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ARTICLE

Blood pressure level and risk of major cardiovascular events and all-cause of mortality in patients with type 2 diabetes and renal impairment: an observational study from the Swedish National Diabetes Register

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Abstract
Aims/hypothesis We assessed the relationship between BP and risk of cardiovascular events (CVEs) and all-cause mortality in patients with type 2 diabetes and renal impairment (estimated GFR<60 ml min^{-1} 1.73 m^{-2}) treated in clinical practice.
Methods A total of 33,356 patients (aged 75±9 years, diabetes duration of 10±8 years) with at least one serum creatinine and BP value available in the Swedish National Diabetes Register between 2005 and 2007 were followed up until 2011 or death. The relationships between mean BPs, CVEs and all-cause mortality were examined using time-dependent Cox models to estimate HRs, adjusting for cardiovascular risk factors and ongoing medications.
Results During the follow-up period (mean 5.3 years), 11,317 CVEs and 10,738 deaths occurred. The lowest risks of CVEs and all-cause mortality were observed with a systolic BP (SBP) of 135–139 and a diastolic BP (DBP) of 72–74 mmHg, and the highest risks were observed for those with SBP intervals 80–120 (CVE HR 2.3 [95% CI 2.0, 2.6] and all-cause mortality HR 2.4, [95% CI 2.1, 2.7]) and 160–230 mmHg (CVE HR 3.0 [95% CI 2.6, 3.3] and all-cause mortality HR 2.0 [95% CI 1.8–2.3]) and DBP intervals 40–63 mmHg (CVE HR 2.0 [95% CI 1.8, 2.2], all-cause mortality HR 2.0 [95% CI 1.8, 2.2]) and 83–125 mmHg (CVE HR 2.3 [95% CI 2.0, 2.5], all-cause mortality HR 2.3 [95% CI 2.0, 2.6]).
Conclusions/interpretation In this nationwide cohort of patients with type 2 diabetes and renal impairment, the risk of CVEs and all-cause mortality increased significantly with both high and low BPs, while an SBP of 135–139 mmHg and DBP of 72–74 mmHg were associated with the lowest risks of CVEs and death.

Keywords Blood pressure · Cardiovascular disease · Epidemiology and outcomes · Renal function · Type 2 diabetes

Abbreviations

CHF	Chronic heart failure
CVD	Cardiovascular disease
CVE	Cardiovascular event
DBP	Diastolic BP
eGFR	Estimated GFR
MAP	Mean arterial pressure
MI	Myocardial infarction
NDR	Swedish National Diabetes Register
PAD	Peripheral arterial disease
PP	Pulse pressure
RI	Renal impairment
SBP	Systolic BP
VADT	Veterans Affairs Diabetes Trial

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Introduction

Hypertension is present in 20–55% of patients at the time of diagnosis of type 2 diabetes [1]. Elevated BP is associated with an increase in the risk of cardiovascular disease (CVD) and death in the general population [2–5]; when hypertension is combined with diabetes, the CVD risk increases further [6]. Previous studies have shown that in patients with type 2 diabetes a systolic BP (SBP) of 140 mmHg or higher increases the risk of CHD, stroke, cardiovascular events (CVEs) and all-cause mortality [7–10]. In addition, other studies have shown an increase in the risk of CVEs and mortality when SBP is reduced to below 120 mmHg [11, 12]. A diastolic BP (DBP) of <70 mmHg at baseline and during follow-up has been associated with a significantly increased risk of CVD [13].

Based on these studies, a hypothesis of a J-shaped relationship between treated BP and the risk of CVEs and mortality has been proposed and is still under debate [7, 14]. The current treatment guidelines by the ADA and EASD, however, recommend a BP target in patients with diabetes of 140/90 mmHg unless signs of end-organ damage such as albuminuria and retinopathy are present; if so, a stricter BP target of 130/80 mmHg is recommended [15]. In patients with renal impairment (RI), the Kidney Disease: Improving Global Outcomes workgroup recommend a BP of <140/90 mmHg in the absence of albuminuria and <130/80 mmHg in the presence of albuminuria to reduce the risk of CVD. In addition, the guidelines mention that other factors such as age and cardiovascular comorbidities should be considered [16].

Optimal BP levels in high risk patients have thus not yet been established. The aim of this study was therefore to assess the relationship between BP level and the risk of cardiovascular events and all-cause mortality in a nationwide observational study of unselected patients with type 2 diabetes and RI who were treated in clinical practice and reported to the Swedish National Diabetes Register (NDR).

