Journal of Diabetes and Its Complications 29 (2015) 699–706

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Relationships between the risk of cardiovascular disease in type 2 diabetes patients and both visit-to-visit variability and time-to-effect differences in blood pressure

Toshiko Takao [a,*], Kumiko Kimura [a], Machi Suka [b], Hiroyuki Yanagisawa [b], Masatoshi Kikuchi [a], Shoji Kawazu [a], Yutaka Matsuyama [c]

[a] Division of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan
[b] Department of Public Health and Environmental Medicine, The Jikei University School of Medicine, Tokyo, Japan
[c] Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan

ARTICLE INFO

Article history:
Received 19 November 2014
Received in revised form 7 March 2015
Accepted 17 March 2015
Available online 24 March 2015

Keywords:
Blood pressure
Cardiovascular disease
Type 2 diabetes
Visit-to-visit variability
Time-to-effect differences

ABSTRACT

Aims: To determine whether visit-to-visit blood pressure (BP) variability can predict cardiovascular disease (CVD) incidence in type 2 diabetes patients independently of mean BP, and to analyze the time-to-effect relationship between BP and CVD risk.
Methods: We retrospectively enrolled 629 type 2 diabetes patients with no history of CVD who first visited our hospital between 1995 and 1996, made at least one hospital visit per year, were followed-up for at least 1 year, and had undergone four or more BP measurements. The patients were followed until June 2012 at the latest.
Results: CVD occurred in 66 patients. Variability in systolic or diastolic BP (SBP and DBP, respectively) was a significant predictor of CVD incidence, independent of mean SBP or DBP. CVD incidence was significantly associated with SBP during the preceding 3–5 years, with the highest risk occurring during the preceding 3 years.
Conclusions: Visit-to-visit BP variability independently predicts CVD incidence in type 2 diabetes patients. Increased SBP over the preceding 3–5 years indicated a significant CVD risk. To prevent CVD, BP management should focus on stable and well-timed control. In particular, BP stabilization at an early phase and BP control during late phases are important.

1. Introduction

Recent studies, mostly of treated hypertensive patients, found an increased visit-to-visit variability in blood pressure (BP) to be predictive of cerebrovascular events (Hata et al., 2000; Rothwell et al., 2010a, 2010b), acute myocardial infarction (Hata et al., 2002), and all-cause mortality (Muntner et al., 2011), independently of the mean BP. In patients with type 2 diabetes, visit-to-visit BP variability was reported to be an independent predictor of macrovascular complications (Hata et al., 2013), and all-cause mortality (Hsieh et al., 2012). It has been suggested that increased BP variability may reflect arterial stiffness and baroreceptor dysfunction, which have been associated with arteriosclerosis and can result in vascular events (Floras et al., 1988; Hata et al., 2000, 2002; Rothwell, 2010; Shan, Dai, & Su, 2001). However, studies regarding the relationship between visit-to-visit BP variability and the incidence of cardiovascular disease (CVD) in patients with type 2 diabetes remain limited. In particular, there have been few studies on this topic conducted in a "real-world" setting.

Most interventional studies on diabetes and hypertension have confirmed that in the short term the effects of antihypertensive treatment on major cardiovascular outcomes usually appear beneficial (ADVANCE Collaborative Group, 2007; Estacio et al., 1998; Heart Outcomes Prevention Evaluation Study Investigators, 2000; Pahor et al., 2000; Tatti et al., 1998). However, evidence of the long-term effects of early BP control with initial treatment is weak. The authors of the Systolic Hypertension in Europe trial enrolled older patients with isolated systolic hypertension and demonstrated the long-term benefits of early BP control with initial antihypertensive treatment, particularly in patients with diabetes (Staessen et al., 2004). In contrast, the Hypertension in Diabetes Study (HDS) conducted within the framework of the United Kingdom Prospective Diabetes Study (UKPDS) revealed that BP control was associated with the short-term persistence of clinical benefits once the intervention was discontinued (Holman, Paul, Bethel, Neil, & Matthews, 2008). However, the UKPDS-HDS finding is considered inconclusive because of several possible limitations of the study (Bloch & Basile, 2009; Parati, Bilo, & Ochoa, 2011).

Conflicts of interest: None.

* Corresponding author at: Division of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, 2-2-6 Nihonbashi Bakurocho, Chuo-ku, Tokyo 103-0002, Japan. Tel.: +81 3 36395501; fax: +81 3 36395520.
E-mail address: t-takao@asahi-life.or.jp (T. Takao).

http://dx.doi.org/10.1016/j.jdiacomp.2015.03.010
1056-8727/

In this study, we sought to determine whether visit-to-visit BP variability can predict the incidence of CVD independently of mean BP, and to analyze the time-to-effect relationship between BP and the risk of these events, using a database of "real-world" observations with long-term follow-up in patients with type 2 diabetes.

2. Methods

2.1. Study subjects

Of the 1,912 patients who first visited the outpatient clinic of our hospital between January 1995 and December 1996, we retrospectively enrolled 629 patients with type 2 diabetes who made at least one hospital visit per year, had been followed-up for at least 1 year, and had undergone four or more BP measurements. Patients were excluded if they had impaired glucose tolerance or had a history of CVD at the first visit or within 1 year thereafter. Patients were followed until June 2012 at the latest. The follow-up period was defined as the time between the first visit and the date of CVD onset or of the last clinic visit. The number of patients confirmed dead from all other causes excluding CVD increased to 38, all of whom were regarded as censored cases at their last clinic visits.

