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Blood pressure and all-cause mortality among patients with type 2 diabetes☆

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ABSTRACT

Background: The recommended goal for blood pressure (BP) control has recently been adjusted for people with diabetes, but the optimal BP control range for the diabetic population is still uncertain.
Methods: We performed a prospective cohort study of 35,261 patients with type 2 diabetes. Cox proportional hazard regression models were used to estimate the association of BP with all-cause mortality.
Results: During a mean follow-up period of 8.7 years, 4199 deaths were identified. The multivariable-adjusted hazard ratios of all-cause mortality associated with different levels of systolic/diastolic BP (<110/65, 110–119/65–69, 120–129/70–80, 130–139/80–90 [reference group], 140–159/90–100, and ≥160/100 mm Hg) were 1.70 (95% confidence interval [CI] 1.42–2.04), 1.26 (95% CI 1.07–1.50), 0.99 (95% CI 0.86–1.12), 1.00, 0.92 (95% CI 0.82–1.03), and 1.10 (95% CI 0.98–1.23) using baseline BP measurements, and 2.62 (95% CI 2.00–3.44), 1.77 (95% CI 1.51–2.09), 1.22 (95% CI 1.09–1.36), 1.00, 0.90 (95% CI 0.82–1.00), and 0.98 (95% CI 0.86–1.12) using an updated mean value of BP during follow-up, respectively. The U-shaped associations were confirmed in both African American and white patients, in both men and women, in those who were or were not taking antihypertensive drugs, and in patients aged 30–49 years and 50–59 years.
Conclusions: The current study found a U-shaped association between BP at baseline and during follow-up and the risk of all-cause mortality among patients with type 2 diabetes.

1. Introduction

Hypertension and diabetes are two important public health problems in the US, with hypertension affecting approximately 65 million Americans and diabetes affecting approximately 24 million Americans [1–3]. About 70% of patients with diabetes aged >40 years are affected by hypertension [2,3]. In the past 2 decades, clinical guidelines recommended maintaining blood pressure (BP) levels to below 130/80 mm Hg in patients with type 2 diabetes which was more aggressive than in the general population (BP < 140/90 mm Hg) [4]. This lower treatment target in diabetic patients was mainly based on the results of early randomized clinical trials (RCTs) such as the United Kingdom Prospective Diabetes Study (UKPDS) [5] and Hypertension Optimal Treatment (HOT) trial [6]. These RCTs showed clear benefit with regard to reductions in cardiovascular outcomes in patients with diabetes receiving tight BP control. However, aggressive targets for BP treatment in diabetes guidelines have been questioned recently. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study did not show further cardiovascular benefits when intensive systolic BP treatment was achieved (Systolic blood pressure [SBP] < 120 mm Hg) compared with standard therapy (SBP < 140 mm Hg) [7]. Based on current evidence, targets for BP control for patients with type 2 diabetes have been adjusted to <140/90 mm Hg [8,9] or 140/85 mm Hg [10]. Until now, there is still uncertainty about the optimal BP target in people with diabetes. The aim of the present study is to examine the association between different levels of BP and the risk of all-cause mortality among patients with type 2 diabetes in the Louisiana State University Hospital-Based Longitudinal Study (LSUHLS).

☆ Novelty and significance: Based on current evidence, targets for BP control for patients with type 2 diabetes have been adjusted to <140/90 mm Hg or 140/85 mm Hg, but the optimal BP control range for the diabetic population is still uncertain. Our study, based on a hospitalized cohort study of 35,261 patients with type 2 diabetes, suggested a U-shaped association between observed BP and the risk of all-cause mortality among patients with type 2 diabetes. We suggested that the lowest risk of all-cause mortality was observed at 130–150 mm Hg for SBP and 80–90 mm Hg for DBP.