Patients and methods

The NDR The NDR was initiated in 1996. Information is collected at least once yearly during patient visits and reported to the NDR. All patients provide informed consent to be registered before inclusion, and all information is stored in a central database. The Regional Ethics Review Board at the University of Gothenburg approved the study, which was performed in accordance with the Declaration of Helsinki.

We included 33,356 patients with type 2 diabetes and RI (estimated GFR [eGFR] of <60 ml min^{-1} 1.73 m^{-2}). Inclusion criteria were a diagnosis of type 2 diabetes with a reported serum creatinine value between >20 and <800 μmol/l at baseline. Reported type 2 diabetes was defined as patients having a reported treatment with diet only or with oral glucose-lowering agents only, or an onset of diabetes at 40 years or older and treated with insulin either alone or combined with oral glucose-lowering agents. Patients with an extreme body composition, i.e. BMI ≤18 or ≥45 kg/m^2 (n=359) were excluded. In addition, patients with severe RI (eGFR <15 ml min^{-1} 1.73 m^{-2}; n=274) were excluded because reporting of this patient group to the NDR is limited and highly selective. The clinical characteristics of patients with type 2 diabetes fulfilling the same inclusion criteria but with normal renal function (n=117,947) are given in electronic supplementary material (ESM) Table 1 for comparison.

Examinations at baseline BP was determined as the mean value of the reported BPs from baseline to an endpoint or the end of the study (usually with annual reporting). All BPs used in this study are the BPs reported to the NDR, and according to the instructions they should be taken according to Swedish standard for BP recording. The Swedish standard for BP recording is the mean value (mmHg) of two supine readings (Korotkoff I–V) with a cuff of an appropriate size, after at least 5 min of rest.

Analyses of serum creatinine, HbA_{1c} and blood lipids were performed at local laboratories. Renal function expressed as the eGFR (in millilitres per minute per 1.73 m^2) was calculated using the Modification of Diet in Renal Disease study equation [17]. Albuminuria was defined as micro- or macroalbuminuria, i.e. a urinary AER of 20–200 or >200 μg/min in two out of three consecutive tests at baseline. A smoker was defined as a patient who smoked one or more cigarette per day or used a pipe, or who had stopped smoking within the past 3 months.

Follow-up and definition of endpoints Patients were followed from the baseline examination (between 1 July 2005 and 31 December 2007) until a first CVE (primary endpoint) and/or death, or otherwise until 31 December 2011. The mean follow-up time was 5.3 years. A CVE was defined as CHD, stroke or peripheral arterial disease (PAD), whichever came first, and the definition of CHD was myocardial infarction (MI) (ICD-10 code I21; www.who.int/classifications/icd/en/), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention and/or coronary artery bypass grafting. Fatal CHD was defined as ICD-10 codes I20–I25, stroke was defined as non-fatal or fatal cerebral infarction, intracerebral haemorrhage or unspecified stroke (ICD-10 codes I61, I63, I64 and I67.9), PAD (ICD-10 codes I70.2, I73.1, I73.9 and I79.2) and congestive heart failure (ICD-10 code I50) [18, 19]. Data on all events were retrieved by data linkage with the Swedish Cause of Death and the Hospital Discharge Registers (National Board of Health and Welfare, Sweden), which is a reliable validated alternative to revised hospital discharge records and death certificates [20, 21].

Table 1 Baseline clinical and biochemical characteristics in patients with type 2 diabetes and RI[a] with and without albuminuria[b]

