Review

Carotid Intima-Media Thickness for Atherosclerosis

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The carotid intima-media thickness (IMT) is a widely used surrogate marker for atherosclerosis worldwide. The carotid IMT can be simply, noninvasively, and reproducibly measured through B-mode carotid ultrasound. The carotid IMT is also a strong predictor of future cerebral and cardiovascular events. In addition, regressions of increased carotid IMT by lipid-lowering and antihypertensive drugs have been reported. Despite the strong association between increased carotid IMT and cardiovascular disease, it remains unclear whether routine carotid IMT measurement is useful for the detection of subclinical atherosclerosis in clinical practice. Researches should consider other methodological aspects, such as the definition of carotid plaques, the choice of measurement sites on the common or internal carotid artery, and the assessment of maximum or minimum IMT. The detailed guidelines for measuring carotid IMT vary by county. Thus, the usefulness of the carotid IMT may be assessed in different countries taking racial differences into account. Other important parameters revealed by carotid ultrasound, such as artery stenosis and the characteristics and size of plaques, should also be considered. Physicians should comprehensively interpret the results of carotid ultrasonography. Therefore, carotid ultrasonography is an essential tool for assessing cardiovascular risk in clinical settings.

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Introduction

Carotid intima-media thickness (IMT) is a surrogate marker for the presence and progression of atherosclerosis[1-4]. Carotid IMT is used worldwide because it can be simply, reproducibly, and noninvasively measured. Many studies have reported that carotid IMT measurements are useful for evaluating the risk and incidence of cardiovascular disease (CVD)[5-9]. The first meta-analysis of several large-cohort studies that assessed the association between increased carotid IMT and the incidental risk of future cardiovascular and stroke events indicated that increased carotid IMT is a strong predictor of future vascular events[10]. Therefore, the 2010 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines advocated the use of carotid IMT at a class IIa level for the assessment of cardiovascular risk in asymptomatic adults with an intermediate risk of CVD[11].

Multiple clinical trials using lipid-lowering, antihypertensive, and/or antidiabetic drugs have used the carotid IMT as a surrogate clinical endpoint[12-20]. However, a meta-analysis of 41 randomized trials showed that decreases in the carotid IMT do not predict a reduction in the cardiovascular events[21]. A meta-analysis of the association between carotid IMT changes and cardiovascular events in the general population also failed to prove the usefulness of the carotid IMT[22]. In addition, recent systematic reviews and a meta-analysis of the use of the carotid IMT for cardiovascular risk assessment found that although increased carotid IMT was associated with future cardiovascular

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events, the addition of the carotid IMT to traditional vascular risk prediction models did not significantly increase the performance of the models[23, 24]. Therefore, the 2013 ACC/AHA guidelines stated that routine carotid IMT measurement is not recommended in clinical practice for the risk assessment of the first cardiovascular event[25].

Despite the strong association between increased carotid IMT and CVD, it remains controversial whether the carotid IMT is useful as a surrogate marker of subclinical atherosclerosis in clinical practice. Several methodological issues should be considered when assessing this topic. Carotid ultrasonography allows the measurement of not only the carotid IMT but also the presence and characteristics of plaques and the severity of carotid stenosis. Several studies have shown that the presence of carotid plaques is better than that of carotid IMT for predicting future cardiovascular events[26, 27]. However, clinical or observational studies using the carotid IMT have varied widely in the definition of carotid plaques and the analysis of plaque data. Physicians should use both the IMT and plaques when interpreting carotid ultrasonography results. Therefore, carotid ultrasonography must be an essential tool for the assessment of cardiovascular risks in clinical practice.

What is Carotid IMT?

