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Visit-to-visit systolic blood pressure variability and microvascular complications among patients with diabetes

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Abstract

Aims—To examine the relationship between systolic blood pressure (SBP) variability and the risk of microvascular complications in a non-elderly diabetic population.

Methods—This is a retrospective cohort study of individuals aged ≥ 60 years treated for diabetes in 2003 in the US Department of Veterans Affairs healthcare system. Individuals were followed for five years for any new diagnosis of diabetic nephropathy, retinopathy, or neuropathy. In each year of follow-up, individuals were classified into quartiles based on their SBP variability.

Results—We identified 208,338 patients with diabetes without diabetic nephropathy, retinopathy, or neuropathy at baseline. Compared to individuals with the least SBP variability (Quartile 1), those with most variability (Quartile 4) had 81% (OR = 1.81; 95% CI, 1.72–1.91), 17% (OR = 1.17; 95% CI, 1.13–1.21), 30% (OR = 1.30; 95% CI, 1.25–1.35), and 19% (OR = 1.19; 95% CI, 1.15–1.23) higher incidence of nephropathy, retinopathy, neuropathy, and any complication, respectively, after adjusting for mean SBP, demographic and clinical factors.

Conclusions—We found a significant graded relationship between SBP variability and the incidence of each complication and of any combined endpoint. This is the first study showing a

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Contributor Statements

M.S., N.E. and E.B. conceived the design of the study, M.S. researched data and wrote manuscript, and Z.H. provided statistical support. All authors contributed to the interpretation of the data, critically reviewed the manuscript, and approved the final version of the manuscript. M.S. is the guarantor of this study, had full access to all the data used in this study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

significant association between SBP variability and the risk of diabetic retinopathy and neuropathy.

Keywords

Blood pressure variability; Microvascular complications; Neuropathy; Retinopathy; Nephropathy

1. Introduction

Blood pressure control is important for individuals with diabetes to reduce the risk of cardiovascular disease (CVD) and other diabetic complications (American Diabetes Association, 2015). Trial evidence shows that intensive blood pressure control reduces both microvascular and macrovascular complications (Curb, Pressel, Cutler, et al., 1996; Tuomilehto, Rastenyte, Birkenhager, et al., 1999; UK Prospective Diabetes Study Group, 1998). In the past few years, studies have shown that blood pressure variability (BPV) is an independent predictor of coronary heart disease, stroke, cognitive dysfunction, and all-cause mortality (Epstein, Lane, Farlow, et al., 2013; Muntner, Whittle, Lynch, et al., 2015; Muntner et al., 2011; Rothwell, Howard, Dolan, et al., 2010a) and that BPV may directly cause end organ damage (Su, 2006). In diabetic patients, several studies (Kilpatrick, Rigby, & Atkin, 2010; Okada, Fukui, Tanaka, et al., 2012; Okada, Fukui, Tanaka, et al., 2013; Okada, Matsumoto, Nagaoka, & Nakao, 2012; Takao, Matsuyama, Yanagisawa, Kikuchi, & Kawazu, 2014) have consistently shown that excessive BPV is an independent predictor of nephropathy and its precursors such as micro- (Noshad, Mousavizadeh, Mozafari, Nakhjavani, & Esteghamati, 2014) and macroalbuminuria (Ushigome, Fukui, Hamaguchi, et al., 2011). However, the relationship between BPV and retinopathy or neuropathy is still uncertain. Our objective in this study is to examine the relationship between visit-to-visit blood pressure variability and diabetic microvascular complications using a large administrative database of patients with diabetes. Our hypothesis is that excessive BPV is associated with increased risk of developing these conditions.

2. Material and methods

2.1. Design overview

We used a retrospective cohort design to follow patients with diabetes for five years and to examine whether their SBP variability in a given year was associated with an increased risk of a microvascular complication in the next year. A person-year data set was constructed in which patients without previous evidence of a microvascular complication were followed each year until they experienced a complication or death.