Variables	RI without albuminuria (n=23,441)	RI with albuminuria (n=9,915)	p value
Age (years)	75±9	75±9	0.003
Diabetes duration (years)	9±8	12±8	<0.0001
HbA_{1c} (mmol/mol)	52±11	56±13	<0.0001
HbA_{1c} (%)	6.9±1.2	7.3±1.1	<0.0001
SBP (mmHg)	140±18	143±20	<0.0001
DBP (mmHg)	74±10	75±10	<0.0001
BMI (kg/m^2)	29±5	29±5	<0.0001
Total cholesterol (mmol/l)	4.9±1.1	4.8±1.0	<0.0001
LDL-cholesterol (mmol/l)	2.7±0.9	2.6±1.0	<0.0001
HDL-cholesterol (mmol/l)	1.3±0.4	1.4±0.4	<0.0001
Triacylglycerol (mmol/l)	1.9±1.1	2.1±1.3	<0.0001
Serum creatinine (μmol/l)	108±23	130±40	<0.0001
eGFR (ml min^{-1} 1.73 m^{-2})[c]	49±8	45±11	<0.0001
Male (%)	36	59	<0.0001
Smokers (%)	7	10	<0.0001
Any retinopathy (%)	28	48	<0.0001
History of CVD (%)	29	37	<0.0001
History of CHF (%)	13	18	<0.0001
Diabetes treatment			
Diet only (%)	29	16	<0.0001
Oral glucose-lowering drug (%)	37	33	<0.0001
Insulin+oral glucose-lowering drug (%)	15	22	<0.0001
Insulin only (%)	19	29	<0.0001
Lipid-lowering drug (%)	54	58	<0.0001
Antihypertensive drug (%)	86	89	<0.0001
Microalbuminuria[d] (%)	–	60	
Macroalbuminuria[e] (%)	–	40	

Data are means±SD or frequencies (%); missing data for triacylglycerol and HDL-cholesterol (n=11,097); LDL-cholesterol (n=7,749); HbA_{1c} (n=276); lipid-lowering medication (n=1,437); smokers (n=2,556); CVD represents CHD and/or stroke

[a] eGFR <60 ml min^{-1} 1.73 m^{-2}

[b] Mean follow-up time 5.3 years

[c] eGFR according to the Modification of Diet in Renal Disease study equation

[d] Urinary AER 20–200 mg/min

[e] Urinary AER >200 mg/min

Statistical methods Baseline clinical and biochemical characteristics are presented as mean values±SD or as proportions (n, %) in Table 1. Patients were categorised into ten groups (deciles) according to SBP or DBP (approximately 3,336 patients in each group). We used time-dependent Cox models to estimate HRs with 95% CIs to examine the relationship between the two mean BPs, the SBP and DBP levels, CVEs and all-cause mortality. Proportional hazards assumptions were established for all time-dependent covariates. Models were adjusted for the following covariants: age, sex, diabetes duration HbA_{1c}, BMI, LDL-cholesterol, the ratio between serum triacylglycerol and HDL-cholesterol, smoking, a previous history of CVD and chronic heart failure (CHF), ongoing treatment with antihypertensive, lipid- and glucose-lowering medications. Crude associations between BP and cardiovascular outcome with and without adjustment for potential confounders were examined in different models. The group with lowest cardiovascular outcome rate was used as the reference group (HR=1). Interactions between mean SBP or DBP and the covariates were tested by maximum likelihood estimation and found to be non-significant (p>0.05) for all covariates.

In order to analyse non-linear relationships, we included both SBP and the squares of SBP for CVE (1-survival rate) in the Cox model; the same analyses were performed for DBP. We also created splines with nine knots at the decile using the Transreg procedure (Figs 1, 2). All statistical analyses were performed in SAS V. 9.3 (SAS Institute, Cary, NC, USA) [22].

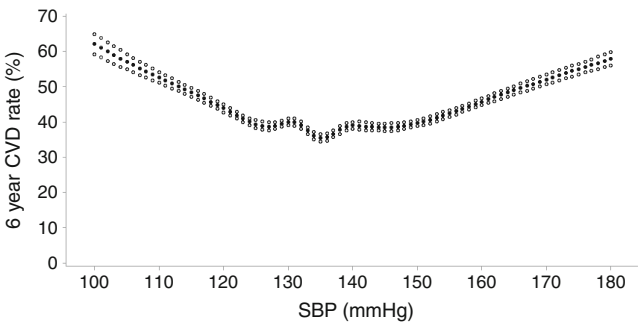

Fig. 1 Spline with nine knots at deciles (filled circles) and 95% CIs (open circles) in patients with type 2 diabetes and RI. The relationship between SBP as a continuous variable and the square of SBP for analysis of non-linear relationship in a Cox regression model, adjustment for covariates as in Table 2 and the 6 year CVD (= CVE) rate