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2. Materials and methods

2.1. Study population

Between 1997 and 2012, LSU Health Care Services Division (LSUHCSD) operated seven public hospitals and affiliated clinics in Louisiana, which provided quality medical care to the residents of Louisiana regardless of their income or insurance coverage [11–14]. Overall, LSUHCSD facilities have served about 1.6 million patients (35% of the Louisiana population) since 1997. Administrative, anthropometric, laboratory, clinical diagnosis, and medication data collected at these facilities are available in electronic form for both inpatients and outpatients from 1997. Using these data, we have established the LSUHLS [11]. A cohort of diabetic patients was established by using the ICD-9 (code 250) between January 1, 1999, and December 31, 2009. Confirmation of diabetes diagnoses was made by applying the American Diabetes Association criteria: a fasting plasma glucose level ≥ 126 mg/dL (in the absence of unequivocal hyperglycemia, the result should be confirmed by repeated testing); 2-hour glucose level ≥ 200 mg/dL after a 75-g 2-hour oral glucose tolerance test; one or more classic symptoms plus a random plasma glucose level ≥ 200 mg/dL [15]. The first record of diabetes diagnosis was used to establish the baseline for each patient in the present analyses due to the design of the cohort study. Before diagnosis with diabetes, these patients have used our system for an average of 5.0 years. We have validated the diabetes diagnosis in LSUHCSD hospitals. The agreement of diabetes diagnosis was 97%: 20,919 of a sample of 21,566 hospital discharge diagnoses based on ICD codes also had physician-confirmed diabetes by using the ADA diabetes diagnosis criteria [15].

After excluding patients with incomplete data or without at least 2 measurements of any of the required variables for analysis (all variables listed in Table 1), the present study included 35,261 newly diagnosed patients with type 2 diabetes (15,504 white and 19,757 African American) who were 30 to 94 years of age with complete repeated data on all risk factor variables. The study and analysis plan including the procedure of data coding were approved by both the Pennington Biomedical Research Center and LSU Health Sciences Center Institutional Review Boards (IRBs), LSU System. IRBs granted a waiver of informed consent for this perspective study because we used anonymized data compiled from electronic medical records.

2.2. Baseline and follow-up measurements

The patient's characteristics, including age of diabetes diagnosis, sex, race/ethnicity, family income, smoking status, types of health insurance, body mass index (BMI), BP, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glycosylated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), and medication (antihypertensive drug, cholesterol lowing drug and antidiabetic drug) within a half year after the diabetes diagnosis (baseline) and during follow-up after the diabetes diagnosis (follow-up) were extracted from the computerized hospitalization records. In Louisiana State University Health Care Services Division hospitals, eGFR is estimated using Modification of Diet in Renal Disease equation: $eGFR = (\text{in mL/mom/1.73 m}^2) = 186 \times [\text{serum creatinine (in mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if black)] [16,17]. BP was measured from the right arm of the participant after 5 min of sitting using a mercury sphygmomanometer or electronic BP meter in each visit. BP was measured first at baseline and second as an updated mean of annual measurement of systolic BP, calculated for each participant from baseline to each year of follow-up. For example, at 1 year, the updated mean is the average of the baseline and 1-year values, and at 3 years, it is the average of baseline, 1-year, 2-year, and 3-year values. In case of an event during follow-up, the period for estimating updated mean value was from baseline to the year before this event occurred. BP measurements during the follow-up period averaged 14.6 assessments for each patient.

2.3. Prospective follow-up

Follow-up information was obtained from the LSUHLS inpatient and outpatient database by using the unique number assigned to every patient who visits the LSUHCSD hospitals. The diagnosis of all-cause death was the primary endpoint of interest of the study. Mortality outcomes were assessed by linkage with the State Center for Health Statistics at Louisiana's Office of Public Health (the Louisiana Office of Public Health Vital Records Registry). Follow-up of each cohort member continued until the date of the death, or June 30, 2013.

2.4. Statistical analyses

Cox proportional hazards models were used to assess the association of BP with the risk of all-cause mortality. We categorized BP groups according to guidelines [18–20] and the target of randomized controlled trials (RCTs) [7]. SBP and diastolic blood pressure (DBP) were evaluated as categories (SBP < 110, 110–119, 120–129, 130–139 [reference group], 140–159, and ≥160 mm Hg; DBP < 65, 65–69, 70–79, 80–89 [reference group], 90–100, and ≥100 mm Hg; SBP/DBP < 110/65, 110–119/65–69, 120–129/70–79, 130–139/80–89 [reference group], 140–159/90–99, and ≥160/100 mm Hg). We fitted incremental models, and all analyses were adjusted for age, sex and race; then for smoking, income, type of insurance (multivariable-adjusted model a); and further for BMI, LDL cholesterol, HbA1c, eGFR, use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents (multivariable-adjusted model b). The proportional hazards assumption in the Cox model was assessed with graphical methods and models including time-by-covariate interactions [21]. In general, all proportionality assumptions were appropriate. To avoid the potential bias due to severe diseases at baseline, additional analyses were carried out excluding the subjects who died during the first two years of follow-up.

