

Carotid ultrasonography: A potent tool for better clinical practice in diagnosis of atherosclerosis in diabetic patients

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ABSTRACT

Cardiovascular disease (CVD) remains the main cause of death in diabetic patients, and once it has developed, diabetic patients have a worse outcome as compared with non-diabetic patients. One reason for this is the difficulty of early diagnosis of atherosclerotic change in these patients. Although cardiovascular risk assessment based on conventional risk factors is recommended for predicting cardiovascular risk, validation studies showed only moderate performance. In contrast, it is unrealistic to screen for subclinical or silent atherosclerosis by sophisticated modalities, such as myocardial perfusion scintigraphy, coronary computed tomography angiography or conventional angiography in all diabetic patients, as these tests are limited by the potential of significant adverse effects, technical difficulty, availability and high cost. Therefore, a non-invasive and inexpensive tool for risk prediction of subclinical atherosclerosis is required for identifying individuals at high risk of CVD. Recently, a number of studies have shown close associations between carotid atherosclerosis and cerebrovascular or coronary artery disease. Carotid ultrasonography has allowed clinicians to visualize the characteristics of the carotid wall and lumen surfaces to quantify the severity of atherosclerosis. Carotid intima-media thickness (IMT) is an especially useful marker of the progression of atherosclerosis throughout the body, and is an excellent predictor of cardiovascular events. As a simple and non-invasive procedure, measurement of carotid IMT is one of the most appropriate screening methods to specify high-risk individuals in subjects with and without diabetes. Therefore, it is expected that carotid ultrasonography will become a potent tool for better clinical practice of atherosclerosis in diabetic patients.

INTRODUCTION

Cardiovascular disease (CVD) remains the main cause of death in diabetic patients, and once it has developed, diabetic patients have a worse outcome as compared with non-diabetic patients. One reason for this is the difficulty of early diagnosis of atherosclerotic change in major arteries, including coronary, cerebral, renal and peripheral arteries. For example, many cases of coronary atherosclerosis develop without symptoms, especially in diabetic patients. Indeed, it is reported that, in patients with ischemic heart disease, the frequency of silent myocardial ischemia is approximately three to sixfold higher in diabetic patients than in

non-diabetic patients¹. According to the Detection of Ischemia in Asymptomatic Diabetes (DIAD) study, as much as 22% of asymptomatic type 2 diabetic patients aged 50–70 years were shown to have silent myocardial ischemia identified by myocardial perfusion scintigraphy². Therefore, early detection of asymptomatic severe coronary artery disease (CAD), as well as cerebrovascular disease, and subsequent rapid intervention, are important to reduce mortality in the management of diabetes.

Atherosclerosis is a multifactorial disease, and the development of atherosclerotic disease involves the interaction of many genetic and environmental factors through conventional risk factors, such as diabetes, dyslipidemia, hypertension and obesity (Figure 1). Therefore, cardiovascular risk assessment based on such conventional risk factors is recommended for predicting

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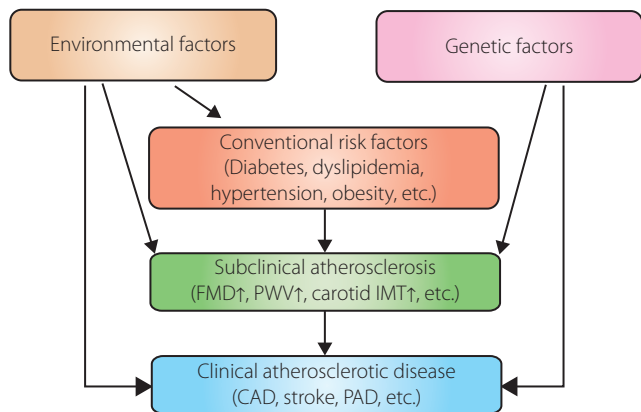


Figure 1 | Atherosclerosis is a multifactorial disease, and the development of atherosclerotic disease involves the interaction of many genetic and environmental factors, as well as conventional risk factors, such as diabetes, dyslipidemia, hypertension and obesity. CAD, coronary artery disease; FMD, flow-mediated vasodilation; IMT, intima-media thickness; PAD, peripheral artery disease; PWV, pulse wave velocity.

cardiovascular risk. However, validation studies showed that this approach had only moderate performance³⁻⁵. In contrast, sophisticated cardiac studies, such as exercise electrocardiogram (ECG), myocardial perfusion scintigraphy, coronary computed tomography angiography (coronary CT angiography) and conventional coronary angiography can determine disease severity with a high degree of sensitivity and specificity. However, it is unrealistic to screen for silent myocardial ischemia

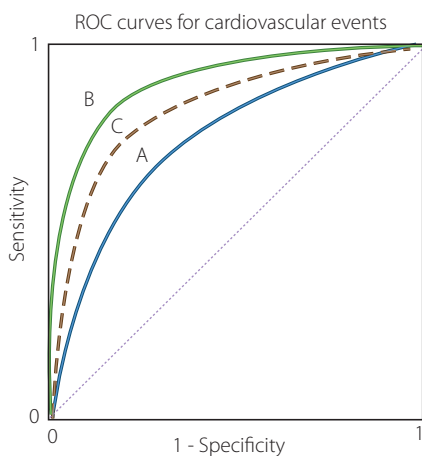
with these tools in all diabetic patients, as these tests are limited by the potential of significant adverse effects, technical difficulty, availability and high cost. The same is true for cerebrovascular diseases. Therefore, a non-invasive and inexpensive tool for prediction of risk of subclinical or silent atherosclerosis with more than moderate predictive ability is required for identifying individuals at high risk of CVD (Figure 2).

