse pressure ≥ 75 mmHg or < 75 mmHg, as 75 mmHg corresponded to the 75th percentile in the distribution of baseline pulse pressure. Those with a baseline pulse pressure ≥ 75 mmHg were older, had higher MBP and more microalbuminuria, and 60% were treated with antihypertensive drugs. Mean values of baseline pulse pressure in the ≥ 75 mmHg and < 75 mmHg subgroups were 85.1 mmHg and 58.4 mmHg, respectively, a difference of 27 mmHg.

Table 3 also shows the corresponding baseline characteristics in the subgroup of 5521 patients with mean pulse pressure ≥ 75 mmHg or < 75 mmHg, as 75 mmHg corresponded to the 75th percentile in the distribution of mean PP. Mean values of pulse pressure in these two groups were 83.7 mmHg and 60.1 mmHg, respectively, a difference of 24 mmHg.

3.1. Pulse pressure and cardiovascular events

Cox regression analysis was performed to determine HRs (95% CI) for pulse pressure ≥ 75 mmHg compared with < 75 mmHg, and first-incident fatal/nonfatal CHD, stroke and CVD, during the mean 5.6 years of follow-up. With baseline (Table 1) and mean (Table 2) pulse pressures, crude HRs for CHD were 1.51 (1.35–1.70) and 1.59 (1.31–1.92), respectively (P < 0.001, Model 1).

The corresponding HRs for CHD were 1.48 (1.30–1.68) and 1.58 (1.29–1.93), respectively (P < 0.001), after adjusting for age, diabetes duration, HbA<sub>1c</sub>, BMI, smoking status, lipid-lowering drugs, cumulative microalbuminuria, antihypertensive drugs and type of hypoglycaemic treatment (Model 2). HRs for CHD were further attenuated after adjusting for age and MBP (Model 3: 1.23 (1.07–1.40; P = 0.003) and 1.32 (1.07–1.62; P = 0.009), respectively.

Crude HRs for stroke with baseline pulse pressure ≥ 75 mmHg vs < 75 mmHg and mean pulse pressure ≥ 75 mmHg vs < 75 mmHg were 1.75 (1.50–2.03) and 1.76 (1.36–2.29) (P < 0.001; Model 1), respectively, but were nonsignificant after adjustment.
adjustment according to Model 3: 1.17 (0.98–1.39) and 1.21 (0.90–1.61), respectively. Crude HRs for CVD with baseline pulse pressure \( \geq 75 \text{ mmHg} \) vs \(< 75 \text{ mmHg}\) and mean pulse pressure \( \geq 75 \text{ mmHg} \) vs \(< 75 \text{ mmHg}\) were 1.63 (1.48–1.79) and 1.64 (1.40–1.93) \((P < 0.001; \text{Model 1})\), and 1.23 (1.10–1.37; \(P < 0.001\)) and 1.28 (1.07–1.52; \(P = 0.007\)) after adjustment according to Model 3.

HRs for baseline pulse pressure increased per quartile in relation to risk of CHD, stroke and CVD, adjusted according to Model 3, and were 1.09 (1.03–1.16; \(P = 0.004\)), 1.14 (1.05–1.23; \(P = 0.002\)) and 1.11 (1.05–1.17; \(P < 0.001\)), respectively. The effect of pulse pressure on CHD, stroke and CVD was consistent across subgroups, as defined by all covariables in the study \((P \text{ value for heterogeneity} > 0.05 \text{ in all comparisons due to no interaction with the subgroup covariables})\).

### 3.2. Population-attributable risk proportions

The percent partial population-attributable risk with mean pulse pressure \( \geq 75 \text{ mmHg} \) in the subgroup of 5521 patients was 15\% (95\% CI: 9–21\%) for fatal/nonfatal CHD, 17\% (8–26\%) for fatal/nonfatal stroke and 17\% (11–22\%) for fatal/nonfatal CVD, after adjustment according to Model 2. In contrast, after adjustment according to Model 3, the percent partial population-attributable risk with mean pulse pressure \( \geq 75 \text{ mmHg} \) was 10\% (3–17\%) for CHD, 8\% (−3–18\%) for stroke and 10\% (3–16\%) for CVD.

### 3.3. Pulse pressure and baseline variables

Univariate regression analyses showed that baseline pulse pressure in all 11,128 patients, and mean pulse pressure during the study in the subgroup of 5521 patients increased by 8.0 mmHg and 6.0 mmHg, respectively, per 10 mmHg increase in baseline MBP \((P < 0.001)\), while also increasing by 7.7 mmHg and 6.8 mmHg, respectively, per 10-year increase in age \((P < 0.001)\).

