REVIEW ARTICLE

Clinical utility of carotid ultrasonography: Application for the management of patients with diabetes

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ABSTRACT

Carotid ultrasonography is a non-invasive, simple and inexpensive modality to assess the severity of atherosclerosis. This article reviews related articles, summarizes the rationale for the application of carotid ultrasonography in clinical practice, and addresses the features and the limitations of carotid ultrasonography in cardiovascular risk prediction. Numerous large studies have confirmed that various carotid ultrasound measures, such as carotid intima-media thickness, the presence or absence of carotid plaque, plaque number and plaque area, can be independent predictors of cardiovascular diseases in individuals with and without diabetes mellitus. Furthermore, many studies showed that the use of carotid intima-media thickness (especially maximum intima-media thickness, including plaque thickness) and/or carotid plaque in addition to traditional risk factors significantly improved the prediction of the occurrence of cardiovascular diseases, while controversy remains. Several studies showed that the progression of carotid intima-media thickness also can be a surrogate end-point of cardiovascular events. However, the accumulated evidence has not been sufficient. Further study with sufficient power should be carried out. As plaque disruption, which plays a crucial role in the pathogenesis of cardiovascular events, is dependent on the content of lipid in the atheroma and the thickness of the fibrous cap, tissue characterization of a plaque might be useful for determining its fragility. Interestingly, recent studies have shown that ultrasonic tissue characterization of carotid lesions could improve the prediction ability of future cardiovascular diseases. Thus, carotid ultrasonography is a useful modality for better clinical practice of atherosclerosis in patients with diabetes.

Patients with diabetes mellitus are at a high risk of atherosclerotic cardiovascular (CV) diseases (CVDs), such as cerebrovascular diseases, coronary artery disease (CAD), peripheral arterial disease and other vascular diseases. CVDs are major causes of mortality in patients with diabetes mellitus, and significantly impair their quality of life. In addition, once a CVD has developed, patients with diabetes mellitus have worse outcome than non-diabetic patients. Therefore, early identification of individuals at high-risk for CVD and subsequent intervention are required.

As the development of atherosclerotic CVDs involves several traditional risk factors, such as sex, aging, hyperglycemia, dyslipidemia, hypertension, obesity, family history and smoking, assessment of CV risk based on traditional risk factors is recommended for identifying individuals with high risk for CVD. However, this approach showed only moderate performance in validation studies[1–3].

In contrast, sophisticated cardiac imaging modalities (e.g., myocardial perfusion scintigraphy, coronary computed tomography angiography and coronary angiography) can determine the presence and severity of CAD with a high degree of sensitivity and specificity. However, it is difficult to use these modalities as a screening tool, because of their potential of significant adverse effects, technical difficulty and high cost. The same is applicable to other CVDs. Therefore, non-invasive and inexpensive indices of subclinical and silent atherosclerosis with more than moderate predictive ability are required.

Carotid ultrasonography is one of the probable candidates. Numerous large studies have confirmed that various carotid ultrasound measures, such as carotid intima-media thickness (CIMT), the presence/absence of carotid plaque, plaque number and plaque area, can be predictors of CVD.

The present article reviews related articles, summarizes the rationale for the application of carotid ultrasonography in clinical practice, and addresses the features and the limitations of carotid ultrasonography in CV risk prediction.

RATIONALE FOR USING CAROTID ULTRASONOGRAPHY FOR CV RISK ASSESSMENT

Compared with other methods, carotid ultrasonography has several advantages: (i) it can be carried out in a reproducible manner, because of its simple, non-invasive and inexpensive nature; (ii) it can be carried out with equipment often already available; and (iii) it is not focused on the arterial lumen, but on the arterial wall, which is the real target of atherosclerosis.

Carotid ultrasonography allows clinicians to visualize the carotid wall and lumen surfaces, measure hemodynamic parameters, and thus, quantify the severity of atherosclerosis. Various extents of atherosclerotic changes, including intima-media thickening, plaque formation, stenosis and occlusion in carotid arteries, can be identified. In particular, CIMT measured with B-mode ultrasound is related well with that obtained by pathological measurement, and is confirmed to be a quantitative and reproducible measure of carotid atherosclerosis[4]. In addition, numerous studies have shown that CIMT is associated with both CVD and its risk factors[5,6]. Thus, CIMT is one of the best indices for the detection of "early-stage" atherosclerosis, which is located between CV risk factors and "hard" clinical CVD.

Furthermore, a recent study investigated whether providing ultrasound-based pictorial information about subclinical carotid atherosclerosis to both physicians and patients improves CV risk scores. Notably, the pictorial presentation of silent atherosclerosis by carotid ultrasonography significantly improved the CV risk scores at the 1-year follow up[7].

STANDARD METHOD FOR CAROTID ULTRASONOGRAPHY

Although the detailed guidelines vary by country, and universally standardized methods of carotid ultrasonography have not been established, major guidelines are almost consistent regarding the appropriate means of carrying out ultrasonic scans for the evaluation of CIMT and carotid plaques.

In general, the extracranial common carotid arteries (CCA), the carotid bulbs (Bul or Bif) and the internal carotid arteries (ICA) are scanned bilaterally in more than three different longitudinal projections, as well as transverse projections.

In B-mode, the carotid wall is visualized as three layers: 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 is defined as the CIMT. The intima-media complex on the far 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 (Figure 1). The CCA "far wall" IMT measurement is validated as accurately representing the true biological thickness of the arterial far wall. In contrast, the CCA "near wall" IMT measurement is at higher risk of a measurement error, as the echogenicity of the adventitial layer could affect the visualization of the adventitial–medial boundary. However, CIMT should also be measured in the near wall, as it is not rare for atherosclerotic changes to be located in the near wall alone.

As the differences among individuals and annual changes are small, a high degree of accuracy and good reproducibility is critical in CIMT measurement. Therefore, training of sonographers and strict adherence to scanning protocol are critical. Recently, ultrasound devices equipped with automatic IMT measuring software have become widely used to reduce the inter-examiner error, as well as the examination time[8]. In particular, in the clinical studies using CIMT as an end-point, automatic measurement using automated digital edge-detection software is essential (Table 1).