The carotid IMT is measured between the intimal-luminal and the medial-adventitial interfaces of the carotid artery. The space between the two hyperechoic lines (the "double-line") corresponds to IMT. Carotid ultrasonography should be performed using a linear-array transducer operating at a fundamental frequency of at least 7 MHz. The appropriate depth of focus ranges from 30 to 40 mm, although an increased depth may be necessary for patients with larger necks or deeper vessels. In B-mode carotid ultrasound, the common carotid artery (CCA) should be scanned from its origin to the carotid bifurcation (BIF), internal carotid artery (ICA), and external carotid artery in transverse and longitudinal sections. The carotid IMT (CCA-IMT) is usually measured in the 1-cm straight segment of the extracranial carotid artery proximal to the BIF[28, 29], although the definitions of the carotid segments measured in previous clinical studies have varied[10]. In addition, the carotid IMT should be measured at least 5 mm below the end of the CCA, which eliminates the inter-individual variability induced by physiological remodeling and reduces the dependence on instrument gain[30]. The carotid IMT should also be measured in the "far wall" of the CCA, which is defined as the carotid wall farthest from the echo transducer. Edge detection systems are useful for the accurate measurement of the carotid IMT because manual measurements depend on the observer. A semi-automated measurement tool is recommended for reliably and reproducibly measuring the carotid IMT. Several observational studies measured the CCA-IMT according to the Mannheim consensus using the same ultrasound protocol[31] and the same software (M'ATH, Intelligence in Medical Technologies, Paris, France) with automated edge detection[30, 32-34]. The details of the mechanical settings and techniques were described in recent consensus statements[29, 30].

The analysis of carotid plaques in the measurement of the carotid IMT, i.e., whether the plaque is included in the carotid IMT and how the plaque is defined, remains controversial. The Mannheim consensus recommends that the carotid IMT should be measured in the absence of plaques[30]. In contrast, a consensus statement from the American Society of Echocardiography indicated that plaques should be traced as part of the carotid IMT[29]. Several population-based studies measured the carotid IMT in a plaque-free region[35, 36], whereas others included the plaques when measuring the carotid IMT[8, 37, 38]. The definition of plaque also varies. For example, the Mannheim consensus advocates that carotid plaques are focal structures that either encroach the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value or have a thickness from the intimal-luminal to the medial-adventitial interface of >1.5 mm. Although the American Society of Echocardiography also defined carotid plaques as a focal region with a carotid IMT >1.5 mm that protrudes into the lumen, several studies used carotid plaques with an IMT $>$ 1.1-1.2 mm[8, 39]. Spence suggested that the most appropriate definition of a carotid plaque is a localized thickening of >1 mm[40]. Racial differences in the size of the carotid IMT should be discussed. Sekikawa *et al*. investigated the carotid IMT of men aged 40-49 years and found that after adjusting for traditional and other risk factors, including fasting insulin, fibrinogen, and C-reactive protein (CRP), the carotid IMT of Caucasian men in the United States is significantly larger than that of Japanese men[41].

Other issues associated with carotid ultrasonography protocols, namely the region used for the measurement of the different carotid segments (CCA, BIF, and ICA) and the use of the mean or maximal IMT, should also be discussed. Although several cohort studies have shown that the carotid IMT values measured at all of the segments (CCA, BIF, and ICA) predict future cardiovascular events to nearly the same

extent[5, 9, 35, 37], increased ICA-IMT is associated with a relatively higher risk of cardiovascular events compared with increased CCA-IMT[37]. Polak *et al.* compared the mean CCA-IMT with the maximal ICA-IMT as indicators of prevalent CVD and as predictors of cardiovascular events (average follow-up of 7.2 years) in the Framingham Offspring cohort[36, 42]. The researchers found that both the mean CCA-IMT and the maximal ICA-IMT were statistically significant indicators of prevalent CVD, although the ICA-IMT had a larger area under the ROC curve[42]. In addition, the maximal ICA-IMT but not the mean CCA-IMT significantly improves the net reclassification index of future CVD[36]. The CCA-IMT is mainly affected by age and blood pressure[43], whereas the ICA-IMT probably reflects the presence of focal plaques and may be more representative of exposure to cardiovascular risk factors. The pattern of progressive carotid plaque atherosclerosis may be distinct from that of the CCA-IMT[40]. Although the maximal ICA-IMT may be preferable when including carotid plaques, it remains uncertain whether a single maximal IMT measurement or the average of various maximal IMT measurements is preferable.

