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Systolic Blood Pressure Variability and Lower Extremity Amputation In a Non-Elderly Population with Diabetes

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Abstract

Objective—Systolic blood pressure (SBP) variability is emerging as a new risk factor for cardiovascular diseases, diabetic nephropathy, and other atherosclerotic conditions. Our objective is to examine whether it has any prognostic value for lower-extremity amputations.

Research Design and Methods—This is a nested case-control study of a cohort of patients with diabetes aged < 60 years and treated in the US Department of Veterans Healthcare system in 2003. They were followed over five years for any above-ankle (major) amputations. For each case with a major amputation (event), we randomly selected up to five matched controls based on age, sex, race/ethnicity, and calendar time. SBP variability was computed using three or more blood pressure measures taken during the one-year period before the event. Patients were classified into quartiles according to their SBP variability.

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Author contributions

EB, MS, and NE derived the hypothesis, planned and supervised all analyses. MS, EB, and MB wrote the paper. ZH conducted analyses. MG, RS, ZH, and NE participated in the interpretation of results and revision of the manuscript.

Conflict of interest

There are no conflicts of interest to disclose.

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Results—The study sample included 1038 cases and 2932 controls. Compared to Quartile 1 (lowest variability), Quartile 2 had 1.4 times (OR = 1.44, 95% CI = 1.00 – 2.07) and Quartiles 3 and 4 (highest) had 2.5 times (OR for Quartile 3 = 2.62, 95% CI = 1.85 – 3.72; OR for Quartile 4 = 2.50, 95% CI = 1.74 – 3.59) higher risk of major amputation (P for trend < 0.001). This gradient relationship held in both normotensive and hypertensive groups as well as for individuals without prior peripheral vascular disease.

Conclusions—This is the first study to show a significant graded relationship between SBP variability and risk of major amputation among non-elderly persons with diabetes.

Keywords

systolic blood pressure; lower-extremity amputation; diabetic complication

Diabetes-related non-traumatic lower-extremity amputation (LEA) is frequent and costly (1; 2). One in four patients with diabetes will develop a foot ulcer in their lifetime, and 5% of them will go on to have an above-ankle (major) amputation (3; 4). In the last quarter century, there has been a steady decrease in the amputation rates in the US (5), UK(6), and other parts of the world (7). The decrease has been rapid at first after the introduction of specialist diabetic foot clinics and multi-disciplinary approaches to diabetic foot care (6; 8; 7). However, the trend has slowed, especially in the US, in the last five to ten years (5).

To further reduce amputation rates among patients with diabetes, we need to identify and target novel risk factors, such as those driving peripheral vascular disease and local perfusion (4). In this regard, a recent resurgence of interest in the potential end-organ damage caused by systolic blood pressure (SBP) variability in individuals with hypertension (9; 10) is notable. SBP variability may increase the risk of LEA through intermittent local ischemia and neuropathy. Both factors predispose patients to ulceration and make limb salvage more difficult.

The objective of this study is to examine the association between SBP variability and LEA. Our hypothesis is that excessive SBP variability is associated with increased risk of major amputations.

Research Design and Methods

We used a nested case-control design to account for the time-dependent nature of SBP variability and to minimize selection bias (11; 12). Cases and controls were selected from a retrospective cohort of patients with diabetes treated in the Department of Veterans Affairs (VA) healthcare system. Cases were defined as those patients who underwent incident major amputations between 2004 and 2008. Controls were required to be amputation-free at least until the date of the case amputation (index date). Controls could subsequently undergo major amputation and be included at that time as a case. All time-dependent covariates (e.g., blood pressures, HbA1c, and cholesterol levels) were taken from the year immediately before the index date.

Cohort

The cohort from which cases and controls were selected included all patients with diabetes treated in the US Department of Veterans Affairs (VA) healthcare system in the fiscal year 2003 (October 1, 2002 to September 30, 2003; all years henceforth are fiscal years) (13). We used inpatient and outpatient records to identify patients with diabetes who had one or more prescriptions of diabetes medications filled in 2003 or had one or more hospitalizations or two or more outpatient visits with a diagnostic code for diabetes (ICD-9-CM 250.xx) in 2002 – 2003, a definition with 93% sensitivity and 97% specificity (14). Patients were excluded if they experienced a major amputation or died between 2002 and 2003. Because we did not have access to Medicare data, we excluded patients who turned 65 years of age before the end of the follow-up (September 30, 2008), mitigating the potential ascertainment bias in study outcomes.

