Evaluation of Intima-Media Thickness and Arterial Stiffness as Early Ultrasound Biomarkers of Carotid Artery Atherosclerosis

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ABSTRACT

Carotid atherosclerosis is a major and potentially preventable cause of ischemic stroke. It begins early in life and progresses silently over the years. Identification of individuals with subclinical atherosclerosis is needed to initiate early aggressive vascular prevention. Although carotid plaque appears to be a powerful predictor of cardiovascular risk, carotid intima-media thickness (CIMT) and arterial stiffness can be detected at the initial phases and, therefore, they are considered important new biomarkers of carotid atherosclerosis. There is a well-documented association between CIMT and cerebrovascular events. CIMT provides a reliable marker in young people, in whom plaque formation or calcification is not established.

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However, the usefulness of CIMT measurement in the improvement of risk cardiovascular models is still controversial. Carotid stiffness is also significantly associated with ischemic stroke. Carotid stiffness adds value to the existing risk prediction based on Framingham risk factors, particularly individuals at intermediate cardiovascular risk. Carotid ultrasound is used to assess carotid atherosclerosis. During the last decade, automated techniques for sophisticated analysis of vascular mechanics have evolved, such as speckle tracking, and new methods based on deep learning have been proposed with promising outcomes. Additional research is needed to investigate the imaging-based cardiovascular risk prediction of CIMT and stiffness.

Keywords: Intima-media thickness; Arterial stiffness; Carotid atherosclerosis; Speckle tracking; Cardiovascular risk

Key Summary Points

Subclinical carotid atherosclerosis is an early marker of atherosclerosis disease and its timely recognition is necessary for a prompt primary prevention.

carotid intima-media thickness (CIMT) and arterial stiffness are strong predictors of stroke and cardiovascular events. Recent studies showed that increased CIMT and arterial stiffness are noninvasive biomarkers of atherosclerotic disease, even in the asymptomatic stage.

Several methods for assessing CIMT and arterial stiffness have been developed. Speckle tracking ultrasound and new technological images based on automated measurements and artificial intelligence are evolving in this setting.

Current primary prevention guidelines for cardiovascular disease determine risk stratification by using clinical risk scores. Nonetheless, the current data are rather limited regarding the value of cardiovascular risk scores associated with CIMT and arterial stiffness as biomarkers of subclinical atherosclerosis.

CIMT and arterial stiffness might improve the cardiovascular risk stratification in asymptomatic patients.

INTRODUCTION

Worldwide, stroke is a leading cause of death and disability. According to the 2019 Global Burden of Disease Stroke Statistics, ischemic stroke affected an estimated 77.2 million people [1] and caused 2.7 million deaths each year [2].

Carotid atherosclerosis is a major and potentially preventable cause of cerebral ischemic events, accounting for 15–20% of all ischemic strokes [3, 4]. Atherosclerosis begins early in life and remains latent for a long time before the formation of atherosclerotic plaques [5, 6]. Identification of individuals with subclinical atherosclerosis is needed to initiate early aggressive vascular disease prevention [7, 8]. This has led to an increasing interest in finding new markers for carotid atherosclerosis. Carotid intima-media thickness (CIMT) and arterial stiffness changes can be recognized early and are thus considered important markers of future severe atherosclerosis [5, 9]. Carotid atherosclerotic plaques represent later stages of disease than CIMT and arterial stiffness [10].

Carotid ultrasound is a widely used noninvasive technique for measurement of early structural changes in the carotid artery such as CIMT and arterial stiffness [8, 10]. Ultrasound imaging enables practitioners to predict future cerebrovascular events and thus stratify patients into different risk groups. Subjects with low risk should reduce their risk factors; high-risk subjects are also given medical therapy [11]. These biomarkers seem to be best applicable in individuals with intermediate risk in order to

readjust cardiovascular risk. Standardization of measurements is necessary to detect subclinical carotid atherosclerosis.

Consequently, the purpose of the present review is to identify the role of CIMT and carotid artery stiffness as biomarkers of subclinical carotid atherosclerosis and their clinical implications in improving the cardiovascular risk stratification.

A PubMed search was performed using the string "intima-media thickness OR arterial stiffness AND cardiovascular risk". English-language articles on carotid ultrasound atherosclerosis were reviewed in detail.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

HISTORICAL PERSPECTIVE

Carotid atherosclerosis has been conventionally assessed by the degree of stenosis and surface irregularities in the artery. Other biomarkers have been suggested as valuable surrogates for future significant carotid disease.