It is also important to assess the number, size, and characteristics of plaques. Handa *et al.* developed plaque scores by adding the maximal thickness of plaques (>1.0 mm) on the near and far walls at each of the four divisions of both sides of the carotid artery[44]. This scoring system is used to assess the severity of atherosclerosis because multiple studies have shown that plaque scores are associated with cardiovascular risk factors, CVDs, and cerebral white matter lesions[39, 45-47]. The carotid plaque type (echolucent, low echoic, and soft) is also associated with the incidence of ischemic stroke[48-50]. However, issues associated with the reproducibility and quantitative assessment of carotid plaque characterization remain to be addressed.

Carotid ultrasonography is useful for not only the assessment of atherosclerosis but also for the assessment of the other etiologies of ischemic stroke and the diagnosis of several rare diseases. An oscillating intraluminal mass echo in the CCA or ICA has been reported in patients with cardioembolic stroke[51]. A diffuse circumferential mild hypoechoic thickening of the intima-media complex resulting from granulomatous inflammatory changes, termed the "macaroni sign," has been detected in patients with Takayasu disease[52]. This "macaroni sign" has been widely used not only for the diagnosis for Takayasu disease but also for the evaluation of inflammatory activity. A rapid reduction in the internal diameter of the proximal portion of the extracranial ICA, termed the "bottle neck sign," is an important and unique finding in patients with Moyamoya disease[53]. Carotid ultrasonography is useful for evaluating the clinical course of these diseases because carotid ultrasonography is a simple, repeatable, and noninvasive procedure.

Factors Affecting the Carotid IMT

Associations between the Carotid IMT and Vascular Risk Factors

Many studies have shown that the carotid IMT is associated with aging, vascular risk factors, and prevalence of CVD, although the regions of the carotid segments used for the measurements (CCA, BIF, and ICA) varied among the studies[2, 37, 39, 54-56]. Increased carotid IMT is strongly associated with aging and hypertension[43]. The carotid IMT increases nearly 3-fold in patients between the ages of 20 and 90 years[57], and the mean estimates of the CCA-IMT progression in the general population range from 0.001 to 0.030 mm per year[22]. Left ventricular hypertrophy, which is caused by hypertension, is also associated with increased carotid IMT[58]. Raitakari *et al.* showed that exposure to cardiovascular risk factors (LDL-cholesterol, systolic blood pressure, body mass index, and smoking) in childhood is correlated with increased carotid IMT[59]. Based on an analysis of the population included in the Suita study conducted in Japan, Mannami *et al.* found that the carotid IMT is associated with age, systolic blood pressure, fasting blood glucose, pack-years of smoking, total serum cholesterol, and HDL cholesterol in men and with age, systolic blood pressure, pack-years of smoking, and total serum cholesterol in women[39]. Because dyslipidemia is also associated with increased carotid IMT, several clinical trials have evaluated the effect of statins on the progression of carotid IMT[15, 17-19]. A recent meta-analysis showed that the LDL-C/HDL-C ratio is strongly associated with the carotid IMT and that low HDL-C levels are associated with the carotid IMT independently of the LDL-C levels[60]. In a systematic review, patients with diabetes mellitus or impaired glucose tolerance were found to have a greater carotid IMT than control subjects[61]. Associations were also found between the carotid IMT, insulin resistance, and metabolic syndrome[62-66].