Case Definition

Cases were defined as those individuals in the cohort who underwent a major amputation during the five-year follow-up. We only used the first major amputation for each individual; once a patient was identified as a case, they were no longer followed. A major amputation was defined as above-ankle amputation identified by ICD-9-CM or CPT-4 codes in VA inpatient and outpatient datasets (n=1,217; ICD-9-CM 84.13 – 84.15 and 84.16 – 84.17; CPT-4 27880–27889 and 27590–27598).

Controls

The risk set from which controls were selected (11) consisted of all individuals in the cohort who did not experience a major amputation by the case's index date. Controls were matched for age, sex, and race/ethnicity. Up to five controls were randomly selected for each case (n=4,189, average 2.8 controls per case).

Systolic Blood Pressure Variability

We obtained all outpatient BP measures from the VA Corporate Data Warehouse. We accepted measures of BP as valid if they were between 50 – 300 mm Hg for SBP and 30 – 180 mm Hg for diastolic blood pressure (DBP). We used the date of major amputation as the index date for both cases and their matched controls and all BP measures taken during a 365-day period before extracting the index date. Any BP measures taken during ER visits or a hospitalization were excluded. All individuals who did not have three or more measures taken during this period were excluded from the analysis (n=115 cases, 937 controls). After all exclusions, we additionally found 64 cases without any controls and 320 controls without cases in the same matched set and were excluded. The final sample included 3,970 individuals with 1,038 cases and 2,932 controls (Figure 1).

We computed the within-subject mean and standard deviation of systolic and diastolic blood pressures based on all available measures. Because mean and standard deviation in BP tended to be correlated (e.g., persons with higher BP tended to have more BP variability), we computed the SBP variability independent of the mean (VIM) (15; 9).

Covariates

We identified covariates associated with the LEA risk to reduce confounding. All time-dependent covariates were measured during the 365-day period immediately preceding the index date to mitigate any potential time decay bias between the measure and the outcome. Time-independent variables including matching factors were measured at baseline.

Demographic factors—We obtained patient demographic characteristics (age, sex, race/ethnicity, and marital status) from VA inpatient and outpatient records. We used age, gender and race/ethnicity as the matching factors and so they were not included in multivariable modeling.

Systemic factors—In addition to the mean SBP, we calculated body mass index (BMI) from heights and weights. We obtained HbA1c and low-density lipoprotein cholesterol (LDL-c) levels from the laboratory datasets. Multiple measures found in the 365-day window were averaged. All patients without any measures were assigned to the Unknown group and kept in the analysis. Other comorbidities were identified using the Elixhauser method (16). The diabetes duration was identified by searching the first date of diabetes diagnosis in VA inpatient and outpatient records available since September, 1997.

We identified pharmacologic treatment of diabetes and hypertension using detailed data on hypoglycemic and antihypertensive medication prescriptions dispensed from the VA pharmacies during the 365-day period before the index date. We coded a patient as a user of antihypertensive medications if they filled a prescription of at least 30-day supply of any antihypertensive medication during the year preceding the index date. Usage of calcium channel blockers, known to be effective in reducing SBP variability, was separately identified (17; 15). All persons with calcium channel blockers alone or in combination with other classes were classified as “users of calcium channel blockers” and users of all other classes were classified in a separate category.

We also identified diabetes medication use based on whether a patient filled at least one 30-day supply of insulin and/or any oral medications. We classified patients into four categories: no medication used, oral medications alone, insulin alone, or both oral medications and insulin.

Limb and pedal factors—Peripheral vascular disease (PVD), diabetic neuropathy, foot ulcers, and osteomyelitis were identified from patient records. We included vascular procedures as a proxy for severe PVD. Specific codes used to identify these conditions and procedures are shown in Table A1 in the appendix.

Statistical Analysis

The focus of our analysis is to examine whether the SBP variability was associated with the risk of major amputation. Cases and controls were divided into quartiles based on their VIM values with Quartile 1 having the lowest variability and Quartile 4 the highest variability (<0.738 , $0.738-0.9721$, $0.9722-1.2211$, or >1.2211). We used conditional logistic regression to compare the five-year risk of major amputation across these quartiles. We obtained odds

ratios and 95% confidence intervals from unadjusted and adjusted models that included marital status, clinical factors, comorbidities and history of vascular procedures, and medication use.