DEFINITIONS OF CAROTID ULTRASOUND MEASURES

Although CIMT is roughly defined as the distance between the lumen-intima and media-adventitia interfaces of a carotid segment, it should be noted that the detailed definitions of CIMT varied among individual studies. For example, some studies measured only one side of the neck, whereas others investigated bilaterally. Some measured CIMT in the CCA segment only, but others included multiple segments (CCA, Bul and ICA). There are also inconsistencies in the type of CIMT measurements (e.g., mean-IMT or max-IMT, etc.), definition of plaque and whether plaques were included in the CIMT measurements. Such variability in the assessment of CIMT makes it difficult to compare studies or to combine the results from different studies, as each of these CIMT measures might reflect different phenotypes.

In particular, whether the plaque lesion is included in CIMT measurement or not is critical, as the pathophysiology of the development of carotid plaque and that of CIMT are somehow different. Plaque, a localized elevated lesion into the vascular lumen, is an atherosclerotic lesion that consists of a collection of vascular smooth muscle cells and inflammatory cells often accompanied with intracellular and extracellular lipid accumulation. In contrast, increased IMT could reflect both the progression of atherosclerotic process and non-atherosclerotic compensatory enlargement of the artery.

Generally, guidelines on carotid ultrasonography published in Japan[9–12] and the USA[13] recommend that plaque lesions should be included in the measurement of IMT, whereas those in Europe[14] recommend that plaque lesions should not be included (Table 2).
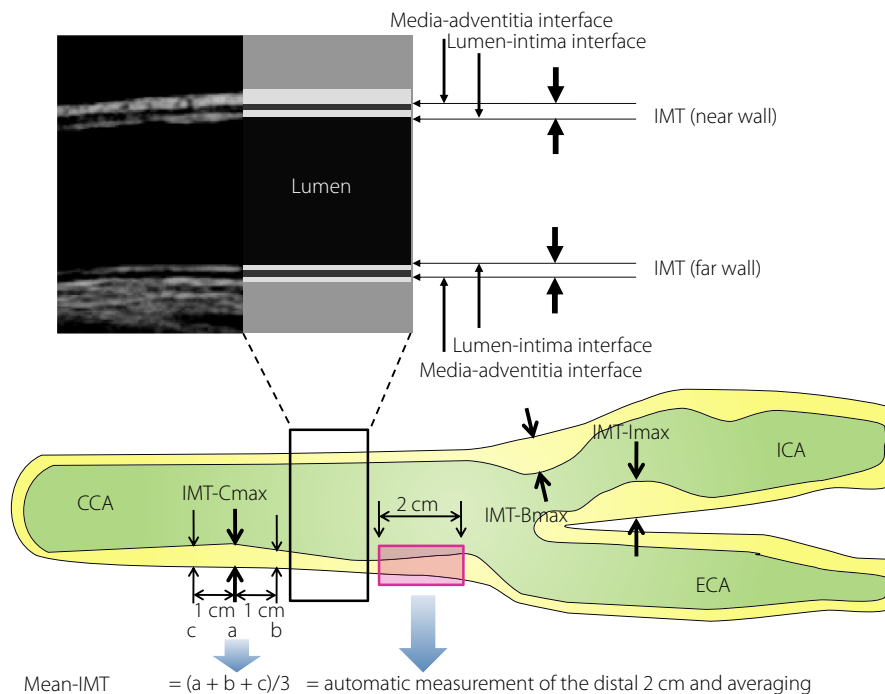
Figure 1 | Definitions of carotid ultrasound measures. The intima-media thickness (IMT) is a double-line pattern on the near and far walls of the carotid arteries when visualized by ultrasound. It is shown by two parallel lines that delineate the leading edges of two anatomical boundaries, the lumen-intima and media-adventitia interfaces. The Japan Academy of Neurosonology recommends: (i) measuring carotid IMT at the common carotid artery (IMT-Cmax), carotid sinus or the bifurcation of the common carotid artery (IMT-Bmax), and internal carotid artery (IMT-Imax) as the thickness at the thickest point, including plaque; (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 (= (a + b + c) / 3). In the clinical studies using CIMT as an end-point, automatic measurement of multiple points of the far wall of the distal 1 or 2 cm of each common carotid artery (CCA) using automated digital edge-detection software is essential. ECA, external carotid artery; ICA, internal carotid artery.

ASSOCIATIONS BETWEEN CAROTID ULTRASOUND MEASURES AND CVD

Coronary artery disease
Despite the above-mentioned inconsistencies in the definitions and assessment methods, many studies have shown that carotid ultrasound measures, such as CIMT (whether plaque thickness was incorporated in measurements) and carotid plaque-related indices, are associated with the presence or severity of coronary atherosclerosis[15–17] and myocardial ischemia[18,19], and the presence and/or past history of CAD[20,21].

Furthermore, recent studies using c-statistic (i.e., area under the receiver operating characteristic curve) have shown that carotid ultrasound measures represent a more than moderate predictive ability for the presence of CAD[22–26].

Cerebrovascular disease
Carotid atherosclerotic plaques are one of the major direct sources of cerebral emboli, and carotid stenosis is closely related to cerebral ischemic events[27–29] and silent cerebral infarction[30,31]. There is also a close association between cerebrovascular disease and more early-stage atherosclerotic changes observed in carotid arteries, such as increased IMT[32], as they share common CV risk factors underlying both processes.

Peripheral arterial disease
High CIMT has a significant association with the presence[33] and development of peripheral arterial disease[34].

CIMT AS AN INDEPENDENT PREDICTOR OF CV EVENTS
As shown in Table 3, many longitudinal studies have demonstrated that CIMT and plaque are independent predictors of CV events[35–50]. A meta-analysis of some of these studies also confirmed that CIMT is an independent predictor of CV events[51].

Similarly, regarding diabetes patients, it has been reported that CIMT is a predictor of the future development of non-fatal CAD[52]. The PROG-IMT Study Group carried out a comprehensive meta-analysis of the data from 3,902 patients with type 2 diabetes mellitus from 21 population-based cohorts. They concluded that the hazard ratio (HR) of CVD events was 1.22 (95% confidence interval [CI] 1.12–1.33) per standard deviation difference in mean CCA-IMT and 1.23 (95% CI

Table 1 | Basic points of attention in carotid ultrasonography and comparisons of predictive ability for cardiovascular disease among carotid ultrasound measures

	Predictive ability for CVD	
	Higher	Lower
Mean or max	Max	Mean
Plaque or CIMT	Plaque	CIMT
Plaque-incorporated CIMT or not	Plaque-incorporated CIMT	Plaque non-incorporated CIMT
Whole carotid tree or CCA only	Whole carotid tree	CCA only

B-mode ultrasonography of the carotid artery should be carried out using an ultrasound machine equipped with a linear probe with a center frequency of ≥7.5 MHz. (ii) Scanning should be carried out bilaterally in more than three different longitudinal projections, as well as transverse projections. As compared with the near wall, the far wall IMT measurement has a lower risk of systematic measurement error. The images should be acquired during the final part of the diastolic phase. Training of sonographers and strict adherence to scanning protocol are critical. Automatic intima-media thickness measurement using automated digital edge-detection software reduces the inter-examiner error. CCA, common carotid artery; CIMT, carotid intima-media thickness; CVD, cardiovascular disease.