Associations between the Carotid IMT and Biological Markers

High-sensitivity C-reactive protein (hs-CRP) is widely used as a marker of CVD[67-69]. In the Carotid Atherosclerosis Progression Study (CAPS), Sitzer *et al.*

found an association between increases in the mean CCA-IMT and CRP values[70]. A meta-analysis showed that high levels of hs-CRP are associated with increased carotid IMT despite the marked heterogeneity of the results presented in the literature[71]. Fibrinogen is also used as a predictive biological marker of CVD[72]. Several studies have shown that elevated fibrinogen is correlated with increased carotid IMT in asymptomatic subjects after adjustment for other factors, including CRP and von Willebrand factor[73, 74]. Although LDL is related to atherosclerosis, the oxidation of LDL was recently hypothesized to be important in the early development of atherosclerosis. Several studies have found that the oxidized LDL concentrations are associated with increased carotid IMT in the general population[75, 76], in familial hyperlipidemia families[77], and in patients with coronary artery disease[78]. The serum level of LOX-1 ligand containing ApoB (LAB), which is considered a novel biomarker for predicting cardiovascular events, was found to be associated with carotid IMT in US Caucasian men but not Japanese men[79]. Adiponectin, the most abundant adipokine produced by adipocytes, provides an important association between obesity, insulin resistance, and related inflammatory disorders. Rundek et al. found that adiponectin provides a small but significant contribution to variances in the carotid IMT[80]. Traditional cardiovascular risk factors explain only a small part of the variance observed in the carotid IMT. We have shown that plasma adrenomedullin and circulating $CD34^+/CD144^+$ endothelial cells are associated with carotid atherosclerosis in ischemic stroke patients[81, 82]. Although there is limited evidence regarding whether these novel biological markers are independently associated with future cardiovascular events, the carotid IMT is widely used as a surrogate marker for evaluating the association between these markers and the progression of atherosclerosis.

Is the Carotid IMT Useful for CVD Risk Stratification?

Many large-cohort studies that investigated the association between the carotid IMT and the risk of future cardiovascular and stroke events found that the carotid IMT is useful for CVD risk stratification (**Tables 1** and **2**). In the first meta-analysis, Lorenz *et al.* showed that the carotid IMT is a strong predictor of future vascular events[10]. These researchers also found multiple sources of heterogeneity between the published studies and thus asserted that ultrasound protocols should be aligned in future studies.

The USE Intima-Media Thickness (USE-IMT) collaboration, a global meta-analysis project using individual participant data from prospective cohort studies, was formed to determine the added value of the mean CCA-IMT to risk prediction models for the analysis of asymptomatic individuals at risk for CVD[24]. The USE-IMT database consists of 14 population-based cohorts, which together include 45,828 individuals and their baseline data for the Framingham Risk Score (age, sex, cigarette smoking status, antihypertensive medication use, diabetes mellitus status, blood pressure, and lipid profiles). The CCA-IMT was found to be related to first-time myocardial infarction and stroke with a hazard ratio (HR) of 1.09 (95% CI: 1.07-1.12) per 0.1-mm difference in the CCA-IMT. However, the addition of CCA-IMT measurements to the Framingham Risk Score was associated with only a small improvement in predicting first-time cardiovascular events based on the C statistic and the net reclassification improvement (NRI). These results indicate that the CCA-IMT should not be routinely measured in the general population because it adds little overall value and is unlikely to be of clinical importance. The USE-IMT project then focused on individuals with elevated blood pressure because asymptomatic individuals with hypertension are recommended for the assessment of subclinical vascular damage. However, the CCA-IMT provided no added value to the prediction of cardiovascular risk in 17,254 hypertensive individuals[83]. Similarly, no improvement in risk prediction was obtained for 4,220 individuals with diabetes mellitus by the addition of the mean CCA-IMT to the Framingham Risk Score[84].

Another meta-analysis found that the carotid IMT is predictive of myocardial infarction and stroke[23]. **Table 3** summarizes the meta-analysis of the association between the carotid IMT and future cardiovascular events. The overall performance of risk prediction models did not significantly increase after the addition of carotid IMT data because the C statistic increased from 0.726 to 0.729 for 32,299 subjects ($p = 0.8$). The C statistics, NRIs, and integrated discrimination improvements (IDI) are shown in **Table 4**. The results showed that the CCA-IMT (excluding carotid plaques) presented no added value compared with traditional risk score models. In contrast, Polak *et al.* evaluated various carotid parameters, including the ICA-IMT and carotid plaques, as predictors of future cardiovascular events[36, 85]. These researchers found that the addition of carotid plaques or the ICA-IMT to the Framingham Risk Score may improve the prediction of the risk of cardiovascular events.