2.2. Setting and participants

We used a cohort of diabetic patients treated in the US Department of Veterans Affairs (VA) healthcare system in the fiscal year 2003 (October 1, 2002–September 30, 2003; all years henceforth are fiscal years). Inpatient and outpatient records (Veterans Affairs Information Resource Center, 2005a, 2005b) were used to identify diabetic patients 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 previous study showed that this method had a 93% sensitivity and 97% specificity (Miller, Safford, & Pogach, 2004) against self-reported diabetes.

Because Medicare data were not available, patients who turned 65 years of age before the end of the study period (September 30, 2008) were excluded to mitigate the potential bias in ascertaining study outcomes occurring outside the VA healthcare system.

2.3. Visit-to-visit variability of systolic blood pressure

We obtained all outpatient BP measures recorded in 2003–2007 for our study cohort from the VA Corporate Data Warehouse. All measures taken on days patients were hospitalized or made an emergency room visit were dropped. We then selected measures of BP as valid if they were between 50 and 300 mm Hg for systolic blood pressure (SBP) and 30–180 mm Hg for diastolic blood pressure (DBP). Multiple BP measures taken during the same day for the same patient were averaged as the measure of the day and only patients with three or more BP measurements in the same year were included in the study cohort. For patients with more than 12 measures in a year, we randomly selected 12 measures for that year (Rothwell et al., 2010a). We computed within-subject means and standard deviations of SBP for each year and used them to compute the SBP variability independent of the mean (VIM) by following the method used in previous studies (Rothwell, Howard, Dolan, et al., 2010b; Rothwell et al., 2010a; Schutte, Thijs, Liu, et al., 2012).

2.4. Outcomes and follow-up

Four main outcomes were identified using ICD-9-CM codes reported in both inpatient and outpatient data for 2000–2008: retinopathy, 250.5x, 366.41, and 362.0x; nephropathy, 250.4x and 583.81; neuropathy, 250.6x, 354.xx, 337.1 and 357.2, or any of the three complications. We searched inpatient and outpatient records for four years (2000–2003) before the baseline (October 1, 2003) to identify individuals with pre-existing complications and excluded them from the study cohort. The incidence date of a condition was determined as the earliest date the condition was recorded.

We constructed a separate longitudinal data set for each outcome, in which the time interval was a year (to allow for adequate time for multiple BP measures), each individual was observed for the outcome event once every year for five years (2004–2008) or until death, and the SBP variability and other covariates were derived from one year prior (2003–2007). A patient's record was repeated once each year in the analytic file as long as the patient had three or more BP measures in a year, had not been diagnosed with the condition during the year or before, and did not die until the end of the next year. A patient could thus be included in our person-year data up to five times.

2.5. Statistical analysis

We conducted bivariate and multivariable analyses to compare the differences in risks of diabetic microvascular complications between VIM quartiles. Multivariable models included adjustments for year, demographic factors (age, sex, race/ethnicity, and marital status), clinical factors that indicate diabetes severity or are known to affect BP or vascular health (A1c, diabetes duration >5 years, diabetes medication treatment type, BMI, antihypertensive

medication treatment, and statin use), and mean SBP. Demographic factors were measured at baseline. All clinical factors and mean SBP were measured using data recorded during one year before outcomes. Because access to care and frequency of healthcare encounters can affect timing of disease diagnosis, we also obtained copayment status for VA healthcare services, geographic distance to the nearest VA outpatient clinic from patients' residence, and the number of visits and hospitalizations in the previous year. These variables were excluded in final models, because otherwise identical models with or without these variables showed virtually identical estimates for VIM quartiles.

Diabetes treatment was defined based on diabetic medications filled for 30 days or more during a given year as follows: no use, insulin only, oral medication only, and both insulin and oral medication use. Antihypertensive medication use or statin use was indicated when any antihypertensive medication or statin prescription was filled for 30 days or longer in a year.

For each outcome, we estimated a separate but identically specified model that adjusted for all covariates including mean SBP. Each model was analyzed using a random-intercept logistic regression to account for the repeated nature of data.