In 1986, Pignoli et al. documented the first in vitro results investigating arterial wall thickness. They demonstrated a significant association between the intima-media thickness (IMT) measured on histological study of the CCA (common carotid artery) and the distance between two parallel echogenic lines found on ultrasound studies using B-mode imaging. The authors concluded that B-mode ultrasound represented a useful tool for the measurement of CIMT of in vivo human arteries [12].

Persson et al. used B-mode ultrasound for quantification of early (thickening of the intima-media complex) and late (plaque) atherosclerosis in the carotid and the femoral arteries. They demonstrated that IMT measurement with B-mode ultrasound was highly reproducible and allowed for accurate intra-observer and inter-observer differences [13].

In 1982, Kawasaki et al. measured the stiffness of the CCA wall using an ultrasound system. The stiffness parameter was the β-stiffness index, which expressed the relationship of stress strain on the artery. They found higher values of β-stiffness index in a group of patients with stroke compared with a healthy group. They confirmed the usefulness of carotid stiffness measurements from an echo system as an indirect diagnostic method of carotid arteriosclerosis [14].

During the past decade, further automated techniques have evolved. Clinical investigation of circumferential and longitudinal mechanics of the carotid wall better identified early local vascular stiffening [15]. The presence of a well-defined motion pattern was shown in the carotid artery using B-mode echo-tracking ultrasound images [13, 16–19].

CAROTID ULTRASOUND METHODOLOGY

Several studies suggest that carotid artery B-mode ultrasound imaging is safe, noninvasive, and relatively inexpensive. This permits an assessment of subclinical carotid atherosclerosis [20–22] and could improve risk stratification for cardiovascular disease (CVD) [23–25].
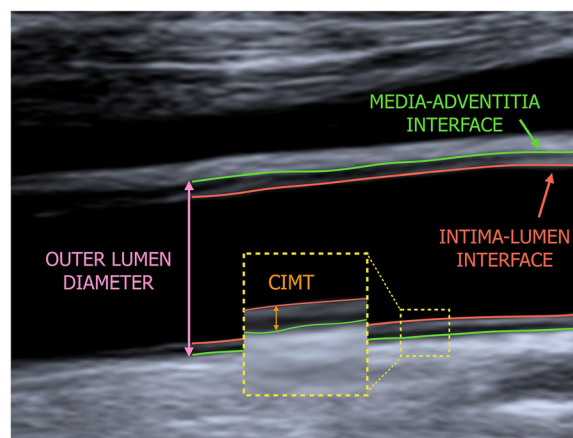

Fig. 1 B-mode ultrasound image of the common carotid artery (longitudinal axis) with tracing lines at the intima-lumen interface (red line) and the media-adventitia interface (green line). The pink colored line represents the outer lumen diameter

In 2012, the Mannheim Carotid Intima-Media Thickness and Plaque Consensus published the last update guidelines for CIMT measurement [20]. CIMT is observed as a double line pattern visualized between the intimal-luminal and the medial-adventitial interfaces of the carotid wall in a longitudinal view by B-mode ultrasound (Fig. 1). CIMT should be measured near the carotid bifurcation in a region that is free of plaque usually found in a segment of the distal CCA. The arterial wall should be assessed in a lateral probe position with an insonification angle of 90° to acquire good-quality images. CIMT is measured along a 10 mm length, preferably on the posterior wall of the CCA at least 5 mm below its termination to avoid inter-individual variability. Semiautomated reading software provides accurate measurements of CIMT. Manual reading demonstrates a higher reader-subjectivity compared to automatic or semiautomatic measurement software. Moreover, automated systems can perform 150 measurements on a 10-mm segment of CCA instantaneously [20].

Many invasive and noninvasive techniques to measure arterial stiffness have been described (Table 1) [9, 26, 27]. A classic method to assess arterial stiffness is the carotid-femoral pulse-wave velocity (PWV). This is based on pulse pressure and its waveform and estimates the propagation speed of the arterial pulse wave. It is measured directly, using the foot-to-foot velocity method from various waveforms obtained, transcutaneously at the right CCA and the right femoral artery. PWV is calculated as the ratio of the distance between two measurement points divided by the time required for the pressure wave to travel this distance. To date, the measurement of PWV is generally accepted as the most simple, noninvasive, robust, and reproducible method to determine arterial stiffness [28]. Other classic methods such as distensibility, compliance, elastic modulus, and β-stiffness index are based upon the assessment of diameter and volume change during the cardiac cycle for the corresponding change in arterial pressure [19, 29].