To test whether there is a dose–response or non-linear association of BP as a continuous variable with the risk of all-cause mortality, we used restricted cubic splines to develop a hazard ratio (HR) curve to examine full-range association of SBP and DBP with the risk of all-cause mortality. We chose five knots at quintiles 5th, 27.5th, 50th, 75th and 95th. HR between two points of a continuous variable can be estimated by EXP $(Y_2 - Y_1)$, where Y_1 and Y_2 are the corresponding spline function values of the two points. If we select a proper point Y_1 as the referent, EXP $(Y_2 - Y_1)$ stands for the HR of point 2 versus point 1. Thus, we obtained the HR curves by plotting the HRs of all other points versus the referent point [22]. According to the nadir of the curve, we chose the reference group of categories of BP. Both baseline BP levels and updated mean values of BP during follow-up were used in the analyses. Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed with SAS for Windows, version 9.3 (SAS Institute, Cary, NC).

Table 1
Baseline characteristics of African American and white patients with diabetes.

	African American	White	P value
No. of participants	19,757	15,504	
Male, %	35.5	40.8	<0.001
Age, mean (SD), year	51.1 (0.1)	53.7 (0.1)	<0.001
Income, mean (SD), $/family	18,963 (192)	19,741 (218)	0.008
Body mass index, mean (SD)	33.6 (0.1)	35.0 (0.1)	<0.001
Baseline blood pressure, mean (SD), mm Hg			
Systolic	146 (0.2)	141 (0.2)	<0.001
Diastolic	82 (0.1)	78 (0.1)	<0.001
HbA1c, mean (SD), %	7.94 (0.02)	7.35 (0.02)	<0.001
LDL cholesterol, mean (SD), mg/dL	113 (0.3)	110 (0.3)	<0.001
Glomerular filtration rate (mL/min/1.73 m^2), %			<0.001
≥90	53.8	35.9	
60–89	35.2	47.0	
30–59	9.3	15.6	
15–29	1.1	1.1	
<15	0.6	0.4	
Smoking status, %			<0.001
Never smoking	67.8	63.3	
Past smoking	7.0	7.6	
Current smoking	25.3	29.1	
Type of insurance, %			<0.001
Free	78.3	76.1	
Self-pay	5.8	3.8	
Medicaid	6.1	4.0	
Medicare	8.2	13.2	
Commercial	1.7	2.9	
Uses of medications, %			
Glucose-lowering medication			<0.001
Oral hypoglycemic agents	33.4	34.5	
Insulin	32.8	26.6	
Lipid-lowering medication	55.1	58.2	<0.001
Antihypertensive medication	75.4	69.6	

*Values represent mean or percentage. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters.

3. Results

General characteristics of the study population are presented in Table 1. During a mean follow-up period of 8.7 years, 4199 (2146 white and 2053 African American) deaths were identified. After adjustment for all confounding factors, a significantly increased risk of all-cause mortality was observed among diabetic patients with SBP < 120 mm Hg and ≥160 mm Hg and DBP < 65 mm Hg and ≥100 mm Hg at baseline (multivariable-adjusted model b, Table 2). When SBP and DBP were considered as continuous variables by using restricted cubic splines, a nadir of the U-shaped association of BP with all-cause mortality risk was observed at 130–150 mm Hg for SBP and 80–90 mm Hg for DBP (Fig. 1).

The multivariable-adjusted HRs of all-cause mortality associated with different levels of joint SBP/DBP at baseline (<110/65, 110–119/65–69, 120–129/70–80, 130–139/80–90 [reference group], 140–159/