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

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

Conflict of Interest: There is no conflict of interest to declare.

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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 (≥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 ± 13.8/8.3 mm Hg and 88.7% of person-years were treated with antihypertensive medications.

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