Recently, a number of studies have shown close associations between carotid atherosclerosis and cerebrovascular or coronary artery disease. Carotid ultrasonography has allowed clinicians to visualize the characteristics of the carotid wall and lumen surfaces to quantify the severity of atherosclerosis. Carotid intima-media thickness (IMT) measured with B-mode ultrasound correlates well with that obtained by pathological measurements, and has been confirmed to be a quantitative and reproducible measure of carotid arteriosclerosis⁶. Carotid IMT measured by ultrasonography also correlates well with aortic IMT measured by transesophageal echocardiography, and is believed to reflect the severity of systemic atherosclerosis. As it is a non-invasive, convenient and economical procedure, carotid ultrasonography could be useful in the diagnosis and screening of atherosclerosis.

MEASUREMENT OF CAROTID IMT

Methods

Using B-mode ultrasonography, the carotid arteries are scanned in transverse sections from the origins of the common carotid arteries, carotid sinuses, internal carotid arteries and external carotid arteries, and then examined for carotid lesions in longi-



	Marker	AUC of ROC
A	Conventional risk factors	0.6–0.7
B	Conventional risk factors + sophisticated study	0.9–0.95
C	Conventional risk factors + non-invasive, inexpensive surrogate marker	0.6–0.7 + α

Association between AUC and predictive ability

AUC 0.9 – 1.0	High accuracy	↑ high low
AUC 0.7 – 0.9	Moderate accuracy	
AUC 0.5 – 0.7	Low accuracy	

Figure 2 | Previous studies reported that a conventional risk assessment approach showed limited performance (blue solid line). In contrast, sophisticated studies, such as exercise electrocardiogram, myocardial perfusion scintigraphy, computed tomography, magnetic resonance imaging and coronary angiography, can determine disease severity with a high degree of sensitivity and specificity (green solid line). However, it is unrealistic to screen for cardiovascular disease (CVD) with these tools in all diabetic patients, as these tests are limited by the potential of significant adverse effects, technical difficulty, availability and high cost. Therefore, a non-invasive and inexpensive risk prediction tool with more than moderate predictive ability (dot line) is required for identifying individuals at high-risk of CVD. AUC, area under curve; ROC, receiver operator characteristic.

tudinal sections at different angles. High-resolution ultrasound images with a range resolution of 0.1 mm can be obtained when carotid ultrasonography is carried out using a linear probe with a center frequency of 7.5 MHz or higher. Ultrasound devices equipped with automatic IMT measuring software that recently became available might reduce the interexaminer error and shorten the examination time. In clinical studies using carotid IMT as an end-point, automatic IMT measurement is becoming essential.

Definitions of Carotid IMT and Plaques

B-mode ultrasonography visualizes the carotid wall as three layers, consisting of a hyperechoic layer, a hypoechoic layer and another hyperechoic layer. The two layers closer to the vascular lumen are defined as the intima-media complex, and the thickness of the intima-media complex as the IMT. The intima-media complex on

the distal wall of the carotid artery is defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface, which are in parallel.

There are controversies regarding the definition of plaque and whether plaque thickness should be included in IMT. In Japan, several guidelines on carotid ultrasonography have been published, and all of them include plaque thickness in IMT. For example, the Japan Academy of Neurosonology⁷ recommends: (i) measuring carotid IMT at the common carotid artery, carotid sinus or the bifurcation of the common carotid artery and internal carotid artery as the thickness at the thickest point, including plaque (IMT-Cmax, IMT-Bmax and IMT-Imax); (ii) recording the highest value among the three carotid IMT measurements as the maximum carotid IMT (max-IMT); (iii) calculating the mean carotid IMT (mean-IMT) as the mean value of the IMT values at the thickest point in the