We conducted sensitivity analyses to compare the outcomes between VIM quartiles by stratifying the cohort into individuals with high ($\geq 130/80$ mm Hg) and low ($<130/80$ mm Hg) BP according to recommended BP targets for younger diabetic patients in the American Diabetes Association (ADA) Standards of Medical Care in Diabetes (American Diabetes Association, 2014) and into individuals with 3–6 BP measures and those with 7 or more measures a year. Six was the median number of BP measures per year in our study cohort. The latter stratified analysis was intended to address the concern that the association between SBP variability and outcomes may be confounded by the number of BP measures.

We further limited our sample to a subset of normotensive patients (BP $< 130/80$ mm Hg) and stratified them into antihypertensive medication users and non-users to examine whether they are different in their SBP variability-outcome associations.

In this study, all outcomes were identified by any single code during the study period. We conducted another sensitivity analysis to test whether our results would change substantially if outcomes were identified by different methods. We considered two alternative methods of outcome identification, the first one requiring only an inpatient or two outpatient ICD-9-CM codes and the second, two codes, any time during the study period (Lee, Shields, Vogeli, et al., 2007; Miller et al., 2004; Sohn, Budiman-Mak, Stuck, Siddiqui, & Lee, 2010).

This study was approved by our institutional review board for the research of human subjects.

3. Results

The study cohort included 208,338 patients, followed for an average of 3.5 ± 1.4 years. Patients were 53.7 ± 5.2 years old during follow-up, mostly male (95.4%), and married in 46.5% of person-years (Table 1). Fifty-three percent were non-Hispanic white, 19.8% were

non-Hispanic black, and 5.3% were Hispanic. Their mean BP was $134.5/76.4 \pm 13.8/8.3$ mm Hg and 88.7% of person-years were treated with antihypertensive medications.

Persons with older age, non-Hispanic white or black races, hemoglobin A1c >9%, diabetes duration >5 years, BMI <25 kg/m², and those who used insulin alone or antihypertensive medications were more likely to be in Quartile 4 (most variable) than Quartile 1 (least variable, $P < 0.001$).

Mean SBP increased slightly between Quartiles 1 and 4 but mean within-subject SBP standard deviations (SD) increased by 4 mm Hg or more between each successive quartiles (6.0, 10.2, 13.8, and 20.8 mm Hg for Quartiles 1–4; $p < 0.001$). Mean DBP did not substantially change between quartiles but mean within-subject DBP SDs increased monotonically by 1 mm Hg or more in each higher quartile (5.7, 6.8, 7.8, and 10.1 mm Hg; $P < 0.001$).

One-year incidence rates were 2.2%, 6.1%, 6.5%, and 11.1%, respectively, for nephropathy, retinopathy, neuropathy, and any complication in 2004 (Table 2). Five-year cumulative incidence rates were 8.5%, 23.8%, 23.3% and 39.8%, respectively.

Table 3 shows a summary of results from multivariable models (full models are shown in Table A in the online supplement). All odds ratios were statistically significant at $P < 0.05$ and all VIM quartiles had a significant graded relationship with the risks of all outcomes (P for trend <0.001 in all models). Compared to persons in Quartile 1 (lowest variability), the risk of developing a microvascular complication for persons in Quartile 4 (highest variability) was 81% higher (OR = 1.81; 95% CI, 1.72–1.91) for nephropathy, 17% higher (OR = 1.17; 95% CI, 1.13–1.21) for retinopathy, 30% higher (OR = 1.30; 95% CI, 1.25–1.35) for neuropathy, and 19% higher (OR = 1.19; 95% CI, 1.15–1.23) for any complication. When used as a continuous variable, SBP variability was linearly associated with increased risks of all four outcomes (see Table B).

In sensitivity analyses, we found strong graded relationships between SBP variability and all outcomes for both persons with elevated mean BP ($\geq 130/80$ mm Hg) and those with normal mean BP (P for trend <0.05 for all models; Table 4). A subgroup analysis of patients with BP <130/80 mm Hg stratified by antihypertensive medication use (Table 4) showed a significant graded relationship between SBP variability and the incidence of nephropathy and neuropathy for both antihypertensive users and non-users (P for trend = 0.05 for all outcomes). For retinopathy and any complication, there was a significant graded relationship (P for trend <0.001) among users but not among non-users. In another sensitivity analysis stratified by the median number of BP measures (six measures per year), we found that both groups (≥ 6 measures and 7 or more) showed significant graded relationships between SBP variability and all outcomes with P for trend <0.001 (Table 4).