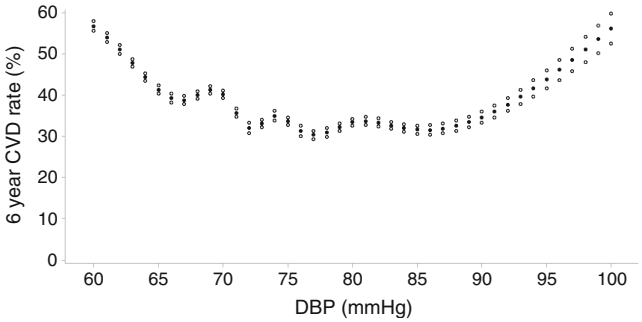

Fig. 2 Spline with nine knots at deciles (filled circles) and 95% CIs (open circles) in patients with type 2 diabetes and RI. The relationship between the DBP as a continuous variable and the square of DBP for analysis of non-linear relationship in a Cox regression model, adjustment for covariates as in Table 3, and the 6 year CVD (= CVE) rate

Results

Clinical and biochemical characteristics at baseline The mean overall eGFR in patients with RI (N=33,356) was 48.2±9.4 ml min^{-1} 1.73 m^{-2}; thus, the majority of patients with RI had stage 3 chronic kidney disease. Seventy per cent of patients with RI were normoalbuminuric and one-third of patients with RI had previous CVD at the beginning of the study (shown in ESM Table 1). Clinical and biochemical characteristics of patients with type 2 diabetes and RI with and without albuminuria at baseline are shown in Table 1. Sixty per cent of patients with albuminuria had microalbuminuria and 40% had macroalbuminuria. Patients with albuminuria had a significantly longer diabetes duration, worse glycaemic control, higher mean SBP but lower DBP, i.e. a higher pulse pressure (PP), in spite of more antihypertensive treatment compared with normoalbuminuric patients. Patients with albuminuria were more often men and smokers and more often had a history of CVD, CHF and retinopathy at baseline.

Association between SBP and both cardiovascular events and all-cause mortality in patients with RI During the follow-up period, 11,317 (34%) CVEs were observed, including 7,704 (23%) episodes of CHD and 2,284 (6.8%) of stroke. Overall, 10,738 (32%) patients died. The two most common causes of death were CVD (34%) and malignancies (18%). Table 2 displays the incidence and HRs of CVEs and all-cause mortality in each group by deciles of overall reported mean SBP. The lowest incidence of CVEs was observed in patients with a SBP of 135–139 mmHg (n=719, 21.7%). Approximately half of patients with the lowest SBP (80–120 mmHg, n=1,526 [46.0%], HR 2.3 [95% CI 2.0, 2.6]) and half of patients with the highest SBP (160–230 mmHg, n=1,621 [48.8%], HR 3.0 [95% CI 2.6, 3.3]) had a CVE during the follow-up period. Among patients with CVEs, the highest incidence of CHD was seen in patients with a SBP of 80–120 mmHg (n=1,211 [36.5%], HR 2.6 [95% CI 2.3, 3.0]) and a SBP of 160–230 mmHg (n=1,000 [31.1%] HR 2.9 [95% CI 2.5, 3.4]). The incidence of stroke was highest in patients with a mean SBP of 160–230 mmHg (n=376 [11%], HR 2.6 [95% CI 2.0, 3.4]). Half (51%) of patients with a SBP of 80–120 mmHg (HR 2.4 [95% CI 2.1, 2.7]) and 46% of patients with a SBP of

Table 2 Incidence of stroke, CHD, stroke, CVEs and all-cause mortality, and HRs of CVEs and all-cause mortality by deciles of mean SBP[a]

SBP interval (mmHg)	SBP (mmHg)	Stroke (*n*/%)	CHD[b] (*n*/%)	CVE[c] (*n*/%)	CVE[d] (HR [95% CI])	All-cause mortality (*n*/%)	All-cause mortality[e] (HR [95% CI])
80–120	114±7	198/6.0	1,211/36.5	1,526/46.0	2.30 (2.03, 2.60)	1,686/50.8	2.40 (2.11, 2.73)
120–127	124±2	193/5.8	719/21.7	1,001/30.2	1.37 (1.20, 1.55)	963/29.0	1.40 (1.22, 1.60)
128–131	130±1	200/6.0	808/24.3	1,128/34.0	1.64 (1.44, 1.86)	1,057/31.8	1.53 (1.35, 1.76)
131–135	134±1	186/5.6	673/20.3	956/28.8	1.36 (1.20, 1.55)	837/25.2	1.22 (1.05, 1.41)
135–139	137±1	169/5.1	458/13.8	719/21.7	1 (reference group)	678/20.4	1 (reference group)
139–142	140±1	250/7.5	826/24.9	1,201/36.2	1.78 (1.57, 2.02)	1,118/33.7	1.61 (1.41, 1.84)
142–146	144±1	209/6.3	662/19.7	994/30.0	1.39 (1.22, 1.58)	893/26.9	1.23 (1.07, 1.42)
146–151	149±2	254/7.6	718/21.6	1,153/34.7	1.77 (1.56, 2.01)	983/29.6	1.30 (1.13, 1.50)
151–160	155±3	249/7.5	629/18.9	1,018/30.7	1.46 (1.28, 1.66)	987/29.6	1.27 (1.10, 1.46)
160–230	169±10	376/11.3	1,000/31.1	1,621/48.8	2.95 (2.62, 3.34)	1,536/46.3	2.02 (1.78, 2.30)

