The Ankle Brachial Index Exhibits Better Association of Cardiovascular Prognosis Than Non–High-Density Lipoprotein Cholesterol in Type 2 Diabetes

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ABSTRACT

Objective: The association between ankle brachial index (ABI) and outcomes in diabetic subjects is controversial. The purpose of this study was to evaluate whether the ABI is more strongly associated with cardiovascular outcomes comparing with non–high-density lipoprotein cholesterol (non–HDL-c).

Research Design and Methods: A total of 452 type 2 diabetic subjects followed up for a mean of 5.8 years were grouped by ABI (<0.9 versus ≥ 0.9) and non–HDL-c (<100 mg/dL versus ≥ 100 mg/dL). Primary outcomes were composite events including all-cause mortality, hospitalization for coronary artery disease, stroke, revascularization, amputation and diabetic foot, and the secondary end point was all-cause mortality.

Results: Intergroup differences in percentage of men, duration of diabetes, hemoglobin A1c, total cholesterol, low-density lipoprotein cholesterol, triglycerides and estimated glomerular filtration rate were significant. A total of 64 composite events and 17 deaths were recorded. A higher number of composite events occurred in the group with abnormal ABI but optimal non–HDL-c than in those with suboptimal non–HDL-c but normal ABI (29% versus 11%, $P < 0.05$). A similar trend was observed in all-cause mortality (11% versus 1%, $P < 0.05$). The ABI was the dominant risk factor for both end points after adjusting other factors (for composite events, hazard ratio = 0.02, 95% CI: 0.00-0.10, $P < 0.001$ and for all-cause mortality, hazard ratio = 0.01, 95% CI: 0.00-0.28, $P = 0.006$).

Conclusions: The ABI was more strongly associated with outcomes in diabetes than non–HDL-c. The ABI should be routinely screened in diabetes even without symptom.

Key Indexing Terms: Ankle brachial index; Non–HDL-c; Type 2 diabetes mellitus; Cardiovascular outcome. **[Am J Med Sci 2016;351(5):492–498.]**

INTRODUCTION

Diabetes mellitus affected 371 million people in 2012 globally; this number is expected to rise to 552 million by 2030.[1,2] The type 2 diabetes is categorized as high-risk population for coronary heart disease according to the National Cholesterol Education Program Adult Treatment Panel III Guidelines.[3] The global assessment of modifiable risk factor of myocardial infarction enrolled 15,152 cases of myocardial infarction and 14,820 controls demonstrated that diabetes was one of the dominant risk factors associated with the occurrence of myocardial infarction.[4] A Finnish population–based study with an 18-year follow-up showed that subjects with diabetes had a 1.9-fold increased risk of mortality caused by coronary heart disease compared with nondiabetic individuals even without history of coronary heart disease.[5]

Non–high-density lipoprotein cholesterol (non–HDL-c) has been associated with cardiovascular outcomes.[6,7] In subjects with elevated triglyceride that are commonly observed in subjects with diabetes, non–HDL-c contributes to accurate evaluation of the risk of cardiovascular diseases because it contains another atherogenic triglyceride-rich particle in addition to low-density lipoprotein cholesterol (LDL-c) and very low–density lipoprotein cholesterol.[8] As LDL-c plays a major role in the pathogenesis of atherosclerosis, the meta-analysis that enrolled several statin trials concluded borderline superiority of association of non–HDL-c with cardiovascular events compared with either apolipoprotein B (Apo-B) or LDL-c.[9,10]

The risk of peripheral vascular disease increased 2-fold in patients with diabetes.[11] The ankle brachial index (ABI) is one of the noninvasive diagnostic methods for detecting the existence of peripheral vascular

disease.[12] The Edinburgh Artery Study showed that an ABI < 0.9 increased the credibility of the model for predicting the risk of fatal myocardial infarction after adjusting for conventional risk factors.[13] However, the association between ABI and cardiovascular outcomes in subjects with diabetes has been debated. Mostaza et al[14] demonstrated that the ABI was associated with major cardiovascular events, cardiovascular mortality and all-cause mortality in nondiabetic subjects but the same association was not found in diabetic ones. Furthermore, the 19-year follow-up of a population-based study showed that the association between ABI and all-cause mortality or ABI and cardiovascular mortality was similar whether or history of diabetes was presented.[15]

In view of the controversy of association between ABI and cardiovascular outcomes in subjects with diabetes, the purposes of this study are to test the association between ABI and cardiovascular outcomes as well as to demonstrate which of the ABI or non–HDL-c exhibits the strongest association with cardiovascular outcomes.