The method identifying complications produced considerably different incidence rates but the graded relationship between SBP variability and outcomes persisted in all models, even though the magnitude of association varied from method to method (Table C).

In supplemental analyses, we found that SBP variability was also significantly associated with higher risks of mortality and macrovascular disease (Table D). Compared to those in Quartile 1, patients in Quartile 4 had 2.3 times higher mortality (OR = 2.32; 95% CI, 2.22–2.42) and 1.6 times higher risk of any macrovascular disease (OR = 1.61; 95% CI, 1.55–1.67).

4. Discussion

Our results show a significant graded relationship between SBP variability and the incidence of microvascular complications among non-elderly persons with diabetes. The relationship was the strongest for nephropathy. We also found that patients with the highest variability (Quartile 4) were 17% and 30% more likely to experience incident retinopathy and neuropathy, respectively, than those with the lowest variability (Quartile 1). The risk of any microvascular complication, a combined endpoint, was about 19% higher in the highest variability group than the lowest. The gradient relationship persisted in all sensitivity analyses stratified by mean BP ($\geq 130/80$ mm Hg or below) or by the total number of BP measures taken during a given year (≥ 6 and 7 or more). Three different methods of identifying the endpoints did not substantially change the results either, adding confidence to the robustness of our results. Our analysis further revealed that SBP variability increased the risk of mortality and macrovascular disease (Table D), consistent with previous studies (Hata, Arima, Rothwell, et al., 2013; Rothwell et al., 2010a; Stevens, Wood, Koshiaris, et al., 2016).

These relationships held not only in patients who had BP $\geq 130/80$ mm Hg but also in patients whose BP was controlled $<130/80$ mm Hg with antihypertensive medications (American Diabetes Association, 2014). Furthermore, patients who had BP $<130/80$ mm Hg and did not take any antihypertensive medications also demonstrated a similar graded relationship between SBP variability and both nephropathy and neuropathy. These are normotensive individuals who clinicians are not likely to treat for blood pressure but our results suggest that they may also be vulnerable to the harmful effects of SBP variability.

Since 2010, several studies have reported a significant relationship between SBP variability and nephropathy (Hata et al., 2013; Kilpatrick et al., 2010; Noshad et al., 2014; Okada, Fukui, et al., 2012; Okada et al., 2013; Takao et al., 2014). This is the first study that demonstrated significant graded relationships between SBP variability and diabetic retinopathy and neuropathy. Retinopathy has been examined in three previous studies. The first was a post-hoc analysis of the Diabetes Control and Complication Trial data for patients with type 1 diabetes (Kilpatrick et al., 2010). The second was a case series of about 600 patients with type 2 diabetes and without diabetic retinopathy at baseline (Takao et al., 2014). Neither of these studies found any relationship between the two. A third study by Hata et al. showed a positive relationship but did not achieve a statistical significance for a linear trend (Hata et al., 2013). In contrast, our study showed a significant and robust graded relationship between the SBP variability and retinopathy in our main analysis and all stratified analyses except for the individuals who had BP controlled at $<130/80$ mm Hg without using antihypertensive medications.

Our results regarding neuropathy are novel and clinically significant given its high prevalence among diabetic patients. We could not find any previous study that examined its relationship with SBP variability. This may be because the general relationship between high BP and diabetic neuropathy is not well established yet (Cho, Mold, & Roberts, 2006; Forrest, Maser, Pambianco, Becker, & Orchard, 1997; Stella, Ellis, Maser, & Orchard, 2000; UK Prospective Diabetes Study Group, 1998). Our results suggest an insignificant association between SBP mean and the risk of neuropathy (see Table A).