BPs are means±SD

[a] All patients had RI (eGFR <60 ml min^{-1} 1.73 m^{-2}); the mean follow-up time was 5.3 years

[b] Fatal and non-fatal CHD

[c] Fatal and non-fatal CVE

[d] HR (95% CI) adjusted for age, diabetes duration, sex, HbA_{1c}, BMI, presence/absence of albuminuria, smoking, LDL-cholesterol, triacylglycerol/HDL, history of CVD, previous history of CHF, and antihypertensive and lipid-lowering treatment

[e] SBP of 135–139 mmHg was defined as the reference group

160–230 mmHg (HR 2.0 [95% CI 1.8, 2.3]) died during the follow-up period. An analysis also adjusting for DBP is shown in ESM Table 2.

When using only the initial reported SBP at baseline instead of the overall reported mean SBP, overall HRs were lower and a significantly higher HR was found only for all-cause mortality in the lowest SBP interval (80–120 mmHg, HR 1.25 [95% CI 1.10, 1.41]; ESM Table 3).

As SBP and/or DBP may change prior to a CVE or death, we performed analyses in which we censored the last reported SBP before a CVE or death (ESM Table 4). In these analyses, we found the highest risks in the lowest and highest SBP intervals of both CVEs and all-cause mortality (in a similar pattern). However, the HRs were lower overall than when mean BPs were used for CVEs (HR 1.2 [95% CI 1.0, 1.3] vs HR 2.3 [95% CI 2.0, 2.6] for the lowest and HR 1.4 [95% CI 1.2, 1.5] vs HR 2.9 [95% CI 2.6, 3.3] for the highest SBP interval) and for all-cause mortality (HR 1.0 [95% CI 0.96, 1.3] vs HR 2.4 [95% CI 2.1, 2.7] for the lowest and HR 1.7 [95% CI 1.5, 1.9] vs HR 2.0 [95% CI 1.8, 2.3] for the highest SBP interval).

Unadjusted analyses assessing the relationship of both SBP and DBP with CVE or all-cause mortality show similar patterns, but the magnitudes of risk (i.e. HRs) are higher for all BP groups (data shown in ESM Tables 5 and 6).

When patients with prior CVD and/or CHF were excluded, findings were very similar to those previously described, such that the lowest and highest SBP levels were still associated with the highest risk of CVEs and all-cause mortality (shown in ESM Table 7). It should, however, be noted that the HRs for CVEs and all-cause mortality were somewhat higher overall in the different SBP intervals when comparing patients without prior CVD and/or CHF with all patients.

In addition, stratification for the absence or presence of albuminuria did not alter results substantially (shown in ESM Table 8 and 9). However, it should be noted that the HR for CVE in the lowest SBP group was slightly higher for normoalbuminuric patients than for those with albuminuria (HR 2.4 [95% CI 2.1, 2.8] vs HR 2.2 [95% CI 1.8, 2.6], respectively).

Unadjusted analyses of interaction between both SBP and DBP and potential confounders on risk of CVE and all-cause mortality were also performed. These data for are shown in ESM Tables 10 and 11.

The non-linear spline of the 6 year rate of CVEs by mean SBP as a continuous variable is shown in Fig. 1. The risk of CVE was adjusted as described for the Cox model in Table 2. A progressively increased risk of CVEs was seen with both SBP <110 mmHg and SBP >150 mmHg. In addition, and interestingly, slight increases in risk of CVEs were found for SBPs of 130 and 140 mmHg. These increases in HRs mirrored the results found in the Cox model for the SBP intervals 128–131 and 139–142 mmHg in Table 2.