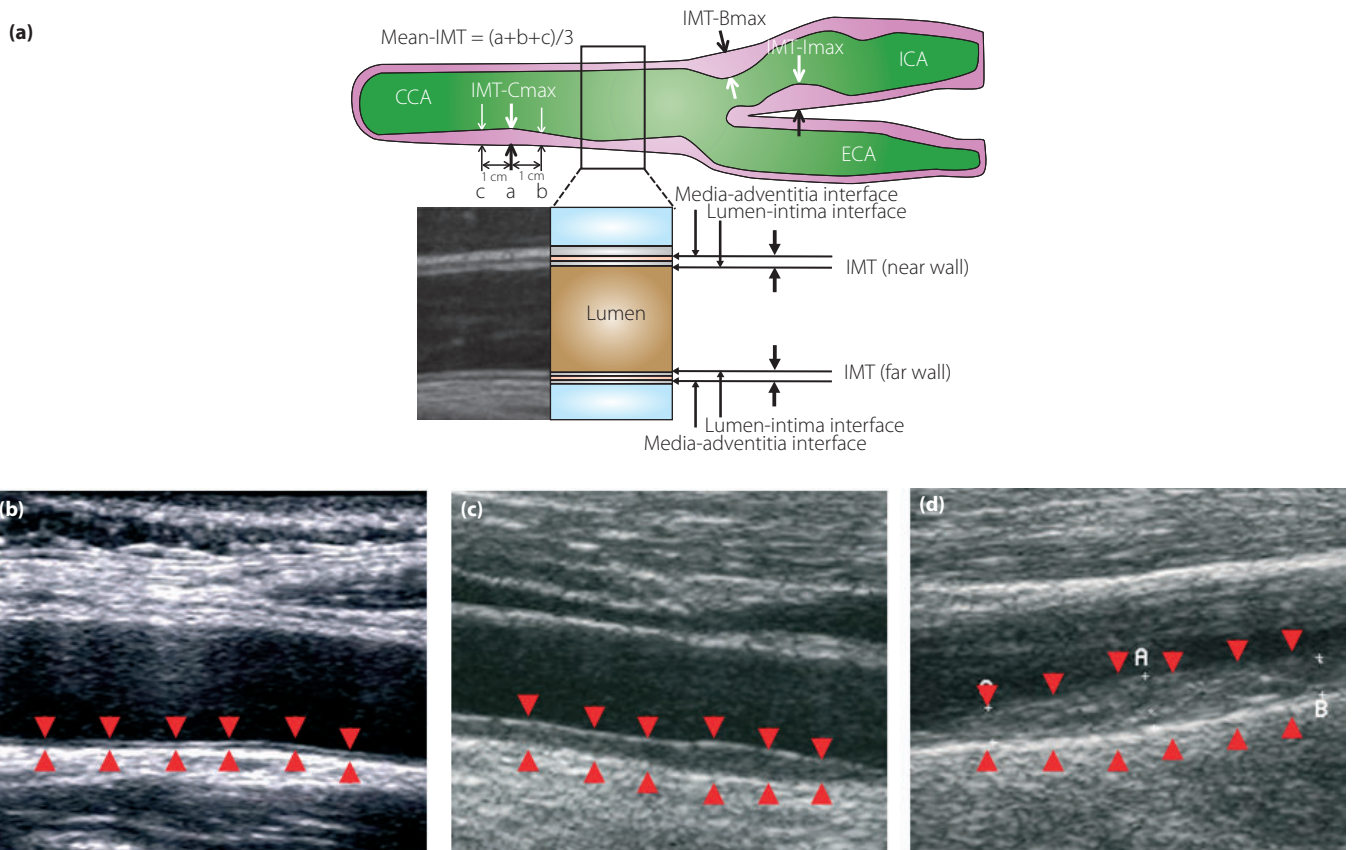


Figure 3 | (a) The intima-media thickness (IMT) is a double-line pattern visualized by ultrasound on both walls of the carotid arteries. It is shown by two parallel lines that delineate the leading edges of two anatomical boundaries, the lumen-intima and media-adventitia interfaces. The Japan Academy of Neurosonology recommends: (i) measuring carotid IMT at the common carotid artery, carotid sinus or the bifurcation of the common carotid artery, and internal carotid artery as the thickness at the thickest point, including plaque (IMT-Cmax, IMT-Bmax and IMT-Imax); (ii) recording the highest value among the three carotid IMT measurements as the maximum carotid IMT (max-IMT); (iii) calculating the mean carotid IMT (mean-IMT) as the mean value of the IMT values at the thickest point in the common carotid artery, and 1 cm distal and proximal from the thickest point; and (iv) handling all wall hyperplasias at a thickness of ≥ 1.1 mm as plaques. B-mode views of (b) a normal carotid, (c) a carotid with moderate IMT thickening and (d) that with severe IMT thickening. Arrowheads indicate the lumen-intima and media-adventitia interfaces. CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery.

common carotid artery, and 1 cm distal and proximal from the thickest point; and (iv) handling all wall hyperplasias at a thickness of ≥ 1.1 mm as plaques (Figure 3).

The guidelines proposed by the Japan Society of Ultrasonics in Medicine (JSUM)⁸ define plaques as 'localized elevated lesions with maximum thickness of more than 1 mm, having a point of inflection on the surface of the intima-media complex (IMC)', and, in cases of vascular remodeling, allow the term 'plaques' to be used irrespective of the presence/absence of elevation of the lesion into the vascular lumen. The JSUM recommends that plaques be included when measuring max-IMT.

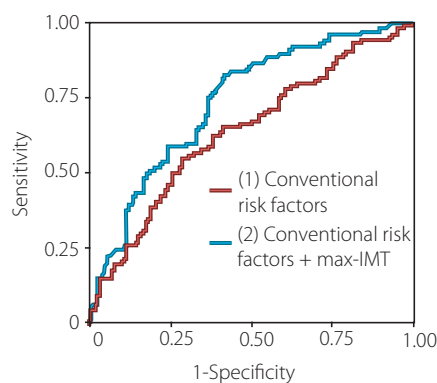
In a guideline document published in Europe⁹, plaque is defined as 'a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value or shows a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface'. This guideline document emphasizes the importance of not including the plaque segment in the determination of IMT.

As an increase in IMT reflects not only the progression of atherosclerotic disease, but also non-atherosclerotic compensatory enlargement of the carotid wall, it appears appropriate to assess IMT and plaque size separately. However, it is not always possible to differentiate early plaque formation from non-atherosclerotic enlargement of the vascular wall on the basis of echographic findings alone. In addition, the maximum carotid IMT that is determined as the thickness of the thickest carotid wall including plaque is superior to the mean IMT in predicting CAD, and using IMT as the size of the carotid wall including plaque would be clinically significant.