Bias in measuring SBP variability may come from including nocturnal BP measures that are known to be lower than daytime measures (18). We conducted a sensitivity analysis, testing whether our results remained robust when SBP variability was calculated using only daytime measurements (8:00AM – 8:00PM) that are likely to be taken at doctors' offices.

Blood pressures during a few days immediately before amputation may vary more than usual because of anxiety, severe pain, or other reasons underlying the condition necessitating the procedure and may not accurately reflect the usual day-to-day variability. We thus conducted another sensitivity analysis based on VIM quartiles that excluded BP measures taken during the month before the event date by moving the one-year observation period back a month.

We conducted a stratified analysis to test whether and how the SBP variability might affect major amputation differently among individuals with or without PVD or a previous vascular procedure as an indicator of serious previous peripheral vascular condition.

We used the American Diabetes Association recommended BP targets for younger patients (130/80 mm Hg) to identify individuals whose mean BP during the 365-day window exceeded this target. We conducted a stratified analysis to examine how SBP variability might affect amputation risk in hypertensive vs normotensive individuals.

Finally, we conducted a supplemental analysis to compare the relative contribution of SBP regarding traditional risk factors such as peripheral neuropathy, foot ulcers, PVD, osteomyelitis, and history of vascular surgery, and HbA1c levels. The relative importance of predictors was determined by dominance analysis (19).

All analysis was conducted by SAS 9.3 (SAS Institute, Cary, NC) and STATA SE (StataCorp, College Station, TX). This study was approved by the institutional review board of our institution.

Results

Over 50% of the sample was aged 55 years or older, 98% male, and 28% non-Hispanic black. They were well balanced on all of the matching factors (Table 1) but were significantly different on many other characteristics in unadjusted comparisons (Table 2). Cases had worse glucose control (30% vs 21% with HbA1c > 75 mmol/mol [9.0%], $p < 0.001$), longer diabetes duration (45% vs 34% > 5 years in 2003 with diabetes, $p < 0.001$), and more likely to be treated with insulin alone (40% vs 20%, $p < 0.001$) than controls. Cases tended to have lower BMI (44% vs 53% with BMI ≥ 30 kg/m², $p < 0.001$) and LDL-c (6.5% vs 9.4% with LDL-c ≥ 130 mg/dL, $p < 0.001$).

Mean SBP was not significantly different between cases and controls (134.5 vs 133.6, $p = 0.112$). Mean (median) within-subject standard deviation of SBP was 8.1 (8.6), 12.9 (12.9), 16.6 (16.4), and 22.6 (21.7) mm Hg for patients in Quartiles 1–4, respectively. Crude

incidence rate was 10.5% in Quartile 1 and increased linearly to 20.1%, 36.6%, and 37.5% in Quartiles 2–4.

Both unadjusted and adjusted conditional logistic regression results showed a significant graded relationship between the SBP variability and major amputation risk. Compared to Quartile 1, Quartiles 2–4 had significantly higher adjusted odds ratios of major amputations: 1.44 (95% CI, 1.00–2.07; $p=0.049$), 2.62 (95% CI, 1.85–3.72; $p<0.001$), and 2.50 (95% CI, 1.74–3.59; $p<0.001$) (P for trend <0.001).

In the adjusted model, mean SBP was not significantly associated with the risk of major amputation. Poor diabetes control (HbA1c >75 mmol/mol [9%]) was associated with about 70% higher risk (OR=1.73; 95% CI, 1.24 – 2.42; $p=0.001$) compared to HbA1c <53 mmol/mol (7%). Comorbidities such as foot ulcers (OR= 4.38; 95% CI, 3.37–5.69; $p<0.001$), PVD (OR = 3.14; 95% CI, 2.39 – 4.12; $p<0.001$) and osteomyelitis (OR = 4.63; 95% CI, 3.38 – 6.34; $p<0.001$) showed strong and significant associations with major amputation.

In sensitivity analyses, we found graded relationships between SBP VIM Quartiles and amputation risk essentially unchanged and robust (Models 3 and 4, Table 3). When the study sample was stratified by prior PVD status (Model 5, Table 3), we found a significant graded relationship in the group with no prior PVD (P for trend <0.001) but not in the group with prior PVD (P for trend = 0.789). Furthermore, we found that the gradient relationship was significant for both normotensive (P for trend = 0.039) and hypertensive (P for trend <0.001) groups.