In Japan, the Japan Atherosclerosis Society proposed comprehensive lipid and risk management

Table 1. Summary of studies that have reported an association between the carotid IMT and future cardiovascular events

Study	Region	Year	Sample size	Follow-up (years)	Carotid IMT parameters	Plaque	Relative risk (95% CI) for carotid IMT
CHS	USA	1999[37]	4,476	6.2	Average maximal IMT (CCA and ICA), bilateral, far and near wall	Included	MI 1.33† (1.21-1.48) for CCA-IMT per 1SD 1.43† (1.28-1.59) for ICA-IMT per 1SD
		2007[5]	5,020	11	Composite measure that combines the CCA-maximal IMT and the ICA-maximal IMT	Included	MI 1.80§ (1.37-2.38) for IMT, highest tertile CVD death 2.15§ (1.65-2.80) for IMT, highest tertile
ARIC	USA	1997[38]	12,841	5.2	Average mean IMT (CCA, Bif, and ICA), bilateral, far wall	Included	MI 5.07‡ (3.08-8.36) in women for IMT ≥ 1.0 mm; 1.85‡ (1.28-2.69) in men for IMT ≥ 1.0 mm
Rotterdam	Netherlands	2002[7]	2,267	4.6	Average maximal IMT (CCA, Bif, and ICA), bilateral, far and near wall	Not specified	MI 1.44† (1.28-1.62) for CCA-IMT per 1SD; 1.34† (1.17-1.53) for Bif-IMT per 1SD; 1.12† (0.94-1.33) for ICA-IMT per 1SD
		2004[97]	6,389	7-10	Average maximal IMT (CCA), bilateral, far and near wall	Not specified	MI 2.91† (1.80-4.70) for IMT, highest quartile
MDCS	Sweden	2005[8]	5,163	7	Mean IMT (right CCA), far wall	Included	MI 2.05† (1.22-3.43) for IMT, highest tertile
CAPS	Germany	2006[9]	5,056	4.2	Average mean IMT (CCA, Bif, and ICA), bilateral, far wall	Not specified	MI 1.18† (1.08-1.28) for CCA-IMT per 1SD; 1.24† (1.13-1.36) for Bif-IMT per 1SD; 1.11† (1.01-1.36) for ICA-IMT per 1SD
Tromsø Study	Norway	2007[98]	6,226	5.4	Average mean IMT (CCA, Bif, and ICA), right, far and near wall	Included	MI 2.56* (1.51-4.36) for IMT in men, highest quartile 3.80* (1.44-9.99) for IMT in women, highest quartile
MESA	USA	2008[35]	6,698	3.9	Average max IMT (CCA and ICA), bilateral, far and near wall	excluded	CVD events (CHD, stroke, and fatal CVD) 2.3§ (1.4-3.8) for CCA-IMT, highest quartile 3.3§ (2.1-5.2) for ICA-IMT, highest quartile
		2013[85]	6,562	7.8	Maximal IMT (ICA) right, left, or bilateral, far and near wall	excluded	CVD events (CHD, stroke, and fatal CVD) 1.21§ (1.13-1.30) for max-IMT (ICA, either) 1.33§ (1.18-1.49) for max-IMT (ICA, average) 1.48§ (1.21-1.80) for max-IMT (ICA) >1.5 mm
Framingham Offspring Study	USA	2011[36]	2,965	7.2	Mean IMT (CCA), maximal IMT (ICA), bilateral, far, and near wall	excluded	CVD events (MI, stroke, PAD, and CHF) 1.13§ (1.02-1.24) for mean CCA-IMT per 1SD; 1.21§ (1.13-1.29) for max ICA-IMT per 1SD

