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COMMENTARY

# Improved prediction of cardiovascular events in diabetic patients: Role of quantitative ultrasonic tissue characterization

The early prediction of cardiovascular disease in patients with type 2 diabetes has been a subject of great interest for decades. This issue has become critical, as the number of individuals with diabetes is soaring, many of them remain under suboptimal control[1], and the burden of cardiovascular complications of diabetes is overwhelming in both developed and developing countries. In addition to well-known demographic and metabolic characteristics, both genetic and non-genetic risk factors have been shown to have a certain value in predicting cardiovascular events[2,3]. However, current cardiovascular risk assessment does not fully take into account the subsequent events, partly because these risk factors do not directly reflect functional and structural changes in vascular lesions. Thus, recent studies using non-invasive image techniques targeting vascular structure might provide additional information in predicting clinical cardiovascular disease (Figure 1). In this regard, Katakami *et al.*[4] reported that the application of ultrasonic tissue characterization of carotid plaque could improve the prediction of cardiovascular events in Japanese patients with type 2 diabetes.

Ample evidence suggests the usefulness of non-invasive imaging techniques to detect or predict cardiovascular events[5]. Ankle-brachial index (ABI) and toe brachial index (TBI) are the most common measurements of peripheral arterial narrowing or obstruction. An ABI value <0.9 is an independent risk factor for a cardiovascular event, and because medial arterial calcification is less frequent in the toe than in the ankle, TBI is considered for the early detection of atherosclerotic cardiovascular disease[3]. Previous studies showed that aortic stiffness, measured by carotid-femoral pulse wave velocity (cf-PWV), is a predictor of all-cause and cardiovascular mortality. Peripheral arterial stiffness, measured by brachial–ankle pulse wave velocity (ba-PWV), has been shown to be a predictor of the development of coronary artery disease[2]. Carotid intima-media thickness (CIMT), assessed using ultrasound imaging to evaluate the size of plaques and structural changes of the carotid artery, has also been reported to be associated with the presence of systemic atherosclerosis and cardiovascular events[2]. However, in comparison with the other methods, CIMT examination is more skill-dependent and time-consuming. Integrated backscatter (IBS) signal, obtained by ultrasound examination of the carotid artery, can characterize tissue of arterial plaque and has been shown to be significantly lower in patients with a history of cardiovascular diseases. More specifically, a low calibrated IBS (calibrated IBS = IBS values in the intima-media complex − IBS values in the adventitia) can indicate the histological content (more lipidic, fibrotic and calcific components) of carotid plaques, and potentially an association of the presence of a thin fibrous cap with lipid-rich and unstable plaques[4].

In a mean follow-up period of 7.9 years, investigators observed that baseline-calibrated IBS provided additional value in predicting cardiovascular events in asymptomatic, middle-aged and older type 2 diabetic patients who had carotid plaque[4]. In fact, Katakami *et al.*[4] showed that both calibrated-IBS values and plaque thickness (measured by ultrasound-assessed CIMT) were independently associated with cardiovascular events, even after adjusting for the 10-year risk of a general cardiovascular disease estimated using the Framingham risk scoring (FRS) or UK Prospective Diabetes Study (UKPDS) risk engine. Their observations are valuable given a prospective design with a relatively long follow-up period. However, several issues need to be addressed. Although the aforementioned study had originally been designed as a pilot study, the number of study participants was small. During the follow-up period, just 20 new cardiovascular events occurred, (14 coronary heart events and 6 ischemic strokes). It included a wide spectrum of cardiovascular events, ranging from angina attack to death, to both fatal and non-fatal ischemic stroke diagnosed by experts based on clinical symptoms or imaging findings. Few participants and a lower-than-anticipated number of cardiovascular events limited the potential to generalize to other diabetic populations. In fact, this study excluded diabetic patients with a history of coronary heart disease and cerebral infarction. Diabetic patients who have existing cardiovascular disease usually present with various degrees of carotid stenosis and should be the targets of special attention, because many of them develop recurrent cardiovascular events within a short period of time. Another major concern is that the ideal threshold of calibrated IBS remains to be determined. Despite high sensitivity (93%) and moderate specificity (61%) achieved by using a cut-off value of −17.8 dB for calibrated IBS, this suggested value has to be confirmed in further studies enrolling other populations; in particular, age-stratified patients and those with calcified plaques. This is a hospital-based study, and the external validity is limited. In