Table 1 Definitions, formulae, and units of the different measurement parameters of arterial stiffness

Parameter	Formula	Units	Description
Arterial compliance	$\Delta D/\Delta P$	$cm^2/mmHg$	Absolute diameter change for a given pressure step at fixed vessel length
Arterial distensibility	$\Delta D/\Delta P \times D$	$mmHg^{-1}$	Relative diameter change for a pressure increment; the inverse of elastic modulus
Pulse wave velocity	Distance/Δt	m/s	Speed of travel of the pulse along an arterial segment
Elastic modulus	$\Delta P \times D/\Delta D$	mmHg	Pressure step required for theoretical 100% increase in volume
Young's modulus	$\Delta P \times D/(\Delta D \times h)$	mmHg/cm	Elastic modulus per unit area; the pressure step per square centimeter required for resting length
β-stiffness index	Ln (Ps/Pd)/[(Ds − Dd)/Dd]	Nondimensional	Ratio of logarithm (systolic/diastolic pressures) to (relative change in diameter)
Strain	$\Delta L/L1 = (L2 − L1)/L1$	%	Deformation (proportion between the change of length and original length of the vessel)
Strain rate	ε/s	s^{-1}	Amount of strain accumulated in a time interval

D diameter, P pressure, t time, h height, Ln logarithm, Ps systolic pressure, Pd diastolic pressure, L length, ε strain
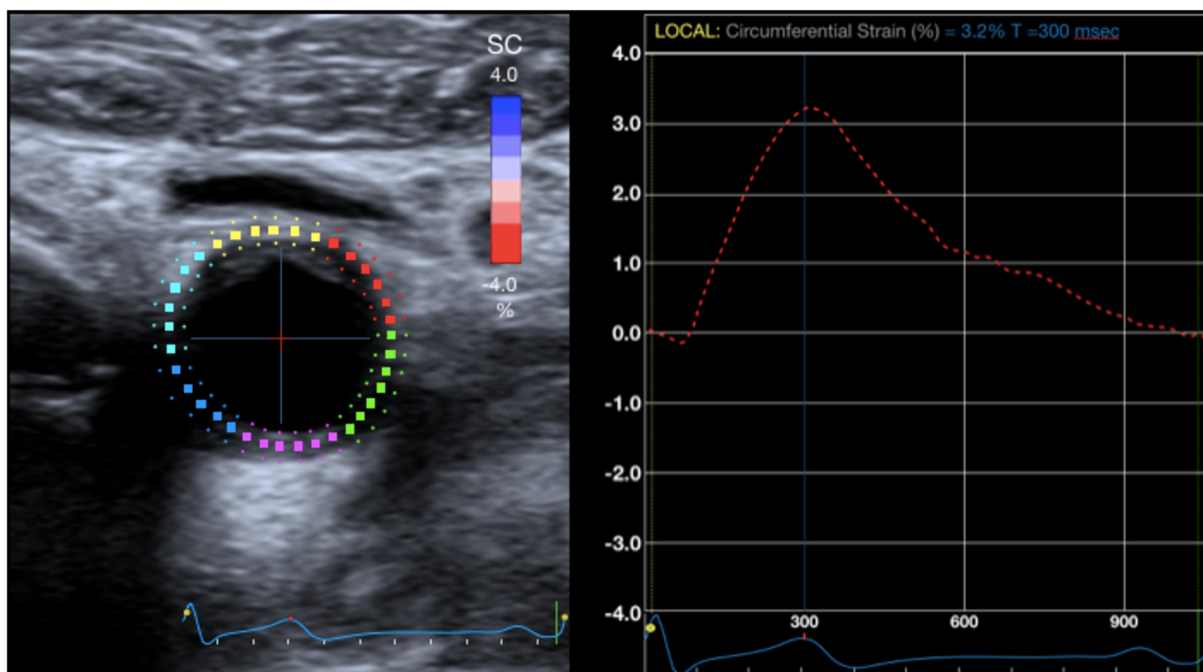
Fig. 2 Measurement of circumferential carotid artery strain. The cross-sectional area of the common carotid artery image (short axis) shows different colors according to the different wall segments included in the strain analysis. The red dotted curve in the graph represents the circumferential strain curve from the common carotid artery