Association between DBP and both cardiovascular events and all-cause mortality in patients with RI Table 3 gives the prevalence and HRs of CVEs and all-cause mortality in each group by DBP. Patients with DBP of 40–63 mmHg and 83–125 mmHg had the highest incidence and risk of CVEs and all-cause mortality: CVEs (n=1,625 [49.0%], HR 2.0 [95% CI 1.8, 2.2]) and all-cause mortality (n=1,662 [50.1%], HR 2.0 [95% CI 1.8, 2.2]), and CVEs (n=1,235 [37%], HR 2.3 [95% CI 2.0, 2.5]) and all-cause mortality (n=1,151 [35%], HR 2.3 [95% CI 2.0, 2.6]), respectively. The highest incidence of CHD occurred in patients with very low DBP (40–63 mmHg, n=1,197 [36.1%], HR 2.1 [95% CI 1.8, 2.4]) but, as expected, the highest incidence of stroke was found in patients with the highest DBP (83–125 mmHg, n=323 [9.7%], HR 2.6 [95% CI 2.0, 3.4]). An additional analysis adjusting for SBP is shown in ESM Table 12.

In a complementary analysis, we censored the last reported DBP before a CVE or death (data presented in ESM Table 13). The highest risks of CVEs and all-cause mortality were found in the lowest and highest DBP intervals but the HRs were lower overall compared with using the mean BPs, except for all-cause mortality in the highest DBP interval (83–125 mmHg), where the HRs were nearly identical in the two different analyses (HR 2.3 [95% CI 2.0, 2.6] for both).

The non-linear spline of the 6 year rate of CVEs with mean DBP as a continuous variable is shown in Fig. 2. The risk of CVE was adjusted as described for the Cox model in Table 3. The risk of CVEs increased significantly with a DBP of <65 and >95 mmHg. A U-shaped relationship between DBP and CVEs was found, except for DBPs around 70, 75 and 80 mmHg. These increases in HRs mirror the results found in the Cox model for the DBP intervals 70–72, 74–76 and 78–80 mmHg shown in Table 3.

Association between mean arterial BP and PP, cardiovascular events and all-cause mortality in patients with RI The highest incidence of CVEs (n=1,570 [47.3%]) and all-cause mortality (n=1,668 [50.3%]) were seen in the lowest mean arterial pressure (MAP) interval (53–85 mmHg). Using the MAP interval 93–95 mmHg as a reference group, the highest risk of CVEs (adjusted HR 2.1 95% CI 1.9, 2.4) and all-cause mortality (adjusted HR 1.60 [95% CI 1.4, 1.8]; both p<0.001) were seen for the highest MAP interval (107–153 mmHg), as shown in ESM Table 14.

The highest incidence of CVD (n=1,543 [46.5%]) and all-cause of mortality (n=1,517 [45.7%]) was seen for the highest PP interval (85–154 mmHg). Using a PP of 61–65 mmHg as the reference group, the lowest PP interval (15–49 mmHg) had the highest risk of all-cause mortality (adjusted HR 2.1 [95% CI 1.8, 2.4]) and the highest PP interval (85–154 mmHg) had the highest risk of CVEs (adjusted HR 2.0 [95% CI 1.8, 2.2]). When PP was also adjusted for MAP, the HRs for CVEs and

Table 3 Incidence of stroke, CHD, stroke, CVEs, all-cause mortality and HRs of CVE and all-cause mortality by deciles of mean DBP[a]

DBP interval (mmHg)	DBP (mmHg)	Stroke (*n*/%)	CHD[b] (*n*/%)	CVE[c] (*n*/%)	CVE[d] (HR [95% CI])	All-cause mortality (*n*/%)	All-cause mortality[e] (HR [95% CI])
40–63	50±3	226/6.8	1,197/36.1	1,625/49.0	2.0 (1.80, 2.22)	1,662/50.1	2.00 (1.78, 2.24)
63–67	65±1	168/5.1	857/25.8	1,141/34.4	1.21 (1.07, 1.37)	1,116/33.6	1.21 (1.07, 1.37)
67–70	68±1	202/6.1	658/19.8	999/30.1	1.15 (1.01, 1.30)	911/27.4	1.14 (1.03, 1.30)
70–72	70±0.5	246/7.4	952/28.7	1,349/40.6	1.88 (1.67, 2.11)	1,311/39.5	1.88 (1.67, 2.11)
72–74	73±1	193/5.8	575/17.3	870/26.2	1 (reference group)	801/24.1	1 (reference group)
74–76	75±0.5	222/6.7	726/21.9	1,076/32.4	1.43 (1.26, 1.62)	1,007/30.3	1.44 (1.28, 1.63)
76–78	77±1	197/5.9	541/16.3	837/25.2	1.23 (1.08, 1.40)	706/21.3	1.24 (1.01, 1.41)
78–80	79±1	261/7.9	753/22.7	1,154/34.8	1.78 (1.58, 2.01)	1,091/32.9	1.81 (1.60, 2.04)
80–83	81±1	246/7.4	655/19.7	1,031/31.1	1.60 (1.40, 1.80)	982/29.6	1.62 (1.42, 1.82)
83–125	88±4	323/9.7	790/23.80	1,235/37.2	2.26 (2.00, 2.54)	1,151/34.7	2.30 (2.03, 2.59)