There have been several explanations of the relationship between excessive SBP variability and cardiovascular outcomes, including arterial stiffness, abnormal autonomic function, and direct damage to end organs (Hata et al., 2013; Parati, Liu, Ochoa, & Bilo, 2013; Rothwell et al., 2010a; Su, 2006). But poor adherence to antihypertensive therapies does not appear to be the main explanation for excessive SBP variability among hypertensive patients (Krousel-Wood et al., 2009). Our results on neuropathy and patients with normotensive BP is an important new clinical observation that may, with additional research, add to the current understanding of the pathophysiological mechanisms by which SBP variability can do direct damages to the nervous system.

Our results have several implications for clinical practice. In addition to the traditional atherosclerotic cardiovascular diseases, microvascular conditions such as nephropathy, retinopathy, and neuropathy may need to be closely monitored for patients with high SBP variability. Treatment for excessive SBP variability in addition to high mean SBP may be necessary for prevention of these complications for hypertensive patients. But, even among individuals whose BP are controlled at <130/80 mm Hg with antihypertensive medications, we observed a significantly elevated risks of all three complications. This means that treatment for hypertension may need to be augmented with a therapy for reducing SBP variability (Rothwell et al., 2010b; Su, 2006). Furthermore, our finding that diabetic patients who have normal BP and are not treated with antihypertensive medications are also subject to the harmful effects of high SBP variability on kidney and peripheral nervous systems suggests that excessive SBP variability alone can produce end organ damages (Su, 2006; Miao, Xie, Zhan, & Su, 2006). Even though they may not be treated for high mean BP, patients may need to be treated for excessive SBP variability (Rothwell et al., 2010b; Su, 2006). Lastly, we observed significantly elevated risks of all three complications between Quartiles 1 and 2 which were separated by a mean within-subject SBP standard deviation of about 4 mm Hg (Table 1). This suggests that clinicians may need to begin therapy for SBP variability as small as 4 mm Hg in standard deviation.

Before any changes in clinical practice are attempted, however, more research is needed to rigorously examine causality and to better understand the underlying pathophysiological mechanisms. Future interventional trials are also needed to examine which antihypertensive medications are the most efficacious in reducing SBP variability or whether lifestyle modification can reduce SBP variability by itself or in addition to medications. Future research is further needed to examine whether there are other conditions such as foot ulcers and amputations, autonomic neuropathy, peripheral vascular disease, or other central nervous system diseases (Epstein et al., 2013) that may be associated with BP variability.

This study has several limitations. This is an observational study in which unmeasured confounding can be a source of bias. Our data need to be carefully interpreted. Second, disease coding in ICD-9-CM may not be accurate and this might have affected our ability to identify diabetic microvascular complications. Previous studies showed 87%–97% sensitivity for retinopathy compared to medical records (Muir, Gupta, Gill, & Stein, 2013) and 93%–99% specificity for nephropathy in the VA healthcare system (Kern, Maney, Miller, et al., 2006). Identification of diabetic retinopathy based on a single code and the other two methods we considered in this study differed considerably. Many patients diagnosed with diabetic retinopathy had no follow-up visits in the year following their diagnosis, likely due to slow disease progression and/or absence of symptoms. In our review of electronic medical records for 15 randomly selected patients with one code for incident diabetic retinopathy in 2008, we found that 11 (73%) had positive diagnoses on clinical examination. This shows that the majority of the patients identified by the single code method indeed had the condition. Our sensitivity analyses further indicate that our results are robust to the method of identification. Third, the blood pressure data used in this study were collected by VA hospitals and outpatient clinics across the country and there is currently no information on how standardized the measurements were. However, the VA follows a national guideline for measuring blood pressure consistent with the JNC7 guideline (Chobanian, Bakris, Black, et al., 2003; The Diagnosis and Management of Hypertension Working Group, 2014) and a uniform policy in maintaining and calibrating BP devices according to the manufacturer recommendations. A validation study found that the BP measures in the VA were reliable to assess quality of hypertension care (Borzecki, Wong, Hickey, Ash, & Berlowitz, 2004). Fourth, we did not have access to lifestyle factors such as smoking, diet, and physical activity that may have affected diabetes management in general. Finally, our cohort was limited to the non-elderly veterans with diabetes who were overwhelmingly male and so the generalizability of our results is limited.