RELATIONSHIP BETWEEN CAROTID IMT AND CARDIOVASCULAR DISEASES (RESULTS OF CROSS-SECTIONAL STUDIES)

Coronary Artery Disease

In an analysis of data of 468 patients undergoing cardiac catheterization and B-mode ultrasound of the carotid arteries, Wofford *et al.*¹⁰ showed that patients with more severe extracranial carotid artery atherosclerosis are several times more likely to have multiple vessel CAD. Hulthe *et al.*¹¹ reported a significant correlation between the IMT of the carotid bulb and diameter stenosis of the included coronary segments ($r = 0.68$). Thus, the degree of carotid atherosclerosis correlates with that of coronary atherosclerosis, and the latter might be estimated to some extent by assessing the former. Recently, we carried out coronary CT angiography in 91 diabetic patients with carotid plaque (IMT ≥ 1.1 mm) to examine the relationship between the presence and extent of coronary atherosclerosis and carotid IMT, and found that more than 30% of the patients had $\geq 50\%$ coronary stenosis, and max-IMT was useful in distinguishing patients with coronary stenosis¹². In another study of 241 patients with asymptomatic type 2 diabetes, we found that carotid IMT was an independent predictor of coronary stenosis, and a receiver operator characteristic (ROC) curve analysis for the prediction of the presence of coronary stenosis showed that the area under curve (AUC) increased significantly after adding max-IMT to conventional coronary risk factors (from 0.64 to 0.74, $P = 0.020$ ¹³; Figure 4). These findings show that the addition of max-IMT to conventional risk factors significantly improved the prediction ability of coronary atherosclerosis.



	AUC	95% CI	P-value	(1) vs (2)
(1) Conventional risk factors	0.64	0.57–0.71	0.001	
(2) Conventional + max-IMT	0.74	0.67–0.80	<0.001	$P = 0.020$

Figure 4 | Receiver operator characteristic (ROC) curves for the prediction of the presence of coronary stenosis. ROC curves were plotted for conventional coronary risk factors, with and without maximum carotid intima-media thickness (max-IMT). This analysis showed that the area under curve (AUC) significantly increased after the addition of max-IMT to conventional coronary risk factors (from 0.64 to 0.74, $P = 0.020$), showing that the addition of max-IMT to conventional risk factors significantly improves the prediction ability of coronary atherosclerosis. Conventional risk factors include age, sex, smoking status, hypertension, dyslipidemia and albumin creatinine ratio. CI, confidence interval

In a study in healthy elderly individuals, Nagai *et al.*¹⁴ reported that those with ischemic ST-segment depression on exercise ECG had a significant increase in carotid IMT, and each 0.1 mm increase in IMT was associated with a 1.91-fold increased risk for concordant positive exercise tests or manifest CAD. In another study of patients with borderline glucose tolerance and those with type 2 diabetes, ischemic ECG changes were rare among patients with a carotid IMT of ≤ 1.0 mm, but were observed in approximately 10% of those with a carotid IMT of ≥ 1.1 mm¹⁵. These findings show that the risk of the presence of myocardial ischemia is higher in patients with higher carotid IMT.

In a cross-sectional survey of 1,257 randomly selected middle-aged men in Finland, Salonen *et al.*¹⁶ reported that for each 0.1 mm of common carotid IMT, the risk of acute myocardial infarction increased by 11%. O'Leary *et al.*¹⁷ also carried out a cross-sectional study in which carotid ultrasound was undertaken in 5,201 men and women aged ≥ 65 years to determine maximum present stenosis, maximum common carotid IMT and maximum internal carotid IMT. They then assessed the relationships between these ultrasound measures, risk factors, and manifestations of coronary heart disease and stroke, and concluded that these ultrasound measures were associated with coronary heart disease and stroke. Based on a cross-sectional study in 3,192 Japanese type 2 diabetic patients, we also confirmed that the prevalence of CAD was significantly higher in patients with a carotid IMT of ≥ 1.1 mm as compared with those with a carotid IMT of ≤ 1.0 mm (11.3% vs 5.2%, $P < 0.0001$). These data show a close association between carotid IMT and CAD.

We investigated the usefulness of carotid ultrasound in differentiating patients with coronary atherosclerosis or asymptomatic myocardial ischemia from those without. In our study¹⁸, 333 patients with asymptomatic type 2 diabetes with

no history of CAD underwent carotid ultrasound, as well as either exercise ECG or myocardial perfusion scintigraphy to screen for CAD. Then, the patients with myocardial ischemia were subjected to coronary CT angiography or conventional coronary angiography, and were examined by cardiologists to determine whether revascularization was indicated according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for percutaneous coronary intervention. Data were analyzed to assess the correlation between the presence of severe CAD warranting revascularization and carotid IMT, and to obtain a cut-off level of maximum carotid IMT to predict severe CAD. The results shown that maximum carotid IMT is an independent predictor of the presence of severe CAD, and that the ability to predict severe CAD significantly increases when the maximum carotid IMT is added to conventional coronary risk factors; that is, age, sex, hypertension, dyslipidemia, smoking history and glycated hemoglobin (HbA^{1c}; AUC of the ROC curve: 0.67 vs 0.79, $P = 0.039$), and that a cut-off value of 2.45 mm for maximum carotid IMT yielded the best predictive value for severe CAD. These findings show that carotid IMT is useful in screening patients with asymptomatic type 2 diabetes for the presence of CAD.