Multiple regression analyses, all including baseline MBP (per SD), age (per SD) and microalbuminuria as independent variables vs either baseline or mean pulse pressure as dependent variables, and adjusted for gender, revealed that MBP was independently associated with both baseline and mean pulse pressures—regression coefficient \(\pm SE\): 7.5 \pm 0.1 and 3.8 \pm 0.2, respectively \((P < 0.001)\), and that age was somewhat less strongly associated with baseline and mean pulse pressures – 4.2 ± 0.1 and 3.8 ± 0.2, respectively \((P < 0.001)\). In addition, microalbuminuria was also independently associated with baseline and mean pulse pressures: 2.0 ± 0.2 and 1.4 ± 0.4, respectively \((P < 0.001)\).

### 4. Discussion

The main finding of this large-scale, observational, prospective study of type 2 diabetic patients was that elevated pulse pressure is a strong risk predictor of fatal/nonfatal CHD, stroke and CVD, independent of other cardiovascular risk factors and clinical characteristics. Furthermore, if elevated pulse pressure could be avoided in such a cohort, then 15–17\% of all cases of CVD might be prevented independent of other risk factors, and 10\% might be prevented after also adjusting for age and MBP.

Blood pressure comprises two components: a stable component (MBP); and a pulsatile component (pulse pressure). The MBP is the pressure that distributes a steady flow of blood and oxygen to the tissues and organs, and reflects the total vascular resistance and the wall-to-lumen ratio in resistance vessels.
systolic BP that could promote cardiac hypertrophy and increase the presence of arterial stiffness is dependent on an increase in central arteries. The increase in pulse pressure observed in changes in the structure and functioning of the larger peripheral arteries. In younger subjects, an increased pulse pressure generally reflects an increased stroke volume ejected from the heart, and of the intermittent ventricular ejection from the heart, and of the exchange capacities of the central (aorta) and larger peripheral arteries. In younger subjects, an increased pulse pressure generally reflects arterial rigidity due to changes in the structure and functioning of the larger peripheral and central arteries. The increase in pulse pressure observed in the presence of arterial stiffness is dependent on an increase in systolic BP that could promote cardiac hypertrophy and increase the risk of stroke. It is also influenced by a concomitant decrease in diastolic BP, thereby compromising coronary perfusion that, in turn, might increase the risk of myocardial ischaemia [4,9,10].

Previously, several studies have shown that elevated brachial pulse pressure is a significant predictor of left ventricular hypertrophy, CHD, stroke, heart failure, and cardiovascular and total mortality in hypertensive patients as well as in the general population [10,23–28]. Increased peripheral arterial rigidity, estimated directly by increased pulse-wave velocity, has also been associated with left ventricular enlargement [29], and an increased risk of cardiovascular and total mortality, in patients with hypertension [9,10,30,31].

Arterial stiffness is increased in type 2 diabetic patients [4–8], and stiffer arteries and the consequently steeper increases in pulse pressure are seen with increasing age in such patients [12]. Furthermore, according to two earlier studies of type 2 diabetic patients [12,13], pulse pressure and peripheral arterial rigidity, estimated directly by increased pulse-wave velocity [32], were predictive of future CHD and CVD mortality. Schram et al. [12] examined 208 type 2 diabetic patients, aged 50–74 years, during 8.6 years of follow-up, and found HRs of 1.27 (95% CI 1.00–1.61) for CVD mortality per 10 mmHg increase in pulse pressure on Cox regression analysis, after adjusting for gender, age and MBP. Further adjustment for other risk factors gave similar HRs. Cockercroft et al. [13] examined 2911 type 2 diabetic patients (mean age 66 years) during 4 years of follow-up, and found a significant odds-ratio of 1.69 (P = 0.002) for fatal/nonfatal CHD per 10 mmHg increase in pulse pressure on logistic-regression analysis, after adjusting for gender, age, smoking status and total-to-HDL cholesterol ratio.

The present observational study has demonstrated, to our knowledge for the first time in a large sample of more than 11,000 patients with type 2 diabetes, a strong, statistically significant and independently increased risk of CVD with elevated pulse pressure. Adjusted HRs were 1.5 (P < 0.001) for fatal/nonfatal CHD, stroke and CVD with baseline or mean pulse pressure ≥ 75 mmHg compared with < 75 mmHg (a difference of 24–27 mmHg), after adjustment for clinical characteristics and several important cardiovascular risk factors, including cumulative microalbuminuria as a marker of diabetic nephropathy as well as a strong risk factor per se for CHD (Model 2). Furthermore, as age and MBP are important confounding variables of outcome, and also have a relatively strong association with pulse pressure, it should be noted that the HRs were somewhat attenuated, but were nevertheless in the range of 1.2–1.3 for CHD and CVD risk (P = 0.009 to < 0.001) with elevated baseline or mean pulse pressure, after also adjusting for age and MBP (Model 3). The significance of the association between baseline pulse pressure increases per quartile and CVD was weaker in the study by Schram et al. [12] than in the present study, probably because of the lower absolute risk of 7.2 compared with 31.4 events per 1000 person-years.