In a supplemental analysis to determine relative importance of predictors, the SBP variability was one of the four most important risk factors after foot ulcers, osteomyelitis, and PVD ahead of HbA1c, diabetes duration, or treatment (Table A2).

Conclusions

This is the first study that showed a graded relationship between SBP variability and the risk of major lower-extremity amputation. Compared to Quartile 1 (lowest variability), the adjusted amputation risk was 1.4 times higher in Quartile 2 and 2.5 times higher in Quartiles 3 and 4 (highest variability). This association held when blood pressure measurements used to calculate SBP variability were restricted and persisted in subgroups without prior PVD or hypertension.

In this study, SBP variability was a significant and strong predictor of major amputations, independent of well-known risk factors such as foot ulcers, osteomyelitis, PVD, and diabetic neuropathy (20; 21; 2). According to our analysis shown in Table A2, SBP variability ranks much higher in importance than diabetic neuropathy (22; 4), or HbA1c level (23). Another notable finding is the magnitude of association between SBP variability and the risk of major amputation. While we consistently observed a significant linear trend, the risk of amputation more than doubled between Quartiles 1 and 3. This suggests that SBP variability may have a good prognostic value for major amputations.

It is noteworthy that the risk of amputation was not significantly different between Quartiles 3 and 4. This may indicate a threshold effect above which the risk does not change or a selective survival where patients in Quartile 4 might have died more than patient in Quartile 3 before they experienced an amputation. The concept of a threshold effect has been advocated by others, citing low-level variability as a healthy physiological circadian phenomenon (24). If the threshold hypothesis is correct, patients with SBP standard deviations > 13 mm Hg, who have about a 50% increased risk of amputation, would be likely to benefit from interventions to prevent this morbidity. In order to identify high-risk patients, electronic health record systems and other information technology could be designed to automatically calculate BP variability and display this information as one of the vital signs on the computer screen. Clinicians could then determine whether the use of calcium channel blockers, known to blunt SBP variability, may be indicated.

This study was not an attempt to explore pathophysiological pathways by which SBP variability may affect the risk of lower-extremity amputation. However, we conjecture that SBP variability may have pervasive downstream effects on proximate amputation risk factors such as PVD, foot ulcers, and peripheral neuropathy. Stroke and coronary artery diseases were the first health conditions for which the importance of SBP variability was recognized (9; 25; 26). One proposed mechanism was that excessive SBP variability creates stress on vessel walls that in turn accelerates cholesterol plaque deposition (27; 24). SBP variability has been associated with carotid artery stenosis and PVD (28). It is highly plausible that the magnitude of the oscillation in SBP correlates with the severity of PVD; this, in turn, increases the risk of major amputation due to ischemia.

However, the effect of SBP variability on amputation seems to extend beyond PVD, because SBP variability was still significant even after this mediator was controlled. Our stratified analysis of patients without prior PVD further showed that the SBP variability affects amputation risk in pathways other than PVD and ischemia. This suggests that SBP variability may have alternative, microvascular mechanisms by which it affects the risk of amputation. In a recent study, we showed that excessive SBP variability was associated with increased risk of peripheral neuropathy, a well-recognized risk factor for foot ulceration and subsequent amputation (29; 21). Increased oscillation in SBP in this case may lead to more frequent dips in transcutaneous oxygen pressure, and the resulting intermittent hypoxia may cause peripheral nerve dysfunction. It is noteworthy that the effect of peripheral neuropathy was significant in an unadjusted analysis but dominated by other more proximate causes such as foot ulcers or osteomyelitis in an adjusted analysis. Another microvascular mechanism may be that the local ischemia impedes healing of foot ulcers (30). Lastly, through its link to heart failure and resulting poor perfusion (31; 26), SBP variability may increase the risk of lower-extremity edema, ulceration, and subsequent amputation. Further research into these possible mechanisms is warranted.