Cerebral Infarction

In a study of 5,858 individuals aged ≥ 65 years without pre-existing cardiovascular disease who lived in the local community, O'Leary *et al.*¹⁹ reported that an increase in carotid IMT is directly associated with an increased risk of stroke in older adults without a history of cardiovascular disease. Hougaku *et al.*²⁰ assessed 117 individuals who had at least one established risk factor for stroke, and found that the prevalence of silent cerebral infarction was high in individuals with higher plaque score, more severe carotid stenosis or ulcerated carotid lesions.

Table 1 | Relative risk of myocardial infarction, stroke and cardiovascular disease associated with carotid intima-media thickness in main prospective studies

Study [ref.]	No. participants	Sex/age	Measured IMT	Follow-up time (event)	Relative risk (95% CI) [Hazard ratio for CIMT]
KIHD ²²	1,288	M/42–60	Max-IMT (CCA)	1.0 (MI)	2.17 (0.70–6.74) [CIMT ≥ 1 vs < 1 mm]
ROT ²³	1,373	M/F/ ≥ 55	Mean-IMT (CCA)	2.7 (MI)	1.43 (1.16–1.78) [per 1SD (0.16 mm) CIMT]*
				2.7 (stroke)	1.41 (1.25–1.82) [per 1SD (0.16 mm) CIMT]*
CHS ¹⁸	4,476	M/F/ ≥ 65	Max-IMT (CCA)	6.2 (MI)	3.17 (1.96–5.12) [5th vs 1st CIMT quintile]*
				6.2 (stroke)	2.76 (1.80–4.24) [5th vs 1st CIMT quintile]*
ARIC ²⁴	5,552	M/45–64	Mean-IMT (overall)	5.2 (MI)	1.85 (1.28–2.69) > 1 mm, yes vs no]†
	7,189	F/45–64	Mean-IMT (overall)	5.2 (MI)	5.07 (3.08–8.36) > 1 mm, yes vs no]†
	6,349	M/45–64	Mean-IMT (overall)	7.2 (stroke)	1.98 (1.24–3.15) > 1 mm, yes vs no]†
	7,865	F/45–64	Mean-IMT (overall)	7.2 (stroke)	3.31 (1.88–5.81) > 1 mm, yes vs no]†
Yoshida, <i>et al.</i> ²⁸	783	M/F/30–75 (T2DM)	Mean-IMT in CCA	7.2 (CVD)	2.39 (1.19–4.81) [per 1SD CIMT]*
Present study	469	M/F/ ≥ 25 (T2DM)	Max-IMT (overall)	6.1 (CVD)	1.62 (1.32–2.00) [per 1SD CIMT]*

ARIC, Atherosclerosis Risk in Communities; CCA, common carotid artery; CI, confidence interval; IMT, intima-media thickness; CHS, Cardiovascular Health Study; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; F, female; KIHD, Kuopio Ischemic Heart Disease Study; M, male; MI, myocardial infarction; ROT, Rotterdam Study; SD, standard deviation; T2DM, type 2 diabetes. *Age and sex adjusted. †Age and race adjusted.

Peripheral Artery Disease

In the Edinburgh Artery Study²¹, the presence of symptomatic or asymptomatic peripheral arterial disease was significantly associated with increased carotid IMT. In the Atherosclerosis Risk in Communities (ARIC) Study²², a prospective study in 1,651 diabetic patients, carotid IMT was an independent risk factor for developing peripheral arterial disease.

CAROTID IMT AS A PREDICTOR OF CARDIOVASCULAR EVENTS

A number of longitudinal surveys have shown that carotid IMT is an independent predictor of cardiovascular events (Table 1). In a prospective study of 1,288 Finnish men to assess the relationship between ultrasonographically assessed carotid morphology and the risk of acute coronary events, Salonen *et al.*²³ reported that the presence of any structural changes in the common carotid arteries or carotid bulbs was associated with a 3.29-fold risk, intimal-medial thickening (>1.0 mm) with a 2.17-fold risk, small carotid plaques with a 4.15-fold risk and stenotic plaques with a 6.71-fold risk of acute coronary events. In the Rotterdam Study²⁴ in which 1,373 individuals aged ≥55 years underwent carotid IMT measurements and were