1.08–1.40) per standard deviation difference in maximum (max) CCA-IMT, after adjustment for traditional risk factors. Although there was no statistically significant difference, the HR in patients with diabetes mellitus was a little higher than in people without diabetes mellitus (1.22 vs 1.15), suggesting that the association between CIMT and CVD might be more evident in individuals with diabetes mellitus[53]. More recently, a combined analysis of data obtained in five longitudinal studies that included 3,263 patients with diabetes, but without CVD, also confirmed that the mean CCA-IMT (HR 1.08 for every 0.1-mm increment, 95% CI 1.05–1.11, $P < 0.001$), CCA-max-IMT (HR 1.07 for every 0.1-mm increment, 95% CI 1.04–1.10, $P < 0.001$) and max-IMT (max-IMT in the CCA, Bul and ICA segments; HR 1.08 for every 0.1-mm increment, 95% CI 1.05–1.11, $P < 0.001$) at baseline could be a predictor for the development of CVD (CAD, cerebrovascular disease or peripheral arterial disease) in asymptomatic patients with type 2 diabetes mellitus, even after adjustment for traditional risk factors[50].

CONTRIBUTION OF CIMT TO CV RISK PREDICTION

Controversy remains regarding the contribution of CIMT to CV risk prediction over and above the traditional risk factors.

In the Multi-Ethnic Study of Atherosclerosis, CCA-IMT did not add significant predictive information for CAD or stroke over and above the Framingham risk score (FRS) alone (c-statistics; 0.78 for FRS plus CIMT vs 0.77 for FRS alone)[54]. Similarly, in the Carotid Atherosclerosis Progression Study, CIMT did not improve the risk classification of study participants when added to the FRS[55]. Furthermore, a summary of

systematic reviews[56] and another meta-analysis[57] concluded that the addition of CIMT did not add clinically useful information to the standard prediction models. Under the influence of these findings, the 2013 ACC/AHA Cardiovascular Risk Guidelines[58] and the 2016 European Guidelines on CVD prevention in clinical practice[59] questioned the contribution of CIMT to risk assessment over and above the conventional risk scores.

In contrast, in participants of the Framingham Offspring Study cohort, max-IMT and the presence of plaque in the ICA significantly improved the classification of risk of CVD over and above the FRS (increase in the c-statistic of 0.009, 95% CI 0.003–0.016). Similarly, in the Atherosclerosis Risk in Communities study, Nambi et al.[60] reported that CAD risk prediction can be improved by the addition of "CIMT + plaque" information to traditional risk factors. Baldassarre et al.[61] also showed that CIMT improved the prediction of CV events. Furthermore, based on a systematic review of the previous studies, Peters et al.[62] reported that the additional predictive value estimated by the increase in c-statistic ranged from 0.00 to 0.03 for CIMT and from 0.01 to 0.05 for carotid plaques. They also reported that net reclassification improvement ranged from −1.4% to 12% for CIMT and 8% to 11% for carotid plaques.

The predictive performance of CIMT has been also evaluated in individuals with diabetes. Yoshida et al.[48] reported that the combination of traditional risk factors and CIMT improved the prediction of CAD in patients with diabetes mellitus. More recently, a combined analysis of data obtained from longitudinal studies showed that the assessment of CIMT, such as CCA-mean-IMT, CCA-max-IMT and max-IMT, in addition to traditional risk factors significantly improved the prediction of the occurrence of CVD in diabetes patients without apparent CVD[50]. It was also reported that CIMT improved the prediction of CV events in dyslipidemic patients[63].

WHAT KIND OF CAROTID ULTRASOUND PARAMETERS SHOULD BE MEASURED?

Comparisons of predictive ability for cardiovascular disease among carotid ultrasound measures are summarized as Table 1.

Plaque or CIMT

Although carotid plaque and CIMT are correlated with each other, they show different patterns of association with traditional risk factors and atherosclerotic diseases[64]. Therefore, plaque assessment in addition to CIMT should be considered in CV risk prediction. Several articles have shown that the assessment of carotid plaque (e.g., presence/absence of plaque, plaque thickness, plaque area or plaque score) is more useful than CIMT for predicting future CVD[22,65,66]. Furthermore, considering not only the largest identified plaque, but also the total plaque burden in both carotid arteries might further improve risk estimation[67].

CIMT including plaque or CIMT not including plaque

According to a cohort study carried out in European countries, when plaques are incorporated into CIMT measurements, the

Table 2 | Differences in the definitions of carotid ultrasound measures among the Japanese, American and European guidelines

	Definition of carotid plaque	Definitions of mean-IMT	Definitions of max-IMT	Inclusion of plaque in CIMT
The Japan Society of Ultrasonics in Medicine (JSUM)[9,10]	Localized elevated lesions with maximum thickness of >1 mm, having a point of inflection on the surface of the intima-media complex are defined as "plaques." In cases of vascular remodeling, the term "plaques" may be used, irrespective of the presence/absence of elevation of the lesion into the vascular lumen.	An average of readings at two or more points of measurement performed on the right and left common carotid artery, excluding the bulbus	Measurements in the observation-possible areas of the CCA, Bul and ICA, and plaque lesion are included in max-IMT measurement.	Included
The Japan Academy of Neurosonology (JAN)[11,12]	All wall hyperplasias at a thickness of ≥1.1 mm	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	Measurements in the observation-possible areas of the CCA, Bul and ICA, and plaque lesion are included in max-IMT measurement.	Included
The American Society of Echocardiography[13]	Focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT >1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary	Average values of far wall of the distal 1 cm of each CCA mean-mean; values from the far walls of the right and left CCAs (average of segmental mean CIMT values)	Regional maximum measurement along the distal 1-cm region of each CCA (mean-maximum; average of segmental maximum CIMT values)	Included
The Mannheim Carotid Intima-Media Thickness Consensus[14]	A focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or shows a thickness >1.5 mm as measured from the intima-lumen interface to the media-adventitia interface	Not clearly defined (however, it is recommended that IMT should preferably be measured on the far wall of the CCA at least 5 mm below its end).	Not clearly defined (however, it is recommended that IMT should preferably be measured on the far wall of the CCA at least 5 mm below its end).	Not included

Bul, bulbs; CCA, common carotid artery; CIMT, carotid intima-media thickness; ICA, internal carotid artery; IMT, intima-media thickness.

predictive power of CIMT is greater compared with the information derived from plaques (regardless of the definition used) alone or from CIMT measured in plaque-free areas alone[61].