BPs are means±SD

[a] All patients had RI (eGFR <60 ml min^{-1} 1.73 m^{-2}); the mean follow-up time was 5.3 years

[b] Fatal and non-fatal CHD

[c] Fatal and non-fatal CVD

[d] HR (95% CI) adjusted for age, diabetes duration, sex, HbA_{1c}, BMI, presence/absence of albuminuria, smoking, LDL-cholesterol, triacylglycerol/HDL, history of CVD, previous history of CHF, and antihypertensive and lipid-lowering treatment

[e] DBP of 72–74 mmHg was defined as the reference group

all-cause mortality did not change to a major extent. These data are shown in the ESM Tables 15 and 16.

Discussion

In this nationwide observational study of more than 30,000 patients with type 2 diabetes and RI followed for a median of 5.3 years, we confirm that patients with the lowest and highest mean systolic and diastolic arterial BP intervals are exposed to the highest risks of CVEs and all-cause mortality. A SBP level of 135–139 and a DBP level of 72–74 mmHg were associated with the lowest risks of CVEs or death in this cohort of patients. A low PP was associated with a high risk of death, but a high PP was associated with an increased risk of a CVE.

Clinical trials have previously shown that a high BP increases the risk of CVEs (especially stroke) and all-cause mortality in patients with type 2 diabetes [23, 24]. However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP study in patients with nearly to normal renal function, a target SBP of ≤120 mmHg did not reduce the risk of major CVE compared with a SBP of ≤140 mmHg [10]. Also, in a subgroup analysis of participants with diabetes and coronary artery disease in the International Verapamil SR-Trandolapril (INVEST) study, tight control of SBP (≤130 mmHg) was not associated with improved cardiovascular outcomes compared with conventional BP control (130–140 mmHg), and a non-significant increase in the rate of all-cause mortality was noted with tight BP control [11]. A J-shaped relationship was found in the Veterans Affairs Diabetes Trial (VADT), in which a higher risk of CVEs was found in patients with SBP ≥140 mmHg and DBP <70 mmHg [13].

Fewer studies have addressed the association between low BP levels and mortality in patients with diabetes and mild to moderate RI, and these studies have reported slightly varying results. In a post hoc analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT), 1,590 patients with type 2 diabetes, albuminuria and mainly mild renal dysfunction, SBP of <120 mmHg was associated with a higher risk of CV mortality and CVEs. In addition, DBP of <85 mmHg was associated with a non-significantly higher risk of all-cause mortality and a significantly higher risk of MI but lower risk of stroke [25]. In the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) trial in which 24% of all participants had type 2 diabetes, there was no improvement in fatal or non-fatal CVEs, except for stroke, when reducing the SBP below 130 mmHg [26]. Similar results were later found in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) and the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trials: findings showed no benefit with respect to mortality or CVEs and that intensive treatment with dual renin-angiotensin-aldosterone system (RAAS) blockade even may even be harmful. The effects of BP lowering and/or RAAS blockade are therefore still under debate [27, 28].

A J-shaped relationship between BP and CVEs or mortality has been discussed in several reports and was, for example, found in the VADT where a higher risk of CVEs was seen in patients with SBP ≥140 mmHg and DBP <70 mmHg [13],

indicating that both too high BP and too low BP are associated with an increased risk of CVEs and mortality [13]. In patients with RI, a low BP is likely to be a marker of either pre-existing CVD (including CHF) or treatment of these conditions with agents with BP-lowering properties, or both [29, 30].