The following baseline characteristics of the patients were analyzed: age, gender, duration of diabetes, BP, body mass index (BMI), HbA1c levels, serum lipid levels, serum creatinine (SCr) levels, estimated GFR (eGFR), smoking habits, alcohol use, type of treatment for diabetes, and use of antihypertensive medication (angiotensin converting enzyme [ACE] inhibitors, calcium channel blockers, α-blockers, and β-blockers) and/or lipid-lowering drugs. In 1995, when our study was initiated, the only renin–angiotensin system inhibitors available in Japan were ACE inhibitors. Initial therapy was defined as treatment initiated before the first visit, at the first visit, or within 1 year thereafter. Thus, the use of antihypertensive drugs was defined as medication which was provided during the initial 1 year. Patients who received a combination of insulin and oral antidiabetic drugs were considered insulin-treated patients.

The study design was consistent with the Japanese government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki. It was reviewed and approved by the institutional review board.

2.2. Endpoint definitions

The endpoint was the first CVD event, defined as fatal or non-fatal acute myocardial infarction, coronary artery procedure (bypass surgery or angioplasty) or stroke (ischemic or hemorrhagic) that required hospitalization. These events were determined according to a thorough review of medical records. Patients who did not have any CVD event, including those who had died from all other causes except CVD, were regarded as censored cases at the last clinic visit.

2.3. Data collection and definition of variables

Systolic BP (SBP), diastolic BP (DBP), and body weight were measured at each visit. BP was, as a rule, measured once in the sitting position by a trained medical technologist using an electronic sphygmomanometer (BP-10; OMRON, Kyoto, Japan). The standard deviation (SD), coefficient of variation (CV), and variation independent of mean (VIM) of both SBP and DBP for each patient during the 1-year period from the first visit were used as a measure of intrapersonal visit-to-visit variability in SBP and DBP. The mean SBP or DBP, and the number of measurements of SBP or DBP were also calculated during the 1-year period from the first visit. The recorded BP value was used, regardless of whether the patient began antihypertensive treatment during the follow-up period. Visit-to-visit BP variability calculated during the 1-year period following the initial visit was assessed as one of the baseline factors to predict future CVD events.

Capillary blood was drawn to determine blood glucose and HbA1c levels, regardless of fasting or postprandial status. HbA1c levels were measured using diabetes analyzers (Tosoh Bioscience, Tokyo, Japan). From November 1994, HbA1c levels were measured using high-performance liquid chromatography, as standardized by the Japan Diabetes Society (JDS). HbA1c values obtained before January 2007 were converted to JDS standard values (reference range, 4.3–5.8%) using linear regression equations. The equations were derived from duplicated assays using old and/or new devices or standard substances. From June 2012, we used the National Glycohemoglobin Standardization Program (NGSP)-certified method. In June 2012, all earlier HbA1c (%) values were converted to NGSP values (%) using the following equation: [HbA1c (NGSP) (%) = 1.02 × HbA1c (JDS) (%) + 0.25 (%)] (Kashiwagi et al., 2012).

Lipids were measured regardless of fasting or postprandial status. Total cholesterol (TC) levels were measured using an enzymatic method. High-density lipoprotein cholesterol (HDL-C) levels were measured using a dextran sulfate Mg precipitation method through April 25, 1996, after which they were measured using a direct enzymatic method. HDL-C data from the precipitation method were converted to direct enzymatic method equivalents using a linear regression equation derived from duplicate assays using the two methods. The baseline TC: HDL-C ratio (TC/HDL-C) was used as a covariate in the analysis because TC/HDL-C was reported to be the best predictor of CVD among men with type 2 diabetes (Jiang et al., 2004; Sone et al., 2012). Furthermore, it was found to be a stronger predictor of CVD compared with non-HDL-C in the UKPDS risk engine (Holman, Coleman, Shine, & Stevens, 2005).

SCr levels were measured using the Jaffe-Rate method through June 11, 1995, after which they were measured using an enzymatic method. SCr data obtained using the Jaffe-Rate method were converted to enzymatic-method equivalents using a linear regression equation derived from duplicate assays. The eGFR was determined using the following equation, as advocated by the Japanese Society of Nephrology: $\text{eGFR}\ (\text{mL/min/1.73 m}^2) = 194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287}$ (×0.739 if female) (Matsuo et al., 2009).

2.4. Statistical analysis

Data are expressed as means ± SD for continuous variables, or as numbers and percentages for categorical variables. Because the follow-up period, the number of BP measurements, and the interval between the successive BP measurements showed skewed distributions, they were expressed as median values (interquartile range). Differences between patients who did and did not develop a CVD event were analyzed by Student's *t*-tests for continuous variables and χ^2 tests or Fisher exact tests, as appropriate, for categorical variables. Logistic regression analysis was used to adjust for age, gender, and duration of diabetes. Univariate correlations between mean BP and BP variability were assessed using Pearson's correlations.

Subjects were classified according to tertiles of the SD, CV and VIM of SBP or DBP. Differences in the number of CVD events among the three groups were analyzed by the Cochran–Armitage trend test. Hazard ratios (HRs), for the incidence of CVD associated with tertiles of the SD, CV, and VIM of SBP and DBP (with the lowest tertile serving as the reference group), were calculated using Cox proportional hazard models. Values for the number of BP measurements were ln-transformed for inclusion in the model to adjust for the possibility that the number of measurements might influence BP variability. The HR and 95% confidence interval (CI) were initially calculated without adjustment, and then after adjustment for age, gender, intrapersonal mean of SBP or DBP, and the number of measurements of SBP or DBP. A subsequent model included adjustment for age, gender, mean of SBP or DBP, the number of measurements of SBP or DBP, use of antihypertensive drugs, duration of diabetes, BMI, HbA1c, TC/HDLC, current smoking, and alcohol use.