Clinicians have traditionally focused on treating diabetes, foot ulcers, PVD, or osteomyelitis to prevent amputation. Our results suggest that excessive SBP variability has even greater prognostic value than HbA1c or diabetes duration. It is too early to make any inference on whether the treatment of excessive SBP variability would reduce the risk of amputation. All the mechanisms discussed above would largely be unaffected by such a treatment once the

mediating state (foot ulcers, PVD, neuropathy, or any combinations thereof) has developed. It is not surprising that the use of calcium channel blocker was not significantly associated with the risk of amputation in our model. It remains possible that very early intervention with these agents, perhaps at the time of diabetes diagnosis, is a more effective risk reduction strategy.

Study strengths include that the cohort was drawn from Veterans' Health Administration national database and represent a geographically diverse population with BP measurements extracted from real-life clinical data. We carefully selected these measures to reflect the SBP variability individuals experience in their day-to-day life by excluding any measures taken during ER visits or hospitalizations.

We recognize several limitations that need to be taken into account when interpreting our results. First, this is a retrospective observational study and selection bias may have affected our results. We used a nested case-control design in which controls were randomly selected from a large cohort to address this limitation. Second, diseases and amputations were identified from administrative data using ICD-9-CM and CPT-4 codes and the accuracy of disease coding may have affected our results. Even though our previous study indicates that some conditions such as foot ulcers can be determined with very high accuracy from the VA administrative data (32), we especially recognize that non-symptomatic PVDs may have been under-identified in our data. Third, we did not have access to some factors that may have affected both the SBP variability and the risk of amputation such as smoking and physical activity. Fourth, the study cohort included non-elderly individuals who were mostly male and our results need to be carefully generalized. Finally but not least, the visit-to-visit variability used in this study measures is known to have a low correlation with the 24-hour ambulatory variability (33). Because the latter is generally considered as the gold standard in measuring BP variability (10), our results should be carefully interpreted in the context of multiple possible measures from short-term, beat-by-beat to long-term, yearly BP variability (10; 24).

In conclusion, our results show that there is a gradient relationship between SBP variability and the risk of lower-extremity major amputation. More research is needed to better understand the pathways by which SBP variability affects amputation on the one hand and whether SBP variability is a prognostic factor that can be used to prevent and further reduce amputation rates in populations with diabetes.

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Highlights

- Excessive systolic blood pressure variability was a significant and strong predictor of major amputations in the lower extremities
- Significant graded relationship between SBP variability and major amputation was found in both normotensive and hypertensive groups
- Persons with existing peripheral vascular disease may not be subject to this graded relationship

Figure 1.
Sample Flow Diagram

Table 1

Patient characteristics used for matching in the nested case-control data set (n = 3,970)

Matching factors	Cases (n = 1,038)	Controls (n = 2,932)	Incidence (%) [*]
	n (%)	n (%)	
Age on October 1, 2003			
< 50 y	157 (15.1%)	403 (13.7%)	28.0%
50 – 54 y	330 (31.8%)	955 (32.6%)	25.7%
55 or older	551 (53.1%)	1,574 (53.7%)	25.9%
Male Sex	1,009 (97.2%)	2,875 (98.1%)	26.0%
Black Race	285 (27.5%)	842 (28.7%)	25.3%

* Incidence indicates the percent of all patients (cases and controls) in a category who were cases (e.g., experienced a major, above-ankle amputation).

Table 2

Unadjusted and adjusted odds ratios and their 95% confidence intervals for SBP VIM Quartiles and other covariates (N = 3,970) *