Which segment should be measured?

CIMT in Bul and ICA segments might reflect atherosclerosis more accurately than those obtained exclusively on the CCA, as Bul and ICA are more influenced by flow turbulence than CCA, and plaques are preferentially localized at Bul and ICA. Indeed, it has been reported that ICA-IMT and composite variables derived from measurements that included Bul and ICA segments are more accurate predictors of CV events than CCA-IMT[24,47,61,68]. Similar results were observed in individuals with diabetes mellitus: it was shown that max-IMT (=maximum value in the CCA, Bul and ICA segments) was more predictive than the mean IMT of the CCA for coronary artery stenosis. The c-statistic for max-IMT was significantly higher than that of the mean IMT (0.73 [95% CI 0.67–0.79] vs 0.64 [95% CI 0.58–0.72], $P = 0.031$)[23].

ULTRASONIC TISSUE CHARACTERISTICS OF CAROTID LESIONS AND CVDS

Assessment of plaque morphology with conventional B-mode ultrasound

Atherothrombotic disease, including acute coronary syndrome, is caused by a disruption of "unstable" plaque, which consists mainly of high lipid content, inflammatory infiltration and neovascular vessels, and is covered by a thin cap. Therefore, it would be important to assess the stability of plaques to specify patients at high-risk for atherothrombotic diseases.

Table 3 | Relative risk of myocardial infarction, stroke and cardiovascular disease associated with carotid intima-media thickness in major prospective studies

Study	Year	Sample number	Sex (male, %)	Age (years)	Follow-up period	Outcome events	Ultrasound parameters	Plaques	Relative risk (95% CI)
KIHD[35]	1991	1,288	100	42–60	1	MI	Mean-IMT (CCA)	Not specified	2.17 (0.70–6.74) [IMT ≥1 vs <1 mm]
							Plaque	—	4.15 (1.51–11.47) [small plaque]
							Plaque	—	6.71 (1.33–33.91) [stenotic plaque]
ARIC[36,37]	1997	5,552	100	54.3	5.2	MI	Mean-IMT (overall)	Included	1.85 (1.28–2.69) [>1 mm, yes vs no][‡]
		7,289	0	53.7	5.2	MI	Mean-IMT (overall)	Included	5.07 (3.08–8.36) [>1 mm, yes vs no][‡]
	2000	6,349	100	54.5	7.2	Stroke	Mean-IMT (overall)	Included	1.98 (1.24–3.15) [>1 mm, yes vs no][‡]
		7,865	0	53.8	7.2	Stroke	Mean-IMT (overall)	Included	3.31 (1.88–5.81) [>1 mm, yes vs no][‡]
Rotterdam[38–40]	1997	1,373	64	71	2.7	MI	Mean-IMT (CCA)	Not specified	1.43 (1.16–1.78) [per 1 SD (0.16 mm)][†]
						Stroke	Mean-IMT (CCA)	Not specified	1.41 (1.25–1.82) [per 1 SD (0.16 mm)][†]
	2003	5,479	38.1	69.3	6.1	Stroke	Max-IMT (CCA, average)	Not specified	1.28 (1.15–1.44) [per 1 SD][§]
							Plaque	—	1.15 (1.07–1.24) [severe plaque][§]
	2004	6,389	38.1	69.3	7–10	MI	Max-IMT (CCA, average)	Not specified	1.95 (1.19–3.19) [highest quartile][§]
							Plaque	—	1.83 (1.27–2.62) [severe plaque][§]
CHS[41,42]	1999	4,476	38.8	72.5	6.2	MI	Max-IMT (CCA)	Included	3.17 (1.96–5.12) [highest quintile][†]
						Stroke	Max-IMT (CCA)	Included	2.76 (1.80–4.24) [highest quintile][†]
	2007	5,020	39.8	72.6	11	CVD	Composite-IMT (overall)	Included	1.84 (1.54–2.20) [highest tertile]
							Plaque	—	1.38 (1.14–1.67) [high risk plaque]
MDCS[43]	2005	5,163	41	46–68	7.0	MI	Mean-IMT (CCA, right)	Included	2.05 (1.22–3.43) [highest tertile][†]
						Stroke	Mean-IMT (CCA, right)	Included	3.00 (1.57–3.75) [highest tertile][†]
CAPS[44]	2006	5,056	49	19–90	4.2	MI	Mean-IMT (CCA)	Not specified	1.18 (1.08–1.28) [per 1 SD][†]
							Mean-IMT (Bif)	Not specified	1.24 (1.13–1.36) [per 1 SD][†]
							Mean-IMT (ICA)	Not specified	1.11 (1.01–1.36) [per 1 SD][†]
						Stroke	Mean-IMT (CCA)	Not specified	1.16 (1.03–1.32) [per 1 SD][†]
							Mean-IMT (Bif)	Not specified	1.21 (1.05–1.40) [per 1 SD][†]
							Mean-IMT (ICA)	Not specified	1.17 (1.03–1.33) [per 1 SD][†]
Tromsø Study[45,46]	2007	6,226	56	25–84	5.4	MI	Mean-IMT (overall)	Included	1.73 (0.98–3.06) [highest quartile] men, 2.86 (1.07–7.65) [highest quartile] women[§]
	2011	6,584	53	25–84	9.6	Ischemic stroke	Mean-IMT (overall)	Included	1.08 (0.95–1.22) [per 1 SD] men, 1.24 (1.05–1.48) [per 1 SD] women[§]
							Plaque area	—	1.23 (1.09–1.38) [per 1 SD] men, 1.19 (1.01–1.41) [per 1 SD] women[§]
Framingham Offspring Study[47]	2011	2,965	44.7	58	7.2	CVD	Mean-IMT (CCA)	Excluded	1.13 (1.02–1.24) [per 1 SD][§]
							Mean-IMT (ICA)	Excluded	1.21 (1.13–1.29) [per 1 SD][§]

