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ORIGINAL INVESTIGATIONS

Association of Systolic Blood Pressure Variability With Mortality, Coronary Heart Disease, Stroke, and Renal Disease

Elvira O. Gosmanova, MD,[a,b] Margit K. Mikkelsen, BS,[c] Miklos Z. Molnar, MD, PhD,[d] Jun L. Lu, MD,[d] Lenar T. Yessayan, MD, MS,[e] Kamyar Kalantar-Zadeh, MD, MPH, PhD,[f] Csaba P. Kovesdy, MD[d,g]

ABSTRACT

BACKGROUND Intraindividual blood pressure (BP) fluctuates dynamically over time. Previous studies suggested an adverse link between greater visit-to-visit variability in systolic blood pressure (SBP) and various outcomes. However, these studies have significant limitations, such as a small size, inclusion of selected populations, and restricted outcomes.

OBJECTIVES This study investigated the association of increased visit-to-visit variability and all-cause mortality, cardiovascular events, and end-stage renal disease (ESRD) in a large cohort of U.S. veterans.

METHODS From among 3,285,684 U.S. veterans with and without hypertension and normal estimated glomerular filtration rates (eGFR) during 2005 and 2006, we identified 2,865,157 patients who had 8 or more outpatient BP measurements. Systolic blood pressure variability (SBPV) was measured using the SD of all SBP values (normally distributed) in 1 individual. Associations of SD quartiles ($<$10.3, 10.3 to 12.7, 12.7 to 15.6, and $\geq$15.6 mm Hg) with all-cause mortality, incident coronary heart disease (CHD), stroke, and ESRD was examined using Cox models adjusted for sociodemographic characteristics, baseline eGFR, comorbidities, body mass index, SBP, diastolic BP, and antihypertensive medication use.

RESULTS Several sociodemographic variables (older age, male sex, African-American race, divorced or widowed status) and clinical characteristics (lower baseline eGFR, higher SBP and diastolic BP), and comorbidities (presence of diabetes, hypertension, cardiovascular disease, and lung disease) were all associated with higher intraindividual SBPV. The multivariable adjusted hazard ratios and 95% confidence intervals for SD quartiles 2 through 4 (compared with the first quartile) associated with all-cause mortality, CHD, stroke, and ESRD were incrementally higher.

CONCLUSIONS Higher SBPV in individuals with and without hypertension was associated with increased risks of all-cause mortality, CHD, stroke, and ESRD. Further studies are needed to determine interventions that can lower SBPV and their impact on adverse health outcomes. (J Am Coll Cardiol 2016;68:1375–86) Published by Elsevier on behalf of the American College of Cardiology Foundation.

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From the [a]Nephrology Section, Stratton Veterans Affairs (VA) Medical Center, Albany, New York; [b]Division of Nephrology, Albany Medical College, Albany, New York; [c]University of Texas Health Science Center, San Antonio, Texas; [d]Division of Nephrology, University of Tennessee Health Science Center, Memphis, Tennessee; [e]Division of Nephrology, University of Michigan, Ann Arbor, Michigan; [f]Harold Simmons Center for Chronic Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, California; and the [g]Nephrology Section, Memphis VA Medical Center, Memphis, Tennessee. This study was supported by grant R01DK096920 to Drs. Kalantar-Zadeh and Kovesdy and is the result of work supported with resources and the use of facilities at the Memphis VA Medical Center and the Long Beach VA Medical Center. Support for VA/Centers for Medicare and Medicaid Services (CMS) data is provided by the Department of Veterans Affairs, Veterans Health Administration,

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BP = blood pressure

CHD = coronary heart disease

CHF = congestive heart failure

CI = confidence interval

CPT = Current Procedural Terminology

eGFR = estimated glomerular filtration rate

ESRD = end-stage renal disease

HR = hazard ratio

ICD-9 = International Classification of Diseases, Ninth Revision

PDC = proportion of days covered

SBP = systolic blood pressure

SBPV = systolic blood pressure variability

SD = standard deviation

VA = Veterans Affairs

VISNs = Veterans Integrated Service Networks

VVV = visit-to-visit variability

Elevated blood pressure (BP) is the most common chronic medical disease observed in a variety of populations (1). It has been consistently demonstrated that higher baseline BP—both untreated and treated—is associated with a higher risk for all-cause mortality, cardiovascular morbidity and mortality, and end-stage renal disease (ESRD) (2–8). However, BP does not remain steady, but instead fluctuates continually, within a 24-h period, from day to day, and from month to month (9). Furthermore, these fluctuations are not random and tend to remain consistent within patients (10,11); therefore, the traditional correlation between baseline BP and outcomes of interest has a potential to underestimate the true risk of elevated BP. This phenomenon, known as "regression dilution," arises from the combined effects of measurement errors and both short-term (diurnal and seasonal) and long-term (changes in BP with aging, antihypertensive medication use, and adherence to antihypertensive medications) within-individual variability of BP (12). A large meta-analysis from the Prospective Study Group unequivocally demonstrated that the mean or "usual" BP, corrected for regression dilution, was strongly and linearly related to increased risk of mortality from coronary heart disease (CHD), stroke, and other vascular causes (13). However, even averaging BP over longer periods of follow-up may not fully address risks associated with BP variations. Visit-to-visit variability (VVV) of BP is being increasingly considered as a newer method to evaluate intraindividual BP fluctuations.

SEE PAGE 1387

Higher systolic blood pressure (SBP) variability (SBPV) has been shown to be a better predictor of all-cause and cardiovascular mortality (14–16), stroke (17,18), and cardiac disease (5,19–21) compared with average SBP. Nevertheless, a strong adverse association between increased SBPV and cardiovascular disease and stroke was not confirmed in all studies (21,22); additionally, some studies found associations between higher SBPV with all-cause mortality, but not with stroke or coronary events (20). Furthermore, these previous clinical observations have important limitations, such as being restricted to very specific or high-risk populations, having a small number of BP measurements and a small sample size, or assessing only selected outcomes. Therefore, we conducted a large cohort study involving 2,865,157 U.S. veterans who had at least 8 outpatient BP measurements to examine the prognostic significance of increased VVV of SBP on all-cause mortality, CHD, stroke, and ESRD.

METHODS

We used data from a historic cohort study examining risk factors in patients with incident chronic kidney disease consisting of 3,582,478 patients with an estimated glomerular filtration rate (eGFR) of ≥60 ml/min/1.73 m^2, based on serum creatinine measurements performed during October 1, 2004, through September 30, 2006, in any U.S. Department of Veterans Affairs (VA) facility (23–25). Of the 3,492,943 patients with any available SBP measurements, we excluded 5,466 with only inpatient SBP measurements and 622,320 patients who had ≤7 SBP records during follow-up. Our final analytic sample consisted of 2,865,157 patients (Online Figure 1).

SOCIODEMOGRAPHIC CHARACTERISTICS AND COMORBIDITIES. Cohort entry was defined as the date of the first eGFR measurement of ≥60 ml/min/1.73 m^2 between October 1, 2004, and September 30, 2006. Information about baseline age, race, sex, marital status, per capita income, comorbid conditions, body mass index (BMI), service connectedness (indicating whether comorbidities were directly caused by military service, resulting in certain privileges such as preferential access to care and lower copayments), and receipt of influenza vaccinations during the cohort entry period, and frequency of health care encounters (defined as the number of health care visits/year throughout the entire follow-up period) were obtained from national VA research data files, as previously described (26–28). Race was determined by combining information from VA sources with those obtained from Medicare through the VA-Medicare data merge project (29). In case of discrepancies, we

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