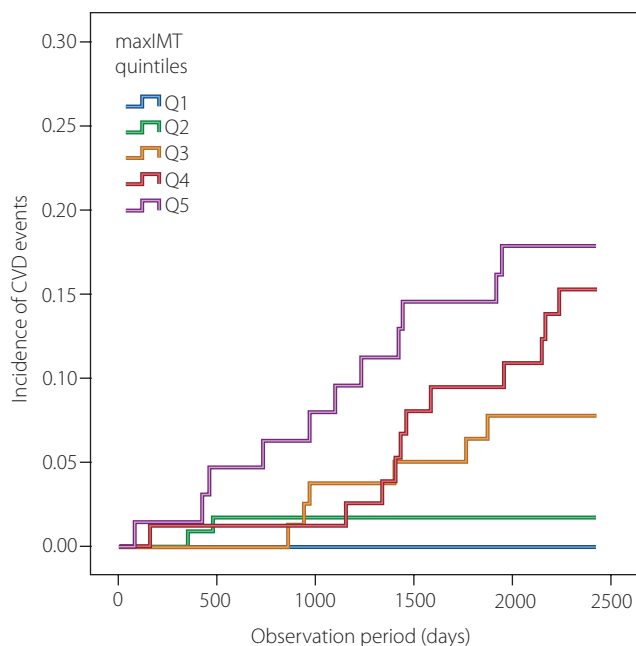


Figure 5 | Kaplan-Meier curves showing the cumulative probability of cardiovascular events in Japanese type 2 diabetic patients. A total of 469 subjects were divided into five subgroups by quintiles (Q) according to their baseline carotid intima-media thickness (max-IMT) values (Q1: ≤0.8 mm, Q2: 0.9–1.1 mm, Q3: 1.2–1.4 mm, Q4: 1.5–1.9 mm, and Q5: ≥2.0 mm) and followed up for 6.1 years to assess the relationship between the baseline carotid IMT and occurrence of cardiovascular events. The risk for cardiovascular events was higher in patients with increased baseline max-IMT ($P < 0.001$, log-rank test). CVD, cardiovascular disease.

Table 2 | Hazard ratio for myocardial infarction and stroke per 1 SD and 0.1 mm difference in common carotid artery intima-media thickness adjusted for age and sex: results of a meta-analysis

IMT difference	Myocardial infarction (Hazard ratio [95% CI])	Stroke (Hazard ratio [95% CI])
+1SD IMT difference	1.26 [1.21–1.30]	1.32 [1.27–1.38]
+0.10 mm IMT difference	1.15 [1.12–1.17]	1.18 [1.16–1.21]

CCA, common carotid artery; CI, confidence interval; IMT; intima-media thickness; SD, standard deviation.

followed up for 2.7 years on average for the development of stroke and myocardial infarction, Bots *et al.* showed that the odds ratio for stroke per standard deviation increase (0.163 mm) in carotid IMT was 1.41 (41% increase in risk), and that for myocardial infarction the odds ratio was 1.43 (43% increase in risk). O'Leary *et al.*¹⁹ followed up 4,476 individuals aged ≥65 years for 6.2 years to assess the relationship between carotid IMT and the occurrence of cardiovascular events, and reported that the incidences of myocardial infarction and stroke were higher in individuals with increased carotid IMT. Chambless *et al.*²⁵ and Hodis *et al.*²⁶ have also reported similar results.

Regarding diabetic patients, Yamasaki *et al.*²⁷ reported that carotid IMT at baseline was a strong predictor of the development of non-fatal coronary heart disease in a study of 287 Japanese type 2 diabetic patients followed up for 3 years. We also confirmed that carotid IMT at baseline could be a predictor for the development of cardiovascular events in asymptomatic type 2 diabetic patients followed up for 6.1 years (Figure 5).

Recently, Lorenz *et al.*²⁸ carried out a systematic review and meta-analysis to review data from 37,197 subjects who were followed up for a mean of 5.5 years in eight studies with general population-based samples for which carotid IMT was measured. The age- and sex-adjusted overall estimates of the relative risks of myocardial infarction and stroke were 1.26 (95% confidence interval [CI] 1.21–1.30) and 1.32 (95% CI 1.27–1.38), respectively, per 1-standard deviation common carotid artery IMT difference, and 1.15 (1.12–1.17) and 1.18 (1.16–1.21), respectively, per 0.10-mm common carotid artery IMT difference (Table 2). Even after adjustment for a complete set of conventional cardiovascular risk factors, carotid IMT was an independent predictor of future cardiovascular events. These results show that carotid IMT provides additional information that cannot be obtained based on the assessment of conventional cardiovascular risk factors alone. As the relative risk of stroke per IMT difference did not differ significantly from that of myocardial infarction, carotid IMT should be used as a non-specific marker of systemic atherosclerosis rather than that of atherosclerotic complications in specific organs.

More recently, it has been reported that the combination of conventional risk factors for coronary vascular disease and

carotid IMT improved the prediction of coronary vascular disease in diabetic patients, and that carotid IMT is useful in identifying patients at high risk for developing macrovascular complications of diabetes²⁹. These results of prospective studies suggest that carotid IMT can be used to predict cardiovascular events.

CAN WE USE CAROTID IMT AS A SURROGATE MARKER OF CARDIOVASCULAR DISEASE?

In a clinical study of a treatment for prevention of cardiovascular events, a large number of participants must be followed up for a long period of time when the occurrence of cardiovascular events is set as an end-point. Such study requires a significant financial commitment. An appropriate surrogate marker might decrease the sample size and the study period. It is generally believed that the surrogate marker should have a pathophysiological relationship to the relevant clinical end-point; should show good correlations with epidemiological evidence and endpoints; and the improvement in the surrogate marker after intervention should correlate well with the improvement in the relevant clinical end-point after the same intervention³⁰.

As carotid IMT is a non-invasive, economical and quantitative measure, change over time in carotid IMT is a good candidate for a surrogate end-point for cardiovascular events in clinical studies. A substantial quantity of evidence has been presented to show that carotid IMT satisfies the first two of the aforementioned conditions; however, sufficient evidence has not been accumulated regarding whether the progression of carotid IMT reflects an increased risk of subsequent cardiovascular events.