In conclusion, our results show a significant gradient relationship between SBP variability and incidence of microvascular complications for non-elderly patients with diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jdiacomp.2016.09.003>.

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Table 1

Demographic and clinical characteristics of the study sample by systolic blood pressure variability independent of the mean quartiles.^a

Demographic and clinical factors	All	SBP variability quartiles				P-Value			
		1 (Least)	2	3	4 (Most)				
N	726,930	(100.0)	181,734	(100.0)	181,733	(100.0)	181,731	(100.0)	
Demographic factors									
Age, mean (SD)	53.7	(5.2)	53.2	(5.6)	53.5	(5.3)	53.8	(5.0)	54.1 (4.7) <0.001
Male sex	693,612	(95.4)	173,729	(95.6)	173,051	(95.2)	173,155	(95.3)	173,678 (95.6) <0.001
Race/ethnicity									
NH White	382,917	(52.7)	92,323	(50.8)	96,164	(52.9)	97,732	(53.8)	96,698 (53.2) <0.001
NH Black	143,720	(19.8)	31,923	(17.6)	34,580	(19.0)	36,677	(20.2)	40,540 (22.3)
Hispanic	38,292	(5.3)	10,373	(5.7)	9899	(5.4)	9216	(5.1)	8804 (4.8)
Other/Unknown	162,001	(22.3)	47,115	(25.9)	41,089	(22.6)	38,108	(21.0)	35,689 (19.6)
Married	338,246	(46.5)	85,046	(46.8)	86,743	(47.7)	85,200	(46.9)	81,257 (44.7) <0.001
Clinical factors									
Systolic blood pressure									
Mean (between-subject SD)	134.5	(13.8)	132.9	(12.6)	133.2	(13.1)	134.4	(13.8)	137.5 (15.2) <0.001
Within-subject maximum	151.4	(18.6)	140.1	(13.3)	146.6	(14.3)	153.1	(15.7)	165.7 (10.0) <0.001
Within-subject standard deviation	12.7	(6.1)	6.0	(1.9)	10.2	(1.1)	13.8	(1.4)	20.8 (4.8) <0.001
Diastolic blood pressure									
Mean (between-subject SD)	76.4	(8.3)	76.6	(7.9)	76.2	(8.0)	76.2	(8.3)	76.7 (9.0) <0.001
Within-subject maximum	86.3	(10.1)	83.3	(8.6)	85.0	(9.1)	86.6	(9.7)	90.2 (11.5) <0.001
Within-subject standard deviation	7.6	(3.4)	5.7	(2.7)	6.8	(2.7)	7.8	(2.8)	10.1 (3.8) <0.001
A1c									
<7%	220,492	(30.3)	56,137	(30.9)	56,043	(30.8)	55,240	(30.4)	53,072 (29.2) <0.001
7%–9%	260,952	(35.9)	66,431	(36.6)	66,309	(36.5)	65,648	(36.1)	62,564 (34.4)
>9%	128,279	(17.6)	30,055	(16.5)	30,982	(17.0)	32,210	(17.7)	35,032 (19.3)
Unknown	117,207	(16.1)	29,111	(16.0)	28,398	(15.6)	28,635	(15.8)	31,063 (17.1)
Diabetes duration in 2003 >5 y	197,611	(27.2)	42,179	(23.2)	47,171	(26.0)	51,135	(28.1)	57,126 (31.4) <0.001
Diabetes treatment									
None	69,986	(9.6)	18,202	(10.0)	17,707	(9.7)	16,901	(9.3)	17,176 (9.5) <0.001