Adjustment Factors	Cases		Controls n (%)	Crude Incidence	Unadjusted ORs		Adjusted ORs	
	n (%)				OR (95% CI)	P-Value	OR (95% CI)	P-Value
SBP VIM Quartiles								
1 (Lowest)	104 (10.0%)		889 (30.3%)	10.5%			ref	
2	199 (19.2%)		793 (27.0%)	20.1%	2.190 (1.689 – 2.841)	< 0.001	1.438 (1.002 – 2.065)	0.049
3	363 (35.0%)		630 (21.5%)	36.6%	5.252 (4.091 – 6.743)	< 0.001	2.623 (1.847 – 3.724)	< 0.001
4 (Highest)	372 (35.8%)		620 (21.1%)	37.5%	5.436 (4.225 – 6.994)	< 0.001	2.495 (1.736 – 3.588)	< 0.001
SBP, mean (sd)	134.50 (15.1)		133.60 (14.1)	-	1.004 (0.999 – 1.009)	0.112	1.001 (0.993 – 1.010)	0.717
Married	429 (41.3%)		1,457 (49.7%)	22.7%	0.717 (0.618 – 0.832)	< 0.001	0.833 (0.664 – 1.045)	0.114
BMI, kg/m ²								
< 25	237 (22.8%)		309 (10.5%)	43.4%	ref			
25 – 29.9	271 (26.1%)		669 (22.8%)	28.8%	0.532 (0.424 – 0.668)	< 0.001	0.839 (0.594 – 1.186)	0.321
30	454 (43.7%)		1,553 (53.0%)	22.6%	0.368 (0.298 – 0.454)	< 0.001	0.546 (0.389 – 0.765)	< 0.001
Unmeasured	76 (7.3%)		401 (13.7%)	15.9%	0.243 (0.178 – 0.332)	< 0.001	0.441 (0.282 – 0.690)	< 0.001
HbA1c, mmol/mol (%)								
< 53 (7.0)	261 (25.1%)		839 (28.6%)	23.7%	ref			
53 – 75 (7.0 – 9.0)	340 (32.8%)		1,034 (35.3%)	24.7%	1.081 (0.895 – 1.305)	0.418	1.376 (1.016 – 1.863)	0.039
> 75 (9.0)	305 (29.4%)		603 (20.6%)	33.6%	1.682 (1.372 – 2.061)	< 0.001	1.728 (1.235 – 2.418)	0.001
Unmeasured	132 (12.7%)		456 (15.6%)	22.4%	0.938 (0.724 – 1.216)	0.631	1.619 (1.079 – 2.430)	0.020
Diabetes Duration > 5 y	463 (44.6%)		984 (33.6%)	32.0%	1.775 (1.524 – 2.067)	< 0.001	1.030 (0.812 – 1.306)	0.808
LDL cholesterol, mg/dL								
< 70	295 (28.4%)		575 (19.6%)	33.9%	ref			
70 – 99.9	273 (26.3%)		870 (29.7%)	23.9%	0.568 (0.465 – 0.695)	< 0.001	1.034 (0.756 – 1.413)	0.836
100 – 129.9	162 (15.6%)		537 (18.3%)	23.2%	0.534 (0.423 – 0.675)	< 0.001	1.158 (0.806 – 1.665)	0.427
130	67 (6.5%)		277 (9.4%)	19.5%	0.432 (0.317 – 0.590)	< 0.001	0.712 (0.438 – 1.157)	0.171
Unmeasured	241 (23.2%)		673 (23.0%)	26.4%	0.700 (0.565 – 0.866)	0.001	1.139 (0.811 – 1.600)	0.453
Co-existing conditions								

Adjustment Factors	Cases n (%)	Controls n (%)	Crude Incidence	Unadjusted ORs		Adjusted ORs	
				OR (95% CI)	P-Value	OR (95% CI)	P-Value
Diabetic Neuropathy	572 (55.1%)	794 (27.1%)	41.9%	3.495 (2.980 – 4.100)	< 0.001	1.271 (0.991 – 1.630)	0.059
Foot Ulcers	617 (59.4%)	267 (9.1%)	69.8%	13.548 (11.015 – 16.664)	< 0.001	4.379 (3.368 – 5.693)	< 0.001
PVD	454 (43.7%)	306 (10.4%)	59.7%	6.490 (5.383 – 7825)	< 0.001	3.137 (2.392 – 4.115)	< 0.001
Osteomyelitis	397 (38.2%)	170 (5.8%)	70.0%	13.797 (10.658 – 17.861)	< 0.001	4.631 (3.381 – 6.343)	< 0.001
CHF	251 (24.2%)	258 (8.8%)	49.3%	3.220 (2.640 – 3.926)	< 0.001	1.647 (1.206 – 2.249)	0.002
Paralysis ¹	65 (6.3%)	53 (1.8%)	55.1%	3.530 (2.419 – 5.152)	< 0.001	3.074 (1.730 – 5.460)	< 0.001
Renal Failure	335 (32.3%)	315 (10.7%)	51.5%	4.144 (3.422 – 5.017)	< 0.001	1.289 (0.933 – 1.780)	0.124
Cancer	35 (3.4%)	152 (5.2%)	18.7%	0.533 (0.362 – 0.784)	0.001	0.549 (0.315 – 0.956)	0.034
Deficiency Anemia	361 (34.8%)	340 (11.6%)	51.5%	4.178 (3.472 – 5.027)	< 0.001	1.838 (1.364 – 2.477)	< 0.001
Prior Vascular Procedure	92 (8.9%)	54 (1.8%)	63.0%	4.982 (3.497 – 7.099)	< 0.001	1.727 (1.006 – 2.964)	0.047
Diabetes Treatment							
None	117 (11.3%)	330 (11.3%)	26.2%	ref			
Oral Drugs Alone	193 (18.6%)	1,138 (38.8%)	14.5%	0.469 (0.356 – 0.619)	< 0.001	0.682 (0.457 – 1.017)	0.061
Insulin Alone	416 (40.1%)	587 (20.0%)	41.5%	2.040 (1.567 – 2.657)	< 0.001	1.155 (0.779 – 1.711)	0.473
Insulin and Oral Drugs	312 (30.1%)	877 (29.9%)	26.2%	1.004 (0.769 – 1.309)	0.979	0.857 (0.566 – 1.296)	0.464
Antihypertensive Drug ² 30 d							
None	108 (10.4%)	313 (10.7%)	25.7%	ref			
Calcium Channel Blockers	350 (33.7%)	837 (28.5%)	29.5%	1.202 (0.917 – 1.577)	0.183	0.887 (0.581 – 1.352)	0.576
All Other Classes	580 (55.9%)	1,782 (60.8%)	24.6%	0.947 (0.736 – 1.217)	0.668	0.747 (0.507 – 1.101)	0.140