In the present study, a more U-shaped relationship was observed between mean BP levels and CVEs despite the fact that only 15% of participants had a history of CHF at baseline and that patients with an eGFR of <15 ml min^{-1} 1.73 m^{-2} were excluded. The mean eGFR was 48±9 ml min^{-1} 1.73 m^{-2}; thus, most patients had only mild to moderate RI. Even so, the number of cardiovascular events and deaths during the follow-up period was very high (CVEs 34%, all-cause mortality 32%) compared with previous studies [31, 32]. When we omitted/censored the last reported BP before a CVE or death, a similar U-shaped pattern was found but the risk estimates were somewhat lower than when using the mean of all BP measurements reported during follow-up. One potential explanation for this U-shaped relationship may be that in this study we divided patients into BP deciles and not according to static BP values, as has been done in other studies.

The risk of CVEs and all-cause mortality was also significantly higher for the lowest and highest MAP intervals (53–85 and 107–153 mmHg). MAP is highly correlated with SBP and DBP, and its value as a better predictor of CVD than SBP and/or DBP has therefore been questioned [33, 34].

We also evaluated the association of PP with both CVEs and all-cause mortality. A high PP is mainly related to increased stiffness in the large arteries, as opposed to a low PP, which is often a marker of low SBP or, rarely, of isolated diastolic hypertension. PP is recognised as a predictor of CVEs and, in agreement with other studies, our result also showed that the risk of CVEs or all-cause mortality is greater for the highest PP interval (85–154 mmHg) [35, 36]. The high risk of death for the lowest PP interval (15–49 mmHg) is likely to be a consequence of low SBP. In this study, the relationship between PP and CVEs was relatively weak and became even weaker when PP was adjusted for MAP. This is consistent with the results of previous studies on the relationships between different BP indices and cardiovascular outcomes [37–39].

Albuminuria was found only in 30% of patients with RI at baseline, in line with previous studies in which the majority of patients with type 2 diabetes and RI were found to be normoalbuminuric [40–42]. Both albuminuria and RI are independent risk factors for CVEs and all-cause mortality in type 2 diabetes, with albuminuria being the strongest risk factor and relevant at all levels of renal function. However, in normoalbuminuric patients, a slight reduction in renal function is an important predictor of CVEs and all-cause mortality [43]. The observation that the majority of patients were normoalbuminuric is of interest because treatment guidelines generally recommend even lower BP targets in patients with albuminuria [16]. Although albuminuria has been recognised as a risk factor for CVEs and mortality, adjustments for the presence of albuminuria did not markedly alter the results in the present study [44]. However, an interesting finding of this study was that the risk of CVEs in the lowest BP interval was actually slightly higher for normoalbuminuric patients than for those with albuminuria.

The major strengths of this cohort study are the nationwide scale, large number of patients and the many person-years of observation and number of events. We included patients who received routine treatment according to national guidelines in both primary and secondary care, supporting high external validity and generalisability of our findings to other type 2 diabetes populations. In this study, participants were divided into deciles to reflect the true variation in BP readings, instead of using the traditional BP cutoffs. However, there are some limitations to this study. Since this is an observational study, a cause–effect relationship cannot be established. Moreover, the data were reported by different medical centres and laboratories, which may have slightly affected the accuracy of the data. Only clinical BP measurements were used in this study and not ambulatory BPs, which could be an even better predictor of cardiovascular risk [45, 46]. However, less than 20% of participants had only one reported BP measurement during the study period. It is also plausible that the true BP value for some patients in these BP intervals were higher when measured at the centres, but rounded downwards when reporting in order to comply with national treatment guidelines. This, we think, might explain the slight variation in risk seen for the lower BP intervals, i.e. participants with an SBP interval of 139–142 mmHg or a DBP interval of 78–80 mmHg were shown to exhibit an increased risk of CVE and all-cause mortality compared with those with either a lower or a higher achieved BP. Thus, if a high risk of CVD is attributed to false low BP readings and a CVE occurs, then this is likely to occur. Further standardisation of BP measurements using automated methods could possibly reduce such bias.

In conclusion, the risk of cardiovascular disease and all-cause mortality was very high in patients with type 2 diabetes and RI in clinical practice, and increased significantly with both high and low SBP and DBP in a U-shaped manner. A SBP of 135–139 mmHg and a DBP of 72–74 mmHg were associated with the lowest risks of CVE and all-cause mortality.

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