Demographic and clinical factors	All	SBP variability quartiles				P-Value
		1 (Least)	2	3	4 (Most)	
Oral medications alone	354,007 (48.7)	99,569 (54.8)	91,047 (50.1)	85,467 (47.0)	77,924 (42.9)	
Insulin alone	107,095 (14.7)	21,173 (11.7)	24,027 (13.2)	27,511 (15.1)	34,384 (18.9)	
Oral and insulin	195,842 (26.9)	42,790 (23.5)	48,951 (26.9)	51,854 (28.5)	52,247 (28.7)	
Body mass index, kg/m ²						
25	67,041 (9.2)	14,027 (7.7)	15,080 (8.3)	16,457 (9.1)	21,477 (11.8)	<0.001
25–29.9	186,383 (25.6)	47,693 (26.2)	46,270 (25.5)	45,699 (25.1)	46,721 (25.7)	
30	462,431 (63.6)	116,552 (64.1)	117,753 (64.8)	117,195 (64.5)	110,931 (61.0)	
Unknown	11,075 (1.5)	3462 (1.9)	2629 (1.4)	2382 (1.3)	2602 (1.4)	
Statin use	378,570 (52.1)	97,655 (53.7)	96,452 (53.1)	94,589 (52.0)	89,874 (49.5)	<0.001
Antihypertensive medication use	644,582 (88.7)	152,469 (83.9)	158,737 (87.3)	164,112 (90.3)	169,264 (93.1)	<0.001

NH = non-Hispanic; SD = standard deviation; A1c = hemoglobin A1c; SBP VIM = systolic blood pressure variability independent of the mean.

^a All numbers inside parentheses are column percentages unless otherwise indicated; systolic blood pressure (SBP) variability quartiles were based on the SBP variability independent of the mean and value ranges in 2003 were as follows: 1st quartile = 0–0.687; 2nd quartile = 0.687–0.950; 3rd quartile = 0.951–1.224; 4th quartile = 1.225–4.93. The ranges for the other years were similar to the ones for 2003.

Table 2

Number at risk and five-year cumulative incidence of microvascular complications.

Year	Nephropathy		Retinopathy		Neuropathy		All complications	
	Number	Incidence	Number	Incidence	Number	Incidence	Number	Incidence
2003	143,736	2.23	112,363	6.08	117,311	6.47	87,135	11.11
2004	133,381	2.14	99,074	5.49	103,333	6.55	72,010	10.68
2005	125,893	2.06	90,305	5.11	92,955	5.75	61,992	9.54
2006	118,241	1.92	81,940	5.74	83,964	5.42	53,614	9.96
2007	114,878	1.87	76,324	5.78	78,899	5.26	48,086	9.88
5-year	190,408	8.48	148,040	23.80	159,409	23.31	115,504	39.79

“Number” indicates the total number of persons who did not have the condition in 2003 and were “at risk” of these complications in 2004–2008; “incidence” is per 100 persons.

Odds ratios and 95% confidence intervals for incident microvascular complications in SBP VIM Quartiles 2–4 compared to Quartile 1, all person-years at risk in 2004–2008.^a

Table 3

Complication	N	VIM quartiles compared to Quartile 1 (Least variable)				P for Trend		
		2	3	4 (Most variable)				
Nephropathy	636,129	1.244	(1.177–1.316)	1.435	(1.359–1.515)	1.813	(1.720–1.910)	<0.001
Retinopathy	460,006	1.056	(1.018–1.095)	1.114	(1.075–1.155)	1.171	(1.129–1.214)	<0.001
Neuropathy	476,462	1.169	(1.128–1.211)	1.270	(1.226–1.315)	1.299	(1.253–1.346)	<0.001
Any complication	322,837	1.119	(1.084–1.156)	1.167	(1.129–1.206)	1.187	(1.147–1.227)	<0.001

^aSBP VIM = systolic blood pressure variability independent of the mean; models were adjusted for age in 2003, male, race/ethnicity, marital status, body mass index, mean A1c, diabetes duration >5 years in 2003, diabetes treatment (none, oral medications alone, insulin alone or oral and insulin medications), statin use, antihypertensive use, and mean systolic blood pressure.