The following studies have provided valuable insights that should be shared for discussion of this matter. In a long-term follow up (mean 8.8 years) of 146 male patients (age range 40–59 years) who previously had coronary artery bypass graft surgery and completed the 2-year Cholesterol Lowering Atherosclerosis Study²⁶, the risk for coronary events or coronary death was higher in patients with a higher progression of carotid IMT. In a meta-analysis of seven placebo-controlled clinical trials of statins reporting both IMT outcomes and cardiovascular events, the impact of statins on carotid IMT progression and cardiovascular end-points were qualitatively similar³¹. Sabeti *et al.*³² followed up 1,065 patients with carotid stenosis for 3.2 years on average for the progression of carotid stenosis and the occurrence of major adverse cardiovascular events, and reported that patients with progressive carotid stenosis had a significantly increased risk for myocardial infarction, stroke and peripheral arterial events compared with patients with non-progressive disease. These reports suggest that the progression of carotid IMT can be used as a surrogate end-point of cardiovascular events.

There have been two meta-analyses of clinical studies in which the relationship between the development of CAD and the progression of carotid IMT was investigated. One meta-

analysis of 28 randomized clinical trials with 15,598 patients has shown that less progression in carotid IMT over time is associated with a lower likelihood of non-fatal myocardial infarction in selected randomized clinical trials³³, whereas the other meta-analysis of 41 randomized trials with 18,307 patients concluded that the regression or slowed progression of carotid IMT does not reflect a reduction in cardiovascular events³⁴.

Recently, Lorenz *et al.*³⁵ carried out an individual participant data meta-analysis of participants of general population studies that assessed carotid IMT at least twice, and followed up participants for myocardial infarction, stroke or death. Of 21 eligible studies, 16 were included, with a total of 36,984 participants. During a mean follow up of 7 years, 1,519 myocardial infarctions, 1,339 strokes and 2,028 combined end-points (myocardial infarction, stroke or vascular death) occurred. Yearly carotid IMT progression was derived from two ultrasound visits 2–7 years (median 4 years) apart. Unexpectedly, there were no associations between the progression of carotid IMT and the development of combined end-points.

As aforementioned, the meta-analysis of general population studies did not provide evidence supporting the usefulness of carotid IMT progression during several years as a surrogate marker of cardiovascular diseases. However, the yearly progression of carotid IMT was as small as approximately 0.01 mm/year in the general population, in which the risk of developing cardiovascular diseases is low. As carotid IMT is usually measured at a resolution of approximately 0.1 mm, it is likely that in observational studies of the general population, individual differences in the progression of carotid IMT during a few years are smaller than the measurement error. In contrast, it is expected that the progression of carotid IMT is several times higher in patients with a history of CAD and patients with diabetes or dyslipidemia than in the general population. Further studies should be carried out to investigate whether carotid IMT can be used as a surrogate end-point of cardiovascular disease in these patient populations.

DIABETES AND CAROTID IMT

Diabetes as a Risk Factor of Carotid IMT Progression

Many cross-sectional and longitudinal studies have already shown that conventional risk factors of atherosclerosis, such as aging, hypertension, hyperlipidemia, diabetes, obese, smoking and a history of atherosclerotic disorders, are risk factors of carotid IMT progression^{19,36–39}.

Through a cross-sectional survey, Yamasaki *et al.*¹⁵ have confirmed that carotid IMT in type 1 and type 2 diabetic patients was larger than that in age-matched non-diabetic individuals. As carotid IMT is higher in individuals with borderline glucose tolerance than in those with normal glucose tolerance, it is considered that atherosclerosis has already progressed in this population^{15,40}. In a meta-analysis of 23 studies in 24,111 participants, including 4,019 diabetic patients and 1,110 individuals with impaired glucose tolerance (IGT), the diabetic patients

and individuals with IGT had greater carotid IMT than the control participants by 0.13 mm (95% CI 0.12–0.14 mm) and 0.04 mm (95% CI 0.014–0.071 mm), respectively⁴¹. We carried out a meta-analysis of eight intervention studies in subjects with type 2 diabetes that evaluated the effect of interventions on change in carotid IMT, and found that the overall weighed rate of change in mean-IMT based on data among control groups (i.e., type 2 diabetes without interventions) was 0.034 mm/year (95% CI 0.029–0.039)⁴². As it has been reported that the annual increase in carotid IMT in healthy populations is 0.007–0.008 mm, carotid IMT progression is substantial among patients with uncontrolled diabetes.

REDUCTION OF CAROTID IMT PROGRESSION BY ANTIDIABETIC DRUGS

The development and progression of atherosclerosis in diabetic patients are significantly affected by: (i) metabolic abnormalities associated with chronic hyperglycemia; (ii) a complex of risk factors related to insulin resistance and visceral fat accumulation; and (iii) postprandial hyperglycemia.