*Corresponding author. Wayne H-H Sheu
Tel.: +886-4-2374-1300
Fax: +886-4-2374-1318
E-mail address: whhsheu@vghtc.gov.tw
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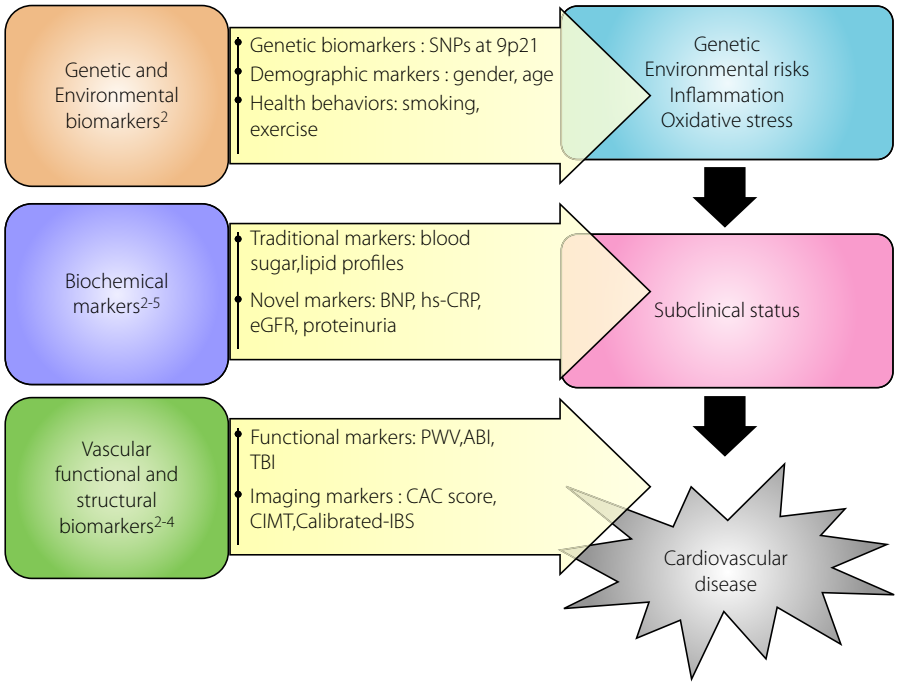


**Figure 1** | Progression of cardiovascular disease – from potential risk to overt cardiovascular disease and the detectable markers of each clinical status. Some interventions, such as lifestyle modification, use of antihypertensive drugs, oral antidiabetic drugs and antidyslipidemic drugs such as statins, might improve these biomarkers, but whether these biomarkers lead to changes in patient management and improvements in outcome is largely unexplored. Proteinurea was measured by urinary albumin to creatinine ratio. ABI, ankle-brachial index; BNP, B-type natriuretic peptide; CAC score, coronary artery calcium score; Calibrated-IBS, calibrated-integrated backscatter analysis; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; PWV, pulse wave velocity including brachial-ankle pulse wave velocity and carotid-femoral pulse wave velocity; SNPs at 9p21, single nucleotide polymorphisms on chromosome 9p21; TBI, toe brachial index.

this study, Framingham risk scoring, as well as the UK Prospective Diabetes Study risk engine, were used to derive the 10-year risk for studied subjects. Whether these estimations originally obtained from general populations are applicable to diabetic and/or Asian individuals remains a subject of debate. Finally, it has been shown that cardiovascular risk factors, such as the components of metabolic syndrome, and concomitant use of several drugs (e.g., pioglitazone and statins) can change the IBS values in coronary and carotid arteries. This study failed to adjust these potential confounders, let alone those in formation of glycemic control, BP changes and medication alterations, which might also affect the changes of calibrated-IBS values and carotid plaques during follow-up periods.

Despite these limitations, we believe the findings of this study are of great interest, as they extend the scope of conventional coronary risk factors to include carotid plaque, as measured by CIMT plus calibrated IBS, in prediction of cardiovascular complications in asymptomatic patients with type 2 diabetes. Multicenter, large-scale studies are required to obtain sufficient information regarding the practical application of quantitative ultrasound examination of carotid plaques in early detection of cardiovascular risk in high-risk type 2 diabetic patients.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

Yi-Jing Sheen[1], Wayne H-H Sheu[2,3,4,*]
[1]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Hospital, Department of Health, Executive Yuan,* [2]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung,* [3]*School of Medicine, National Yang-Ming University, Taipei, and* [4]*School of Medicine, National Defense Medical Center, Taipei, Taiwan*

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