Table 3 (*Continued*)

Study	Year	Sample number	Sex (male, %)	Age (years)	Follow-up period	Outcome events	Ultrasound parameters	Plaques	Relative risk (95% CI)
Yoshida, et al.[48]	2012	783 (T2DM)	—	30–75	7.2	CVD	Mean-IMT (CCA)	Included	2.39 (1.19–4.81) [per 1 SD][†]
MESA[49]	2013	6,562	47.4	61.1	7.8	CVD	Max-IMT (ICA)	Excluded	1.21 (1.13–1.30) [per mm][§]
							Max-IMT (ICA) > 1.5 mm	Excluded	1.48 (1.21–1.80) [per mm][§]
Katakami, et al.[50]	2018	3,263 (T2DM)	65.5	60.9	6.8	CVD	Mean-IMT (CCA) (n = 3260)	Included	1.08 (1.05–1.11) [per 0.1 mm]
							Max-IMT (CCA) (n = 2243)	Included	1.07 (1.04–1.10) [per 0.1 mm]
							Max-IMT (overall) (n = 540)	Included	1.08 (1.05–1.11) [per 0.1 mm]

[†]Age and sex adjusted. [‡]Age and race adjusted. [§]Traditional risk factors adjusted. ARIC, Atherosclerosis Risk in Communities; Bif, bifurcation; CAPS, Carotid Atherosclerosis Progression Study; CCA, common carotid artery; CHS, Cardiovascular Health Study; CI, confidence interval; CVD, cardiovascular disease; ICA, internal carotid artery; IMT, intima-media thickness; KIHD, Kuopio Ischemic Heart Disease Study; MDCS, Malmo Diet and Cancer Study; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Generally, the assessment of carotid plaques is carried out based on the following: (i) echogenicity; (ii) heterogeneity; and (iii) structure (Figure 2). Typically, carotid plaques are classified into hypoechoic (echolucent), isoechoic or hyperechoic (echodense) plaques, and then subclassified into heterogeneous or homogeneous plaques. It is considered that atheroma and hematoma appear as hypoechoic lesions, fibrosis appears as isoechoic lesions and calcification appears as hyperechoic lesions (Figure 3). Echolucent carotid plaques have been reported to predict future strokes[69]. It is also believed that heterogenous plaques with a complex echo pattern are more vulnerable to rupture than homogenous plaques. The surface morphology of the plaque is classified as smooth, irregular or ulcerated, and it has been reported that the risk of stroke is higher in individuals with ulcerated or irregular plaques[70]. However, assessment of tissue morphology using the above-mentioned approach is subjective and qualitative.
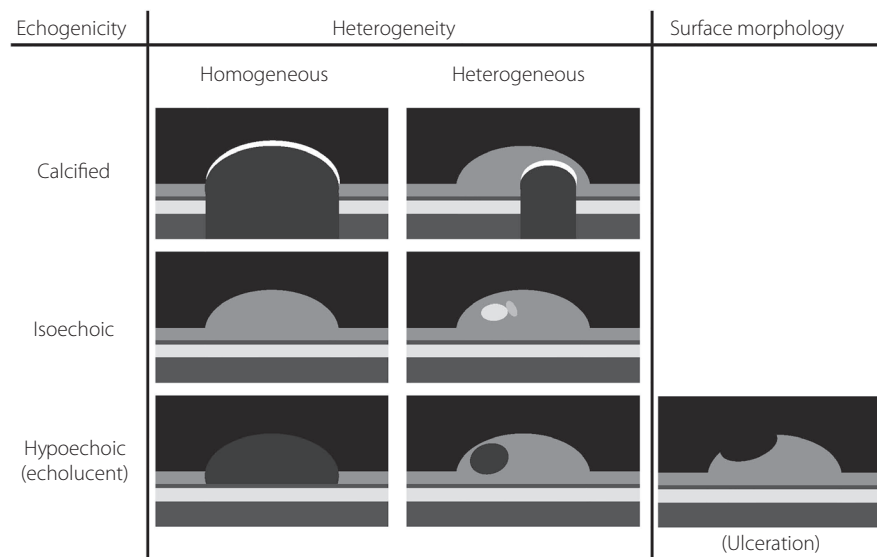

Figure 2 | Assessment of plaque morphology with conventional B-mode ultrasound. Generally, the assessment of carotid plaques are carried out based on the following: (i) echogenicity; (ii) heterogeneity; and (iii) structure. Typically, carotid plaques are classified into hypoechoic (echolucent), isoechoic or hyperechoic (echodense) plaques, and then subclassified into heterogeneous or homogeneous plaques. Plaque surface morphology is classified as smooth, irregular or ulcerated.
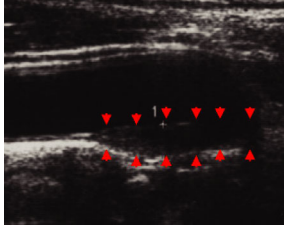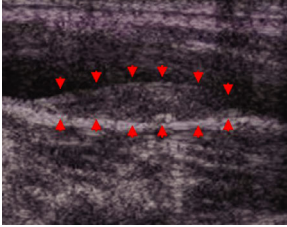
	Unstable plaque	Stable plaque
Conventional B-mode	Hypoechoic	Isoechoic
Gray-scale median	Low	Medium - high
Integrated backscatter	Low	Medium - high
Tissue characteristics	Atheroma Intra-plaque-hemorrhage	Fibrous plaque

Figure 3 | Association between pathological characteristics and ultrasonic tissue characteristics of carotid lesions. Unstable plaques, which consist mainly of foam cells and/or neovascular vessels, appear hypoechoic in conventional B-mode ultrasound imaging and show low gray-scale median (GSM) values and low integrated backscatter values. In contrast, stable plaques, which consist mainly of fibrous tissue and calcific components, appear hyperechoic and show medium (or relatively high) gray-scale median values and medium (or relatively high) integrated backscatter values.

Tissue characterization of carotid plaques using gray-scale median

Recent resolution enhancement of images obtained by B-mode and computer-assisted image processing has enabled semiquantitative evaluation of the echogenicity of carotid plaques. The gray-scale median (GSM) of the frequency distribution of gray values of the pixels within the plaque is used as an index of echogenicity[71]. As the measurement of GSM values requires neither specific software nor a specific ultrasonic diagnostic equipment, it can be a practical approach (Figure 3).