Odds ratios and 95% confidence intervals for incident microvascular complications in SBP VIM Quartiles 2–4 compared to Quartile 1, stratified by BP level, medication use, and number of BP measures.^a

Table 4

	N	VIM quartiles compared to Quartile 1 (Least variable)			P for Trend
		2	3	4 (Most variable)	
Nephropathy					
By BP level					
<130/80 mm Hg	220,180	1.275 (1.144–1.421)	1.499 (1.348–1.667)	1.876 (1.686–2.088)	<0.001
130/80 mm Hg	415,949	1.248 (1.168–1.333)	1.437 (1.348–1.532)	1.824 (1.716–1.938)	<0.001
By medication use					
No	37,435	1.243 (0.906–1.707)	1.214 (0.862–1.712)	1.783 (1.240–2.564)	0.005
Yes	182,745	1.266 (1.126–1.423)	1.495 (1.334–1.676)	1.826 (1.629–2.046)	<0.001
By number of measures					
6 or fewer	350,498	1.067 (0.987–1.154)	1.164 (1.076–1.259)	1.444 (1.343–1.553)	<0.001
7 or more	285,631	1.305 (1.194–1.426)	1.512 (1.387–1.647)	2.015 (1.852–2.192)	<0.001
Retinopathy					
By BP level					
<130/80 mm Hg	162,302	1.061 (0.994–1.131)	1.120 (1.049–1.195)	1.155 (1.078–1.238)	<0.001
130/80 mm Hg	297,704	1.052 (1.006–1.099)	1.107 (1.060–1.157)	1.163 (1.114–1.245)	<0.001
By medication use					
No	29,156	1.130 (0.981–1.303)	1.136 (0.972–1.327)	1.103 (0.918–1.326)	0.159
Yes	133,146	1.044 (0.971–1.123)	1.116 (1.035–1.196)	1.154 (1.070–1.245)	<0.001
By number of measures					
6 or fewer	259,196	1.042 (0.994–1.092)	1.039 (0.989–1.091)	1.091 (1.040–1.145)	0.001
7 or more	200,810	1.057 (0.994–1.124)	1.161 (1.093–1.233)	1.239 (1.165–1.319)	<0.001
Neuropathy					
By BP level					
<130/80 mm Hg	159,767	1.222 (1.151–1.298)	1.270 (1.194–1.350)	1.359 (1.275–1.298)	<0.001
130/80 mm Hg	316,695	1.145 (1.096–1.196)	1.277 (1.226–1.333)	1.281 (1.226–1.338)	<0.001
By medication use					
No	29,252	1.303 (1.134–1.498)	1.324 (1.138–1.541)	1.180 (0.983–1.417)	0.006

	N	VIM quartiles compared to Quartile 1 (Least variable)				P for Trend
		2	3	4 (Most variable)		
Yes	130,515	1.199 (1.121–1.283)	1.252 (1.170–1.339)	1.364 (1.273–1.463)		<0.001
By number of measures						
6 or fewer	278,827	1.071 (1.018–1.126)	1.146 (1.089–1.207)	1.157 (1.099–1.218)		<0.001
7 or more	197,635	1.082 (1.023–1.145)	1.159 (1.097–1.225)	1.239 (1.171–1.311)		<0.001
Any complication						
By BP Level						
<130/80 mm Hg	111,097	1.136 (1.074–1.201)	1.182 (1.116–1.252)	1.179 (1.108–1.254)		<0.001
130/80 mm Hg	211,740	1.111 (1.068–1.156)	1.160 (1.114–1.207)	1.185 (1.138–1.233)		<0.001
By medication use						
No	22,529	1.253 (1.109–1.416)	1.187 (1.036–1.360)	1.096 (0.928–1.293)		0.080
Yes	88,568	1.105 (1.037–1.177)	1.172 (1.099–1.249)	1.175 (1.098–1.258)		<0.001
By number of measures						
6 or fewer	195,667	1.049 (1.006–1.095)	1.069 (1.022–1.117)	1.078 (1.031–1.127)		<0.001
7 or more	127,170	1.109 (1.050–1.172)	1.161 (1.100–1.226)	1.233 (1.165–1.306)		<0.001

^aSBP VIM = systolic blood pressure variability independent of the mean; all models were adjusted for demographic factors (age in 2003, male, race/ethnicity, marital status), clinical factors (body mass index, mean A1c, diabetes duration >5 years in 2003, diabetes treatment, statin use), and mean SBP. Each outcome was stratified by blood pressure level (< or ≥ 130/80 mm Hg), antihypertensive medication use (yes or no for persons with BP <130/80 mm Hg only), and number of BP measures (6 or >6).