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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.

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.

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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]. 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.

1. 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.

1.1. 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.

1.2. 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 ($n = 1217$; ICD-9-CM 84.13–84.15 and 84.16–84.17; CPT-4 27880–27889 and 27590–27598).

1.3. 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 ($n = 4189$, average 2.8 controls per case).

1.4. 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 and 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 3970 individuals with 1038 cases and 2932 controls (Fig. 1).

We computed the within-subject mean and standard deviation of systolic and diastolic blood pressures based on

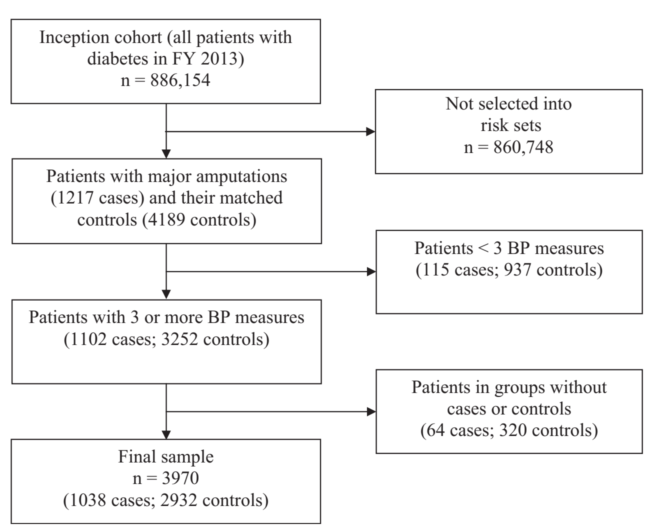

Fig. 1 – Sample flow diagram.