To investigate whether non-invasive ultrasonic tissue characterization of carotid plaque using GSM can predict future CVD, we carried out a prospective study of 287 diabetes patients with carotid plaque, but free from CVD, and showed that both the presence of low GSM plaques and plaque thickness were independent predictors of future occurrence of CV events, even after adjusting for traditional risk factors. The addition of plaque thickness to FRS significantly increased the c-statistic (from 0.60 [95% CI 0.49–0.70] to 0.73 [95% CI 0.63–0.82], $P < 0.05$). Furthermore, the addition of the information about plaque echogenicity (i.e., presence or absence of low GSM plaque) to the FRS and plaque thickness further and significantly increased the c-statistic (from 0.73 [95% CI 0.63–0.82] to 0.82 [95% CI 0.75–0.88], $P < 0.05$), suggesting that ultrasonic tissue characterization of carotid plaque by the GSM method can enhance the risk prediction of CV events in asymptomatic patients with diabetes mellitus[72].

Tissue characterization of carotid plaques using integrated backscatter ultrasound imaging

As B-mode carotid ultrasonography is intended to delineate the edge of carotid plaque tissue, raw signals reflected from the tissue are processed with complex algorithms, such as omission of weak signals and derivation. Therefore, the resultant images have lost detailed information on the plaque tissue characteristics, and do not reflect small differences in reflection strength caused by difference in tissue morphology. Recent advancements in devices and image processing techniques have developed novel ultrasonic techniques that reflect small differences in reflection strength by analyses of ultrasonic signals before image processing. Backscatter signals from a reflector that is much smaller as compared with the wavelengths used in regular ultrasonic devices include scattered waves from inside the structure. In the integrated backscatter (IBS) approach, these backscatter signals are integrated over time. As this approach could quantify reflection of the ultrasound waves in a relatively wide range of 60 dB, it is effective in detecting small differences in echo strength and enables detailed quantitative analysis of lumen morphology.

Urbani *et al.*[73] measured the IBS index in 15 individuals who were scheduled to have carotid thromboendarterectomy, and compared the value with pathological findings after surgery. In that study, they showed that the IBS index in atheroma, thrombi and intraplaque hemorrhage lesions was lower, but that the index in calcified sites was higher than in fibrous sites. Comparison of the ultrasound findings with pathological findings obtained from 12 individuals who had *in vivo*

ultrasound examination of the carotid and femoral arteries in life, and *ex vivo* ultrasound examination after autopsy also showed similar results[74]. These findings suggested that the tissue characteristics of the carotid arterial wall could be estimated with the IBS index of the carotid wall (Figure 3).

Takiuchi *et al.*[75] have reported that the IBS value of the carotid intima-media complex was lower in individuals with at least two coronary risk factors and patients who had myocardial infarction within the past 3 months than in individuals with fewer coronary risk factors. In our study of patients with type 2 diabetes mellitus[76], the IBS value of the carotid artery was significantly lower in individuals with a past history of acute coronary syndrome or atherothrombotic cerebral infarction within 6 months than in those with no apparent atherosclerotic disease, suggesting that tissue characterization using the IBS would be utilized in the risk assessment of future CVD. In our prospective study of 85 asymptomatic individuals with type 2 diabetes mellitus[77], the risk of developing CV events was significantly elevated in individuals with low calibrated IBS values of the thickest point at baseline as compared with higher values, indicating that the IBS value of the carotid wall is an independent risk factor for future CV events. The c-statistic for the prediction of future CV events was 0.63 when using the FRS, and increased significantly to 0.83 when using the FRS, IMT and IBS. These results show that the IBS method is useful for prediction of future CV events.

The calibrated IBS values in the carotid artery wall were significantly lower in individuals with than without untreated hyperlipidemia, and the improvement in the calibrated IBS during statin treatment was larger in individuals with a larger reduction in serum low-density lipoprotein cholesterol levels[78]. The calibrated IBS values of the carotid artery wall were also lower in individuals with a larger number of risk factors for metabolic syndrome[79].

Further clinical data are necessary to establish the IBS approach as a new method of assessment of atherosclerotic lesions.

The above shows that the addition of ultrasonic tissue characteristics of carotid lesions, together with CIMT, to traditional risk factors improves the prediction ability of future CVD (Figure 4).

PROGRESSION OF CIMT AND RISK OF CVD: POTENTIAL AS A SURROGATE OUTCOME

As CIMT is a quantitative and repeatable measure that can be assessed non-invasively, change over time in CIMT is a promising candidate for a surrogate outcome for CV events in clinical trials. Indeed, many clinical trials for antidyslipidemic and antidiabetic agents have used the CIMT as a surrogate clinical end-point for CV events. However, sufficient evidence has not been accumulated regarding whether the progression of CIMT reflects an increased risk of subsequent CV events.

In considering this theme, the following reports will probably be useful references. In 146 men who previously had undergone coronary artery bypass graft surgery and completed the 2-year Cholesterol Lowering Atherosclerosis Study[80], the risk for CAD or coronary death was increased in individuals with a greater progression of CIMT. Sabeti *et al.*[81] observed 1,065 individuals with carotid stenosis for 3.2 years, and found that individuals with progression in carotid stenosis had a significantly higher risk for CV events compared with those without it. More recently, in an epidemiological study of CVD based on a random sampling of more than 15,000 participants in Japan, Kokubo *et al.* showed that the multivariate-adjusted HRs for CVD and stroke were 2.80 (95% CI 1.54–5.11) and 2.30 (95% CI 1.14–4.63) in the fourth quartile, respectively, as compared with the first quartile of 5-year progression of max-IMT[82]. These findings show that the progression of CIMT and
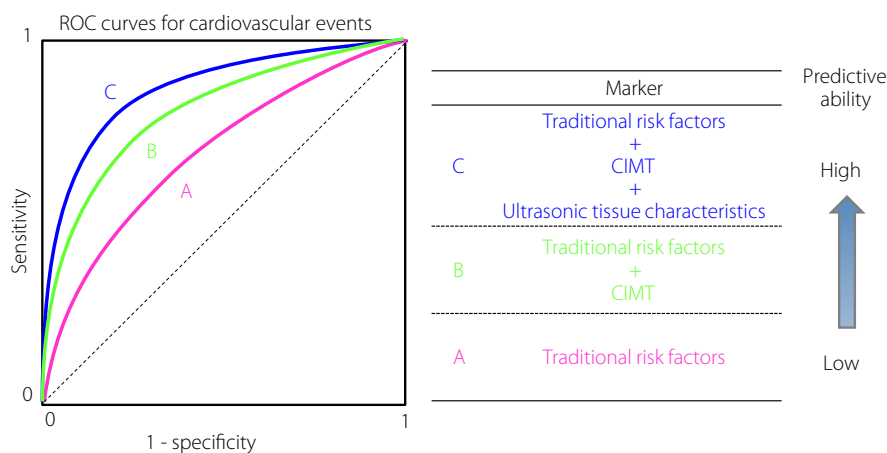