Recently, new methods for assessing vascular tissue motion and deformation (strain) during the cardiac cycle have been developed using speckle tracking ultrasound (Fig. 2). The analysis of vascular wall motion is performed with short- and long-axis views of the carotid artery using conventional 2D grayscale echocardiography combined with a stable electrocardiographic (ECG) recording. The technique identifies acoustic tissue markers, the speckles, in a 2D grayscale image and tracks these speckles frame by frame during the cardiac cycle and calculates the motion and deformation of the carotid wall [5, 19, 30]. Parameters of arterial mechanics, including displacement, velocity, strain, and strain rate, can be measured. Speckle tracking strain is relatively angle independent and analyzes the vascular deformation patterns by longitudinal, radial, and circumferential directions. Nevertheless, circumferential analysis is the one typically performed, including strain and strain rate determinations. This is a useful technique in the evaluation of new elastic properties of vascular walls [15, 31].

REFERENCE VALUES

Obtaining accurate reference values requires specific measurement protocols to be utilized on a large population. As a result of a lack of a standardized method for image acquisition, there are differences found in CIMT and arterial stiffness values in healthy populations from different countries [7, 11, 20, 32].

Therefore, there are two main pathways for determining normal CIMT values: the utilization of a fixed cutoff value or a percentile distribution. A value of 0.9 mm is a cutoff in the European Society of Cardiology (ESC) guidelines [33] while a value above the 75th percentile of a reference population is recommended as a threshold by the American Society of Echocardiography [34] (Fig. 3). In a recent systematic review from The Lancet Global Health, Song et al. reported that in 2020, approximately 28%
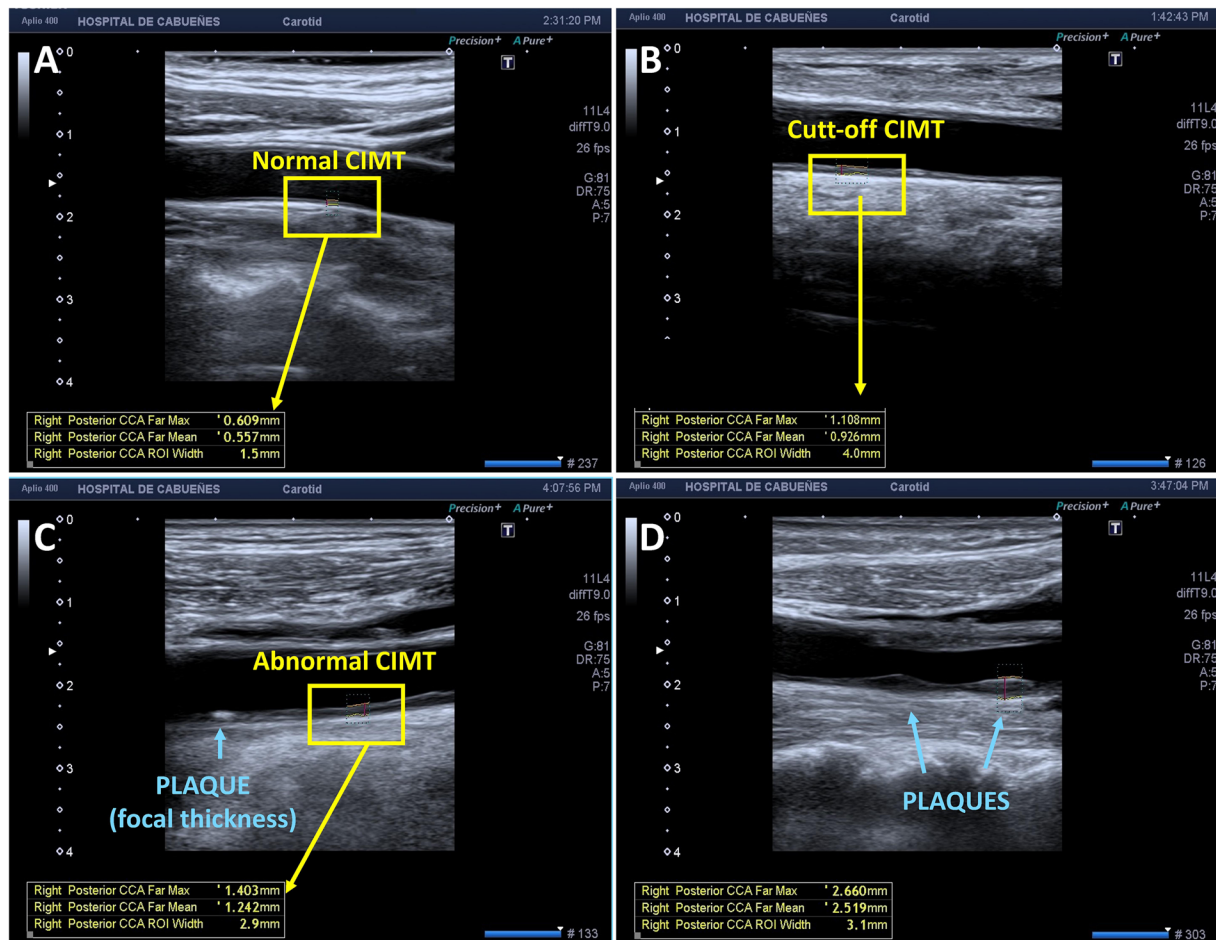
Fig. 3 Measurement of CCA-CIMT. Longitudinal B-mode ultrasound images of the CCA are shown with a normal CIMT = 0.557 mm (**a**), mild thickening of the intima-media = 0.926 (**b**), increased CIMT = 1.242 and a focal calcified plaque at the far wall (**c**), and a large heterogenous non-calcified plaque layered along the CCA (**d**)

