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Usual Blood Pressure and Risk of New-Onset Diabetes

Evidence From 4.1 Million Adults and a Meta-Analysis of Prospective Studies

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ABSTRACT

BACKGROUND Reliable quantification of the association between blood pressure (BP) and risk of type 2 diabetes is lacking.

OBJECTIVES This study sought to determine the association between usual BP and risk of diabetes, overall and by participant characteristics.

METHODS A cohort of 4.1 million adults, free of diabetes and cardiovascular disease, was identified using validated linked electronic health records. Analyses were complemented by a meta-analysis of prospective studies that reported relative risks of new-onset diabetes per unit of systolic blood pressure (SBP).

RESULTS Among the overall cohort, 20 mm Hg higher SBP and 10 mm Hg higher diastolic BP were associated with a 58% and a 52% higher risk of new-onset diabetes (hazard ratio: 1.58; 95% confidence interval [CI]: 1.56 to 1.59; and hazard ratio: 1.52; 95% confidence interval: 1.51 to 1.54), respectively. There was no evidence of a nadir to a baseline BP of 110/70 mm Hg. The strength of the association per 20 mm Hg higher SBP declined with age and with increasing body mass index. Estimates were similar even after excluding individuals prescribed antihypertensive or lipid-lowering therapies. Systematic review identified 30 studies with 285,664 participants and 17,388 incident diabetes events. The pooled relative risk of diabetes for a 20 mm Hg higher usual SBP across these studies was 1.77 (1.53 to 2.05).

CONCLUSIONS People with elevated BP are at increased risk of diabetes. The strength of the association declined with increasing body mass index and age. Further research should determine if the observed risk is modifiable. (J Am Coll Cardiol 2015;66:1552–62) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

In 2011, type 2 diabetes affected 366 million people worldwide; this prevalence is estimated to increase to 552 million by 2030 (1). Individuals with type 2 diabetes are at increased risk of major cardiovascular events, including ischemic heart disease, stroke, and heart failure (2). In a contemporary analysis of a U.K. primary care population, type 2 diabetes was associated with twice the risk of all-cause mortality and 3 times the risk of cardiovascular mortality relative to age- and sex-matched controls (3). Consequently, prevention of diabetes is critically important for reducing the burden of cardiovascular disease.

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Although hypertension has long been recognized as an independent risk factor for fatal and nonfatal vascular events (4), the relationship between blood pressure (BP) and risk of new-onset diabetes is less clear. Elevated BP is associated with chronic inflammation (5) and endothelial dysfunction (6), both of which appear to be mediators of diabetes risk (7,8). There is, therefore, a biological rationale to suspect that elevated BP may cause new-onset diabetes. However, among 30 cohort studies that have reported the association of BP and diabetes, 12 concluded that no such association is apparent, whereas the others reported a considerably variable strength of association (Online Table 1). Moreover, even the largest previous cohorts have had limited power to investigate whether any observed positive association between BP and diabetes varied significantly by important patient features (9).

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A detailed understanding of BP as a potential risk factor for diabetes will help us better understand and communicate risks with patients and can lead to more targeted prevention and management. We therefore undertook both an analysis of 4.1 million individuals free from diabetes and cardiovascular disease in a contemporary U.K. primary care population and a meta-analysis of existing prospective studies to reliably determine the association between BP and diabetes.

METHODS

We used prospectively collected records from the U.K. Clinical Practice Research Datalink (CPRD) to assemble a cohort of 4.1 million patients free from vascular disease and diabetes. An electronic health record system, covering approximately 9% of the U.K. population, CPRD has been validated for epidemiological research into a range of diagnoses (10,11). Eligible patients were additionally linked to Hospital Episode Statistics for secondary care/hospitalization data and to cause-specific mortality data.

PARTICIPANTS, EXPOSURES, AND OUTCOMES. Patients were eligible for inclusion if they had a BP measurement performed between January 1, 1990, and January 1, 2013, and were between 30 and 90 years (inclusive) of age at the time of measurement. Additionally, patients needed to have their age recorded and be registered at a general practice for at least 1 year. To reduce measurement error to which single BP measurements are prone and to diminish the impact of short-term fluctuations in BP on observed associations, the initial measurement was transformed into "usual blood pressure" to adjust for regression dilution bias and the calculated usual BP was used as the exposure. All patients with pre-existing vascular disease (ischemic heart disease, cerebrovascular disease, heart failure, peripheral vascular disease, or renal disease) and diabetes (either type 1 or type 2) were excluded. Baseline covariates (body mass index [BMI], total cholesterol, high-density lipoprotein cholesterol, and smoking status) were defined as the closest measurement within 2 years of the baseline BP measurement for that covariate.

The primary outcome was a diagnosis of type 2 diabetes, defined as either clinical diagnosis of type 2 diabetes or diabetes unspecified (because 90% of diabetes cases are type 2 [12]) or prescription of insulin/antidiabetic drugs, as defined in the British National Formulary (BNF) chapters 6.1.1 and 6.1.2. Participants were censored at the earliest occurrence of the primary outcome, transfer out of practice, death, or last collection date of practice.

STATISTICAL ANALYSES. Cox models, stratified by practice to account for clustering at the practice level, were used to determine hazard ratios (HRs) for BP categories for each outcome. The proportional hazards assumption was tested by plotting Schoenfeld residuals. The primary analysis was adjusted for age, sex, BMI, smoking status, baseline antihypertensive use (BNF chapters 2.2.1, 2.2.3, 2.2.4, 2.4, 2.5, 2.6.2), and baseline lipid-lowering agent use (BNF chapter 2.12), although further adjustment was undertaken in sensitivity analyses. Blood pressure was analyzed both as a continuous variable (per 20/10 mm Hg higher BP) and as a categorical variable. Usual systolic blood pressure (SBP) was defined by category: ≤95 mm Hg, >195 mm Hg, and increments of 10 mm Hg for everything in between (e.g., 96 to 105 mm Hg, 106 to 115 mm Hg, and so on). Usual diastolic blood pressure (DBP) also was defined by the measured diastolic BP categories: ≤65 mm Hg, >115 mm Hg, and for 10 mm Hg increments for everything in between (e.g., 66 to 75 mm Hg, and so on). BP categories were entered simultaneously into the Cox model (separate models for SBPs and DBPs) and estimated simultaneously. Floating absolute risks were used to display HRs for BP categories because floating absolute risks do not require the selection of a baseline group for display of standard errors (13). The variance of each estimate approximates the variance in the underlying category.

Multiple imputation using chained equations was used to impute missing covariates; 5 imputations were generated.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNF = British National Formulary

BP = blood pressure

CPRD = Clinical Research Practice Datalink

DBP = diastolic blood pressure

HR = hazard ratio

RAS = renin-angiotensin system

SBP = systolic blood pressure