The increasing baseline and mean pulse pressures were related to baseline MBP (8.0 mmHg and 6.0 mmHg, respectively, per 10 mmHg increase in MBP) and age (7.7 mmHg and 6.8 mmHg, respectively, per 10-year increase in age) on univariate analyses. These associations were significant (P < 0.001), independent of each other on multivariate analyses. Similar findings have also been reported in type 2 diabetic patients by Schram et al. [12], which suggests that age and MBP may interact to bring about accelerated arterial ageing, as reflected by elevated pulse pressures in middle-aged and older diabetic patients. Static wall stress increases with higher MBP, resulting in tissue fatigue characterized by alterations in collagen and elastin content that could also lead to increased arterial stiffness [33,34].

Cumulative microalbuminuria per se is a strong risk factor for CHD. Indeed, an association between increased pulse pressure and microalbuminuria was reported in a cross-sectional survey of nondiabetic hypertensive and atherosclerotic men [35], suggesting that increased pulse pressure is a predictor of microalbuminuria, although the opposite – that microalbuminuria is a predictor of increased pulse pressure – cannot be excluded. We found baseline cumulative microalbuminuria to be significantly related to pulse pressure, independent of both age and baseline MBP on multivariate analyses. However, as this association included mean and baseline pulse pressures, this analysis could not determine with certainty which of them – cumulative microalbuminuria or pulse pressure – was the predictor.

Thus, a markedly increased risk for CVD in the presence of elevated pulse pressure was found in the present study, independent of the effects of age, MBP and cumulative microalbuminuria, among other covariables on these outcomes, suggesting that pulse pressure needs to be reduced in type 2 diabetic patients. Lifestyle changes, such as physical exercise [36], reduced salt intake [37] and increased intake of omega-3 fatty acids [38] can reduce arterial stiffness. However, more evidence is needed to establish the effect of antihypertensive drugs on pulse pressure. Nevertheless, angiotensin-converting enzyme (ACE) inhibitors are purported to have beneficial effects on large artery wall function and morphology, thereby reducing arterial stiffness [39], as has also been shown by aldosterone blockade using spironolactone [40].

The data on hypoglycaemic treatment, diabetes duration, HbA1c, BMI, BP antihypertensive, both antihypertensive and lipid-lowering drugs were found to be reliable in the present study, although smoking data may be somewhat biased due to underreporting by either the patients or examiners. Plasma creatinine was not available in this study, but the use of cumulative microalbuminuria should be a reasonable reflection of the
presence of diabetic nephropathy. Reduced creatinine clearance has been associated with increased vascular stiffness, indicating that kidney alterations may predict vascular rigidity [41]; other established, long-term, predictors of elevated pulse pressure in healthy subjects are fasting glucose, smoking status, BMI and triglycerides [11]. However, creatinine clearance was not a necessary covariate in our study, as the aim was to analyze the effect of pulse pressure on cardiovascular outcomes irrespective of causative mechanisms for increased pulse pressure.

One limitation of the present study was that blood lipid values were not recorded at baseline in the NDR. However, the evidence from previous studies supports the use of lipid-lowering drugs rather than blood lipids as a marker of the presence of hyperlipidaemia. When lipid-lowering drugs were used instead of blood lipids among other risk-factor predictors in a multivariate analysis to elaborate a model for risk prediction of CVD, it was possible to demonstrate an excellent correlation between the predicted risk and observed risk during the follow-up [17]. In addition, two adjusted models (with and without lipid-lowering drugs as covariables) showed the same relative changes in HRs for obesity and cardiovascular events as found in two adjusted models (with and without blood lipids as covariables) in a previous large study [18].

CVD events retrieved from the National Cause of Death and Hospital Discharge Registers were also reliable, according to previous validations of reporting to these registers [19,20]. The age of the included patients was limited to 50–74 years to avoid younger patients, in whom elevated pulse pressure most likely reflects increased stroke volume, and to avoid the risk of less-precise endpoint diagnoses in older patients. Also, the applied definition of type 2 diabetes should have excluded most of the younger patients who might have had latent autoimmune diabetes in adults (LADA).

One strength of the present study was the large numbers of patients, person-years and CVD events, and the high absolute risk of 31.4 CVD events per 1000 person-years during the mean 5.6 years of follow-up. Another strength was the inclusion of a subgroup of patients for mean pulse pressure throughout the study period, and the fact that the effect of pulse pressure on the outcome was consistent across subgroups, as defined by the covariates in this observational study. Furthermore, patients were collected from the general diabetes population at primary-care centers and hospital diabetes clinics throughout Sweden, with no exclusions because of the presence or absence of risk factors or comorbidities, as is otherwise often the case in randomized controlled trials; the limitations as a result of such strict inclusion and exclusion criteria can limit the applicability of any study findings to the general patient population.

In conclusion, increased pulse pressure is a powerful independent predictor of incident CVD in patients with type 2 diabetes, and a marked risk reduction appears to be possible if pulse pressure is lowered, underscoring the need for therapeutic measures to decrease pulse pressure in such patients. In addition to older age, higher baseline MBP and cumulative microalbuminuria were also independently related to higher baseline and mean pulse pressures.

Conflicts of interest

The authors have no conflicts of interest to declare.

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