RESEARCH DESIGN AND METHODS

Patient Population and Clinical Data

This was a retrospective medical record review study and ethic approval was provided by the Taipei Veterans General Hospital, Taiwan (VGHIRB No.: 2012-07-029BC). The demographic and anthropometric characteristics, coronary artery disease (CAD) or cerebrovascular disease histories and ABI of patients with type 2 diabetes visiting and registered in the intensive diabetes care program of the division of endocrinology and metabolism of the Taipei Veterans General Hospital from July 1, 2005 to December 31, 2007, were reviewed. All ABI measurements were recorded by an Omron noninvasive vascular screening device (VP-1000, Omron Masusaka Company, Japan) for the purpose of screening for peripheral artery disease (PAD). Body mass index was calculated as weight (kg) divided by the square of height (meters). The pulse pressure was defined as the difference between systolic and diastolic blood pressure. The laboratory results obtained within 3 months of ABI measurement (either before or after), including hemoglobin A1c (HbA1C), serum creatinine, estimated glomerular filtration rate (eGFR) calculated by formula of the Modification of Diet in Renal Disease, lipid profiles and 2 consecutive daily urinary albumin excretions were recorded.

Groups and Outcome Definition

Enrolled patients were divided into 4 groups according to the combination of status of ABI ($\geq$ or $<$0.9) and lipid profile (non–HDL-c $\geq$ or $<$100 mg/dL). The rationale of grouping for the non–HDL-c was organized according to the suggestion of guideline of National Education Cholesterol Program for subjects with a very high cardiovascular risk, which was defined as diabetes comorbid with documented cardiovascular disease or multiple cardiovascular risk factors.[3] The outcomes of ABI measurement up to August 31, 2012, were retrospectively reviewed. The primary outcomes were composite events that included all-cause mortality, hospitalization for CAD, stroke, carotid or peripheral revascularization, lower-limb amputation and hospitalization for diabetic foot, and the secondary outcomes were all-cause mortality.

Statistics

An independent analysis of variance test was conducted to detect the differences of continuous variables that were expressed as mean $\pm$ standard deviation. The categorical variables were expressed as numbers and percentages and were compared with one another by the Pearson chi-square test. The cumulative events–free probabilities of primary and secondary end points were estimated by Kaplan-Meier analysis. The log-rank test was used to identify significant differences. All relevant variables were analyzed by univariate Cox proportional analysis and those with $P < 0.1$ were further subtracted to multivariate Cox proportional analysis and hazard ratio (HR) with corresponding probability values were calculated. The SPSS software package (version 18, IBM Corporation, Armonk, NY) was conducted for above analysis.

RESULTS

Baseline Characteristics

We analyzed the medical records of 452 type 2 diabetic individuals who were followed up for a mean duration of 5.8 years. All patients' baseline characteristics of the 4 groups are listed in Table 1. There were 89 patients in the group with ABI $\geq$ 0.9 and non–HDL-c $<$ 100 mg/dL; 17 patients in the group with ABI $<$ 0.9 but non–HDL-c still $<$100 mg/dL; 303 subjects with ABI $\geq$ 0.9 but non–HDL-c $\geq$ 100 mg/dL and 43 individuals with ABI $<$ 0.9 as well as non–HDL-c $\geq$ 100 mg/dL. The only significant differences among 4 groups were in the proportion of male sex, diabetes duration, HbA1C, total cholesterol, LDL-c, triglyceride and eGFR.

Primary Outcome

There were 64 composite events recorded by the end of the follow-up. The patients with an ABI $<$ 0.9 had higher rate of composite events than those with an ABI $\geq$ 0.9 (38.3% versus 10.4%, $P < 0.001$ by log-rank test) (Figure 1A). Subjects with ABI $<$ 0.9 as well as non–HDL-c $\geq$ 100 mg/dL had the worst outcomes among the 4 groups. Compared with individuals with normal ABI and non–HDL-c $<$ 100 mg/dL, a significantly higher rate of composite events was observed in this analysis (41% versus 8%, $P < 0.001$ for log-rank test). Furthermore, the outcomes of people with ABI $<$ 0.9 but non–HDL-c $<$ 100 mg/dL were worse than the subjects with ABI $\geq$ 0.9 and non–HDL-c $\geq$ 100 mg/dL (29% versus 11%, $P < 0.05$ for log-rank test) (Figure 2A and Table 2).