* The adjusted model included all covariates shown in the table; SBP = systolic blood pressure; VIM = variability independent of the mean; SD = standard deviation; BMI = body mass index; HbA1c = glycated hemoglobin; LDL = low-density lipoprotein; PVD = peripheral vascular disease; CHF = congestive heart failure.

¹ Paralysis refers to forms of hemiplegia.

Table 3

Summary of sensitivity analyses*

Models	n	Odds Ratios (95% CI) for SBP VIM Quartiles vs Quartile 1			P for Trend
		2	3	4	
1 Unadjusted (Table 2)	3970	2.190 (1.689 – 2.841)	5.252 (4.091 – 6.743)	5.436 (4.225 – 6.994)	< 0.001
2 Adjusted (Table 2)	3970	1.438 (1.002 – 2.065)	2.623 (1.847 – 3.724)	2.495 (1.736 – 3.588)	< 0.001
3 Nighttime BPs excluded	3901	2.004 (1.391 – 2.887)	2.432 (1.691 – 3.496)	3.200 (2.208 – 4.637)	< 0.001
4 BPs within 1 month prior excluded	3669	1.290 (0.896 – 1.856)	1.601 (1.121 – 2.286)	1.907 (1.324 – 2.747)	< 0.001
5 Stratified by prior PVD/vascular procedure					
PVD	254	0.644 (0.109 – 3.801)	1.156 (0.256 – 5.223)	0.924 (0.199 – 4.301)	0.789
No PVD	2040	1.350 (0.851 – 2.143)	2.903 (1.836 – 4.591)	2.607 (1.647 – 4.128)	< 0.001
6 Stratified by mean BP					
Normotensive	710	1.429 (0.702 – 2.912)	1.742 (0.895 – 3.392)	2.045 (0.980 – 4.267)	0.039
Hypertensive	1803	1.354 (0.758 – 2.419)	3.412 (1.910 – 6.097)	2.786 (1.562 – 4.970)	< 0.001

* SBP VIM = systolic blood pressure variability independent of the mean; BP = blood pressure; PVD = peripheral vascular disease. Models 1 and 2 are from Table 2. Model 3 was based on VIM quartiles computed using BP measures taken during a year (395 – 30 days) before the index date, excluding the last month. Model 4 was based on VIM quartiles computed using BP measures taken between 8:00AM and 8:00PM during one year before the index date. For Model 5, the sample was stratified by whether one had a pre-existing PVD or a history of vascular surgery. When a case or all controls in a set had PVD or previous vascular procedure, the set (the case and all of its matched controls) were excluded from the analysis. Model 6 was stratified by whether hypertensive (< 130/80 mm Hg) or normotensive (< 130/80 mm Hg) using the American Diabetes Association recommended target blood pressure for non-elderly patients. The sample size used in stratified analysis do not sum up to the total (N = 3870), because the case-control sets that do not belong to the same stratum all drop out from analyses.