*Adjusted for age
†Adjusted for age and sex
‡Adjusted for age and other risk factors
§Adjusted for age, sex and other risk factors

guidelines (JAS guidelines 2012) using the NIPPON DATA80 Risk Assessment Chart to estimate the 10-year absolute risk of coronary artery disease death and stratified individuals into three categories for the primary prevention of the events of CVD[86, 87]. Carotid mean IMT (CCA or ICA) and carotid plaque were strongly associated with the risk stratification of the lipid management proposed by the JAS guidelines

Table 2. Summary of studies that reported an association between the carotid IMT and future stroke events

Study	Region	Year	Sample size	Follow-up (years)	Carotid IMT parameters	Plaque	Relative risk (95% CI) for carotid IMT
CHS	USA	1999[37]	4,476	6.2	Average maximal IMT (CCA and ICA), bilateral, far and near wall	Included	Stroke 1.37† (1.25-1.51) for CCA-IMT per 1SD 1.33† (1.19-1.48) for ICA-IMT per 1SD
		2007[5]	5,020	11	Composite measure that combines the CCA-maximal IMT and the ICA-maximal IMT	Included	Stroke 1.77§(1.36-2.30) for IMT, highest tertile
ARIC	USA	2000[6]	14,214	7.2	Average mean IMT (CCA, Bif, and ICA), bilateral, far wall	Included	Stroke 3.31‡ (1.88-5.81) in women for IMT ≥1.0 mm; 1.98‡ (1.24-3.15) in men for IMT ≥1.0 mm
Rotterdam	Netherlands	2003[99]	5,479	6.1	Average mean IMT (CCA), bilateral, far, and near wall	Not specified	Stroke 1.29† (1.15-1.44) for IMT per 1SD
MDCS	Sweden	2005[8]	5,163	7	Mean IMT (right CCA), far wall	Included	Stroke 3.00† (1.57-5.75) for IMT, highest tertile
CAPS	Germany	2006[9]	5,056	4.2	Average mean IMT (CCA, Bif, and ICA), bilateral, far wall	Not specified	Stroke 1.16† (1.03-1.32) for CCA-IMT per 1SD; 1.21† (1.05-1.40) for Bif-IMT per 1SD; 1.17† (1.03-1.33) for ICA-IMT per 1SD
Tromsø Study	Norway	2011[100]	6,584	9.6	Average mean IMT (CCA, Bif, and ICA), right, far wall	Included	Stroke 2.16* (1.31-3.56) for IMT in men, highest quartile 1.41‡ (0.84-2.35) for IMT in men, highest quartile 1.63* (0.93-2.86) for IMT in women, highest quartile 1.26‡ (0.71-2.25) for IMT in men, highest quartile
Kitamura *et al.*	Japan	2004[101]	1,358	4.5	Average max IMT (CCA and ICA), bilateral, far and near wall	included	Stroke 3.5* (1.3-9.5) for CCA-IMT, highest quartile 1.6* (0.7-3.9) for ICA-IMT, highest quartile

*Adjusted for age
†Adjusted for age and sex
‡Adjusted for age and other risk factors
§Adjusted for age, sex and other risk factors

2012[88]). Fujihara *et al.* reported that combining several risk stratification scores with the carotid max IMT improved the prediction of coronary artery stenosis using the C statistics and NRIs in asymptomatic patients with type 2 diabetes[89]). Further studies are warranted to clarify whether the addition of carotid IMT to those risk stratifications predicts future cardiovascular events in the general population of Japan.

Can the Carotid IMT Serve as a Surrogate Endpoint for Intervention?