It has been reported that carotid IMT correlates with various markers that reflect various metabolic abnormalities caused by chronic hyperglycemia. In the aforementioned meta-analysis in eight studies⁴², a close correlation between HbA_{1c} and carotid IMT was observed during the follow-up periods, which suggests

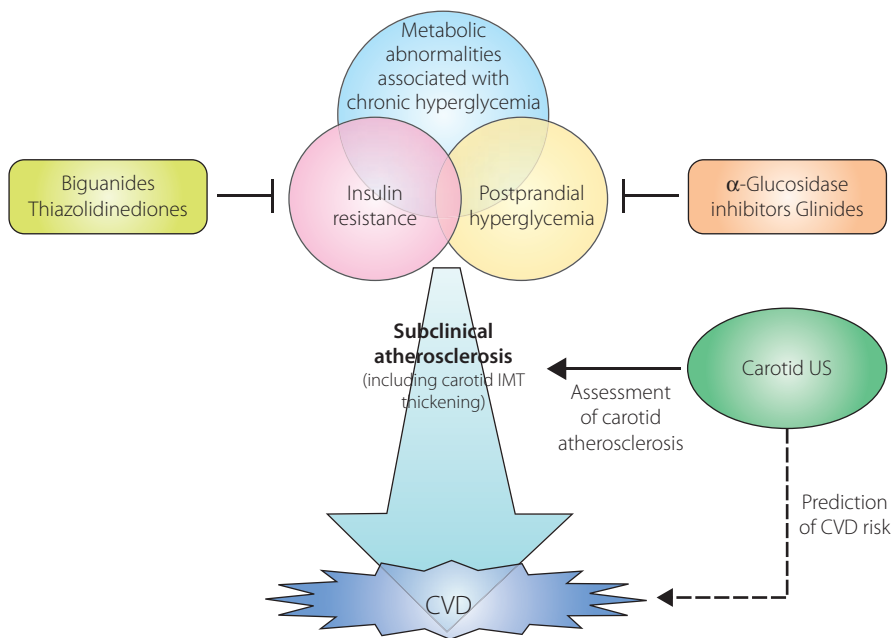


Figure 6 | Strategy for preventing the progression of atherosclerosis in diabetic patients. The development and progression of atherosclerosis in diabetic patients are significantly affected by: (i) metabolic abnormalities associated with chronic hyperglycemia; (ii) a complex of risk factors related to insulin resistance and visceral fat accumulation; and (iii) postprandial hyperglycemia. Previous studies showed that drugs improving insulin resistance were more effective in reducing carotid intima-media thickness (IMT) progression as compared with other types of antidiabetic drugs, and that drugs that ameliorate postprandial hyperglycemia potentially attenuated carotid IMT progression. Besides being a useful marker of the progression of subclinical atherosclerosis and a good predictor of cardiovascular events, carotid IMT can be used to evaluate the efficacy of various treatments. CVD, cardiovascular disease; US; ultrasonography.

Table 3 | Characteristics of major functional/morphological markers of atherosclerosis

	Carotid IMT	Coronary artery calcium	FMD	PWW
Predictive ability	Good	Pretty good	Relatively good	Relatively good
Safety	Very safe	Relatively safe	Safe	Very safe
Convenience	Convenient	Complicated	Complicated	Very convenient
Reproducibility	Good	Good	Relatively good	Relatively good
Cost	Low	High	Low	Low
AHA guideline's comments	Benefit >> risk (class IIa)	Benefit >> risk (class IIa)	No benefit (class III)	No benefit (class III)

AHA, American Heart Association; FMD, flow-mediated vasodilation; IMT; intima-media thickness; PWW, pulse wave velocity.

Utility of carotid IMT as an index of atherosclerosis

- Accurate evaluation of pathological/clinical conditions
- High prediction ability
- Adapt ability to the improvement of clinical endpoint
- Non-invasiveness/safety
- Convenience
- Low-cost
- Good reproducibility



Carotid IMT could be used globally as a screening tool for atherosclerotic diseases and a surrogate marker for cardiovascular events.

Figure 7 | The utility of carotid intima-media thickness (IMT) as an index of atherosclerosis.

that carotid IMT progression is reduced when glycemic control is achieved.

In accordance with the fact that insulin resistance plays an important role in the progression of atherosclerosis in diabetic patients, a large number of reports have shown that drugs improving insulin resistance are more effective in reducing carotid IMT progression as compared with other types of anti-diabetic drugs. Metformin, a biguanide derivative drug^{43,44}, and pioglitazone, a thiazolidinedione derivative^{45–47}, reduce carotid IMT progression as compared with sulfonylurea drugs.

It has also been reported that 2-h post-challenge plasma glucose and maximal plasma glucose levels during an oral glucose tolerance test are more strongly associated with carotid IMT than fasting plasma glucose levels⁴⁸, and that carotid IMT progression was greater in patients with larger incremental glucose peaks in subgroups of all tertiles of HbA_{1c} level⁴⁹. These findings suggest that postprandial hyperglycemia plays an important role in accelerating carotid IMT progression. Indeed, it has been reported that α -glucosidase inhibitors⁵⁰ and gli-nides^{51,52} that ameliorate postprandial hyperglycemia can attenuate carotid IMT progression.

Thus, the drugs that ameliorate insulin resistance, as well as postprandial hyperglycemia, are more effective in reducing carotid IMT progression as compared with other types of anti-diabetic drugs, suggesting that these drugs could potentially inhibit the progression of atherosclerosis accelerated in type 2 diabetic patients (Figure 6).

CONCLUSIONS

Carotid IMT is a useful marker of the progression of atherosclerosis throughout the body, and is an excellent predictor of cardiovascular events. As a simple and non-invasive procedure, measurement of carotid IMT is one of the most appropriate screening methods to specify high-risk individuals in the community (Table 3). Furthermore, carotid IMT can be used to identify unknown risk factors of atherosclerosis and to evaluate the efficacy of new treatments (Figure 7). Therefore, it is

expected that carotid IMT measurement will become a more common procedure.

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