Figure 4 | Ultrasonic tissue characterization of carotid lesions for the prediction of future cardiovascular events. The addition of information about ultrasonic tissue characteristics of carotid lesions assessed by the gray-scale median of the frequency distribution of gray values of the pixels within the plaque or integrated backscatter ultrasound imaging, together with carotid intima-media thickness (CIMT), to traditional risk factors significantly and substantially improves the prediction ability of future cardiovascular events. ROC, receiver operating characteristic.

carotid stenosis can be used as a surrogate endpoint of CV events.

There have been several meta-analyses of clinical studies on the association between the development of CVD and the CIMT progression. In an early meta-analysis of seven placebo-controlled trials of statins that evaluated both CIMT outcomes and CV events, Espeland *et al.*[83] concluded that the effect of statins on CIMT progression and CV events was qualitatively similar. Based on a meta-analysis of 28 randomized clinical trials evaluating various CV therapies in 15,598 patients, Goldberger *et al.*[84] showed that less progression in CIMT was associated with a lower risk for myocardial infarction.

In contrast, another meta-analysis of 41 randomized clinical trials (18,307 patients, mean follow-up period 2.4 years) showed that the regression or slowed progression of CIMT did not reflect a reduction in CV events[85]. The PROG-IMT Study Group[86] carried out an individual participant data meta-analysis of the general population studies that measured CIMT at least twice, and followed up participants for myocardial infarction, stroke or death (16 studies, 36,984 participants, median follow-up period 4 years, 2,028 combined end-points). As a result, there was no significant association between the CIMT progression and the development of combined end-points.

Based on a meta-analysis of 3,902 adults with type 2 diabetes mellitus from population-based cohorts, the PROG-IMT Study Group also reported that the HR per standard deviation difference in the annual progression of mean CCA-IMT over a mean time of 3.6 years was 0.99 (95% CI 0.91–1.08), and concluded that there was no significant association between CIMT progression and future event risk[53]. In contrast, a combined analysis of five longitudinal studies in which CIMT was evaluated in a total of 1,881 Japanese patients with diabetes following a standardized protocol showed that that the increase in the CCA-mean-IMT during the observation period was a significant prognostic factor for CVD (HR 2.37 for every 0.1-mm/year increment, 95% CI 1.63–3.47, $P < 0.001$). Interestingly, the increments in the CCA-mean-IMT remained prognostic factors for CVD even after adjusting for traditional risk factors (HR 1.77 for every 0.1-mm/year increment, 95% CI 1.18–2.66, $P = 0.006$)[50].

It should be noted that there are several limitations in the analysis of the pooled data. First, CIMT is measured in many different ways with different approaches, and this variability might have influenced the adequate detection of significant findings. Second, as hard CV outcomes are considered to be typically apparent only after longer treatment, inclusion of many short-term follow-up trials could lead to incorrect conclusions about the association between CIMT and hard CV outcomes. Third, as the associations derived from meta-regression analysis are observational, it could underestimate the real relationships derived from large, randomized, definitive controlled clinical trials[87]. Therefore, further study with sufficient power should be carried out to evaluate whether CIMT can be used as a surrogate end-point of CVD.

DIABETES AND CIMT

Diabetes promotes atherosclerosis

Individuals with diabetes mellitus and those with borderline glucose tolerance show higher CIMT than individuals with normal glucose tolerance[19,88,89]. A meta-analysis of 23 studies including 24,111 participants with and without glucose intolerance showed that the patients with diabetes mellitus and individuals with impaired glucose tolerance had greater CIMT compared with the controls by 0.13 mm (95% CI 0.12–0.14 mm) and 0.04 mm (95% CI 0.014–0.071 mm), respectively[89].

In a meta-analysis of eight interventional trails in individuals with type 2 diabetes mellitus that assessed the effect of interventions on CIMT progression, the overall weighed rate of change in mean-IMT among untreated type 2 diabetes mellitus patients was 0.034 mm/year (95% CI 0.029–0.039)[90]. As the annual increase in CIMT in healthy individuals has been reported to be 0.007–0.008 mm, CIMT thickening is supposed to be accelerated in individuals with poor-controlled diabetes.

REDUCTION OF CIMT PROGRESSION BY ANTIDIABETIC TREATMENT

It has been reported that CIMT correlates with chronic hyperglycemia. The aforementioned meta-analysis of eight clinical studies[90] showed a close correlation between the averaged HbA1c and CIMT progression during the follow-up periods. This finding indicates that CIMT progression is attenuated when HbA1c, an index of chronic hyperglycemia, is lowered by antidiabetic treatment.

Insulin resistance plays a critical role in the pathogenesis of atherosclerosis. Therefore, it would be compatible that antidiabetic agents that improve insulin resistance, such as metformin[91,92] and pioglitazone[93–95], were more effective in attenuating CIMT progression than sulfonylureas.

Temelkova-Kurktschiev *et al.*[96] reported that 2-h post-challenge plasma glucose and maximal plasma glucose levels during an oral glucose tolerance test were more closely associated with CIMT than fasting plasma glucose levels. Similarly, Esposito *et al.*[97] reported that CIMT progression was greater in patients with larger incremental glucose peaks. These findings indicate that postprandial hyperglycemia plays an important role in CIMT progression. Actually, it has been shown that α-glucosidase inhibitors[98] and glinides[99,100] that ameliorate postprandial hyperglycemia can attenuate CIMT progression.