Several clinical trials using lipid-lowering drugs have used the carotid IMT as a clinical endpoint[12-14, 90, 91]. Amarenco *et al.* showed the existence of a strong correlation between statin-induced LDL reduction and carotid IMT reduction in nine randomized clinical studies published before August 2003 ($n=2,792$, $r=0.65$, $p=0.004$, linear regression weighted by the size of each group)[92]). A recent meta-analysis of 21 randomized clinical studies (6,317 patients) published before December 2011 found that statin therapy is associated with a favorable decrease in the CCA-IMT (−0.029 mm, 95% CI: −0.045, −0.013)[93]). Other clinical trials using antihypertensive, antidiabetic or antithrombotic drugs have also evaluated the carotid IMT as a surrogate marker for subclinical atherosclerosis[15, 16, 20, 94]). A meta-analysis of eight randomized

Table 3. Summary of meta-analyses of the carotid IMT

Authors	Studies	Year	Endpoints	Sample size	Hazard ratio (HR) 95% CI	I^2 for heterogeneity	Adjustment
Lorenz *et al.*[10]	1) ARIC (unpublished data) 2) CHS[37] 3) Rotterdam[7, 99] 4) MDCS[8, 102] 5) CAPS[9]	2007	MI	30,162	1.26 (1.21-1.30) for CCA-IMT per 1SD 1.15 (1.12-1.17) for CCA-IMT per 0.1 mm	65.2% (per 1SD) 45.5% (per 1 mm)	Age and sex
			Stroke	3,4335	1.32 (1.27-1.38) for CCA-IMT per 1SD 1.18 (1.16-1.21) for CCA-IMT per 0.1 mm	28.1% (per 1SD) 28.2% (per 1 mm)	
Den Ruijter *et al.*[24]	USE-IMT Collaboration Group 1) ARIC[103] 2) CHS[5] 3) Rotterdam[104] 4) CAPS[9] 5) Charlottesville[105] 6) FATE[106] 7) Hoorn Study[107] 8) KIHD[1] 9) Malmö[108] 10) MESA[35] 11) Nijmegen Study[109] 12) NOMAS[80] 13) OSACA 2 Study[110] 14) Tromsø Study[98]	2012	MI	45,828	1.08 (1.05-1.11) for CCA-IMT per 0.1 mm	data not shown	Framingham Risk Score (age, sex, smoking status, blood pressure, antihypertensive medication use, total cholesterol level, HDL cholesterol level and presence of diabetes mellitus)
			Stroke	45,828	1.12 (1.10-1.15) for CCA-IMT per 0.1 mm	data not shown	
			MI or Stroke	45,828	1.09 (1.07-1.12) for CCA-IMT per 0.1 mm	12.3%	
van den Oord *et al.*[23]	1) ARIC (unpublished data) 2) CHS[37] 3) Rotterdam[7, 99] 4) MDCS[8, 102] 5) CAPS[9] 6) MESA[35] 7) Tromsø Study (unpublished data) 8) Framingham Offspring Study[36] 9) PRC-USA Study[111]	2013	MI	38,177	1.26 (1.20-1.31) for CCA-IMT per 1SD 1.15 (1.12-1.18) for CCA-IMT per 0.1 mm	14% (per 1SD) 37% (per 1 mm)	Age and sex
			Stroke	45,722	1.31 (1.26-1.36) for CCA-IMT per 1SD 1.17 (1.15-1.21) for CCA-IMT per 0.1 mm	20% (per 1SD) 14% (per 1 mm)	
			MI and Stroke	20,929	1.26 (1.17-1.36) for CCA-IMT per 1SD 1.17 (1.05-1.30) for CCA-IMT per 0.1 mm	0% (per 1SD) 0% (per 1 mm)	

clinical trials involving 3,329 patients with diabetes or coronary heart disease showed that antihypertensive treatment reduces the carotid IMT by a rate of 0.007 mm/year compared with placebo and no treatment ($p = 0.01$)[95]. Similarly, a meta-analysis of five randomized controlled trial studies (411 patients) found that alpha-glucosidase inhibitor therapy may be an effective strategy for preventing increases in the carotid IMT in patients with impaired glucose tolerance or diabetes mellitus[96].

It is less certain whether a regression of the carotid IMT reflects prognostic benefits. In a meta-analysis of 41 randomized clinical trials involving 18,307 patients, Costanzo *et al.* assessed whether a regression of the carotid IMT is associated with a reduced incidence of events[21]. Although active medical treatments induced a significant reduction in cardiovascular deaths, cardiovascular events, and overall death, carotid IMT regression was not correlated with the clinical outcomes. In addition, the carotid IMT changes induced by medical therapies may not consistently reflect improved clinical benefits. In a meta-analysis of 36,984 subjects from the general population (PROG-IMT collaborative project), Lorenz et al. assessed whether changes in the carotid IMT are associated with cardiovascular events[22]. As part of this collaborative project, the yearly carotid IMT progression was derived from two ultrasound scans separated by a

Table 4. Summary of the studies used to generate the C statistics to evaluate the added value of the carotid IMT to traditional risk score models for the prediction of cardiovascular events

Studies	Year	Sample size	Risk score model	Carotid parameter	C statistics		NRI (95% CI)	IDI (95% CI)
					Risk score model	Risk score model + carotid parameter		
ARIC[103]	2010	13,145	ARIC Coronary Risk Score[112]	CCA-IMT	0.742	0.750	0.167 (0.093-0.224)	0.007 (0.004-0.010)
				Carotid plaque (>1.5 mm)	0.742	0.751	0.177 (0.109-0.247)	0.008 (0.005-0.012)
CAPS[113]	2010	4,904	Framingham Risk Score	CCA-IMT	0.719	0.724	−0.0141	0.0004
				ICA-IMT	0.719	0.723	0.0199	0.0007
Framingham Offspring[36]	2011	2,965	Framingham Risk Score	CCA-IMT	0.748	0.751	0.004	Not specified
				ICA-IMT	0.748	0.758	0.058	Not specified
				ICA-IMT (>1.5 mm)	0.748	0.762	0.073	Not specified
USE-IMT Collaboration								
All individuals[24]	2012	45,828	Framingham Risk Score	CCA-IMT	0.757	0.759	0.008 (0.001-0.0016)	0.0024 (0.0012-0.0036)
DM patients[84]	2013	4,220			0.67	0.68	0.017 (−0.018-0.038)	0.0051 (0.0011-0.0091)
Hypertensive patients[83]	2014	17,254			0.732	0.733	0.014 (−0.011-0.037)	Not specified
MESA[85]	2013	6,562	Framingham Risk Score	ICA-IMT	Change in C statistic, 0.0068 (95% CI, 0.0016-0.0120)		0.029 (P=0.079)	0.0062 (P<0.001)
				ICA-IMT (>1.5 mm)	Change in C statistic, 0.0053 (95% CI, 0.0002-0.0104)		0.032 (P=0.060)	0.0022 (P=0.02)

median of 4 years. Although the mean CCA-IMT was associated with cardiovascular events (myocardial infarction and stroke) when adjusted for age, sex, mean CCA-IMT progression, and vascular risk factors (HR 1.16, 95% CI 1.10-1.22), the mean CCA-IMT progression was not associated with cardiovascular events when adjusted for age, sex, mean CCA-IMT, and vascular risk factors (HR 0.98, 95% CI 0.95-1.01). These results may not allow any conclusions regarding the value of carotid IMT progression as a viable surrogate marker in clinical settings. However, these researchers focused only on the mean CCA-IMT. Other parameters associated with the carotid IMT (maximal CCA-IMT and mean or maximal ICA-IMT) should be evaluated in the future. In addition, assessments of the presence, number, and characteristics of plaques are also essential when considering the utility of carotid ultrasonography. Physicians should examine the associations between the effects of medical intervention, carotid ultrasonographic parameters, and future cardiovascular events. Moreover, proper methodologies are needed for reproducibly determining these parameters in clinical research.

Conclusions

Because there is no global standard for measuring the carotid IMT in a clinical setting, it remains controversial whether the carotid IMT is useful in cardiovascular risk stratification. To address this issue, it is essential to determine how to evaluate plaque characteristics. Racial differences should also be discussed. In addition, physicians should comprehensively consider all of the parameters of carotid ultrasonography. Proper interpretations of each parameter of the carotid IMT will yield a better understanding of the useful-

ness of the carotid IMT in clinical settings.

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Conflicts of Interest/Disclosures

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