Experimental studies have shown that dipeptidyl peptidase-4 (DPP-4) inhibitors exert pleiotropic anti-atherosclerotic effects in GLP-1-dependent and -independent manners. However, randomized clinical trials to evaluate the long-term effect on major CV events of adding DPP-4 inhibitors to usual care in patients with type 2 diabetes mellitus and CVD (e.g., the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE), the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus -

Table 4 | Characteristics of major functional/morphological markers of atherosclerosis

	Carotid IMT	Carotid plaque	Coronary artery calcium	FMD	PWV	ABI
Predictive ability	Moderate	Good	Pretty good	Moderate	Moderate	Good
Safety	Very safe	Very safe	Relatively safe	Safe	Very safe	Very safe
Convenience	Convenient	Convenient	Complicated	Complicated	Very convenient	Convenient
Reproducibility	Good	Good	Good	Relatively good	Relatively good	Good
Cost	Low	Low	High	Low	Low	Low
ACC/AHA Guideline comments[†]	III No benefit Level B	(None)	IIb Level B	(None)	(None)	IIb Level B
European Guideline comments[‡]	Class III Level A	Class IIb Level B	Class IIb Level B	(None)	(None)	Class IIb Level B

[†]The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Cardiovascular Risk Guidelines: *Classification of recommendation* – I: Benefit >>> Risk. Procedure/treatment should be performed/administered. IIa: Benefit >> Risk. It is reasonable to perform the procedure/administer treatment. IIb: Benefit ≥ Risk. Procedure/treatment might be considered. III No benefit: Not helpful. III Harm: Excess cost without benefit or harmful. *Level of evidence*: A: Data derived from multiple randomized clinical trials or meta-analyses. B: Data derived from a single randomized clinical trial or non-randomized studies. C: Only consensus opinion of experts, case studies or standard of care. [‡]The 2016 European Guidelines on cardiovascular disease prevention in clinical practice: *Classes of recommendations* – I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful or effective. II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedures. IIa: Weight of evidence/opinion is in favor of usefulness/efficacy. IIb: Usefulness/efficacy is less well established by evidence/opinion. III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases might be harmful. *Level of evidence*: A: Data derived from multiple randomized clinical trials or meta-analyses. B: Data derived from a single randomized clinical trial or large non-randomized studies. C: Consensus of opinion of experts and/or small studies, retrospective studies, registries. ABI, ankle-brachial index; FMD, flow-mediated vasodilation; IMT, intima-media thickness; PWV, pulse wave velocity.

Thrombolysis in Myocardial Infarction 53 trial (SAVOR-TIMI53) and the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)) showed that the addition of DPP-4 inhibitors to usual care did not have a significant influence on the rates of major adverse CV events in these populations. Interestingly, the Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis trial, an RCT in 341 patients with type 2 diabetes mellitus free of apparent CVD, showed that a DPP-4 inhibitor, alogliptin, significantly attenuated the CIMT progression compared with the conventional treatment[101]. Similarly, the results of the Sitagliptin Preventive study of Intima-media thickness Evaluation trial showed that another DPP-4 inhibitor, sitagliptin, also attenuated the CIMT progression in insulin-treated type 2 diabetes mellitus patients free of apparent CVD compared with conventional treatment[102]. However, in the Program of Vascular Evaluation under Glucose Control by DPP-4 Inhibitor (PROLOGUE) study, in which type 2 diabetes mellitus patients both with and without previous CVD were enrolled, the addition of sitagliptin to the usual care failed to attenuate the CIMT progression[103]. Interestingly, the post-hoc analysis of the PROLOGUE study showed significant inhibitory effects of sitagliptin on the mean and maximum internal CIMT in the primary prevention subgroup[104]. These findings suggest a favorable effect of DPP-4 inhibitor treatment on CIMT in patients with type 2 diabetes mellitus but without apparent CVD.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, which enhance urinary glucose excretion, improve glycemic control with a low risk of hypoglycemia and ameliorate a variety of CV risk factors. The Empagliflozin Cardiovascular Outcome
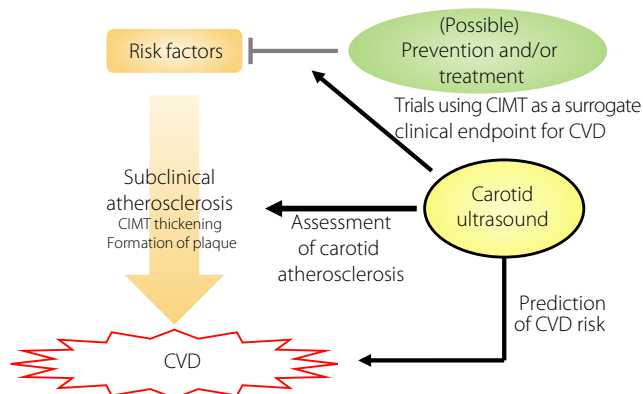

Figure 5 | Carotid ultrasonography as a useful modality for clinical practice of atherosclerosis in patients with diabetes. Carotid ultrasound measures, including carotid intima-media thickness (CIMT) and carotid plaque, are useful markers of the progression of atherosclerosis throughout the body, and can be independent predictors of cardiovascular events. Although sufficient evidence has not been accumulated, change over time in CIMT is a good candidate for a surrogate outcome for cardiovascular events in clinical trials. CVD, cardiovascular disease.

Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) OUTCOME and the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, randomized clinical trials to evaluate the long-term effect on major CV events of adding SGLT2 inhibitors to the usual care in

diabetes patients with high risk for CVD, showed that the addition of SGLT2 inhibitors to usual care reduced the risk of major adverse CV events in these populations. However, the preventive effects of SGLT2 inhibitors on the CIMT progression remain unclear, whereas one small-scale single-arm study reported that 52 weeks of ipragliflozin treatment did not change CIMT. Ongoing RCTs, such as The Study of Using Tofogliflozin for Possible better Intervention against Atherosclerosis for type 2 diabetes patients (UTOPIA)[105] and the Prevention of atherosclerosis by SGLT2 inhibitor; multicenter, randomized controlled study (PROTECT)[106], are expected to show the preventive effect of SGLT2 inhibitors on CIMT progression.

CONCLUSION

Carotid ultrasonography is now widely used as a major marker of atherosclerosis (Table 4). Carotid ultrasound measures, including CIMT and carotid plaque, are useful markers of the progression of atherosclerosis throughout the body, and can be independent predictors of CV events in the general population and patients with diabetes. However, whether CIMT provides additional prognostic information over and above the traditional risk factors remains controversial. This confusion would not be irrelevant to the lack of a standardized and univocally accepted protocol for measurement of CIMT. Establishment of universally standardized methods is required. Notably, recent studies have shown that ultrasonic tissue characterization of carotid lesions using novel approaches (e.g., GSM, IBS) improves the prediction ability of future CV events. Thus, carotid ultrasonography is a useful tool for better clinical practice of atherosclerosis in patients with diabetes (Figure 5).

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