of individuals aged 30–79 years in the general population had an abnormal CIMT of 1.0 mm and above, implying this effect applies to just over one billion people [6].

Many methods have been studied to quantify arterial stiffness, also with a variability in the measurement approach and values obtained [14, 30–32, 35–42]. Currently, normal and reference values for PWV have been defined in the Caucasian population by "The Reference Values for Arterial Stiffness Collaboration" [41]. Table 2 summarizes the main values provided from a literature survey.

CIMT AND ARTERIAL STIFFNESS AS EARLY BIOMARKERS OF CAROTID ATHEROSCLEROSIS AND STROKE

The measurement of CIMT by ultrasonography remains a strong predictor of CVD in various populations [24, 43–45]. Increased CIMT has also been associated with diabetes [46, 47], chronic kidney disease [48], subclinical hypothyroidism [49], rheumatic disease [50], low serum vitamin D [51], peripheral artery disease [52], HIV-positive persons [53], long-term exposure to particulate air pollution [54],

Table 2 Mean carotid stiffness values with the different measurement parameters

Parameter	Author (study)	n	Age (years)	Value mean (SD)	Unit
Elastic modulus	Kawasaki et al. [14]	70	20–39	0.7	Dynes $\times 10^{-6}$/ cm^2
	Liao et al. (ARIC) [35]	6992	56	124.0	kPa
	Yang et al. (ARIC) [36]	10,407	56	153.0 (65.0)	kPa
Arterial distensibility	Van Sloten et al. (HOORN) [37]	579	67	11.2 (4.2)	10^{-3}/kPa
	Gepner et al.(MESA) [32]	389	59	3.2 (1.3)	10^{-3} mmHg^{-1}
	Mattace-Raso et al. (Rotterdam) [38]	2265	71	10.6 (4.4)	10^{-3}/kPa
	Yang et al. (ARIC) [36]	10,407	56	1.5 (0.6)	% kPa
Arterial compliance	Laurent et al. [39]	39	50	8.7	$m^2 \times kPa^{-1} \times 10^{-7}$
	Yang et al. (ARIC) [36]	10,407	56	7.7 (2.8)	Mm^2/kPa
	Van Sloten et al. (HOORN) [37]	579	67	0.5 (0.2)	Mm^2/kPa
Young's modulus	Liao et al. (ARIC) [35]	6992	56	678.0	kPa
	Yang et al. (ARIC) [36]	10,407	56	895.0 (422.0)	kPa
	Gepner et al. (MESA) [32]	389	59	1526.0 (780.0)	mmHg
	Van Sloten et al. (HOORN) [37]	579	67	980.0 (460.0)	kPa
PWV	Mattace-Raso et al. (Rotterdam) [38]	2835	71	13.3 (2.9)	m/s
	Yang et al. (ARIC) [36]	100	44	8.3	m/s
	Van Sloten et al. (HOORN) [37]	579	67	10.0 (3.5)	m/s
	Wei et al. (Chinese community) [40]	583	56	8.4 (1.8)	m/s
	Mattace-Raso et al. (Arterial Stiffness Collaboration) [41]	11,092	50	7.4 female	m/s
				8.2 male	m/s
Stiffness index	Kawasaki et al. [14]	70	6–81	4.3–11.3	Dimensionless
	Liao et al. (ARIC) [35]	6992	56	11.8	Dimensionless
	Yang et al. (ARIC) [36]	10,407	56	0.1	Dimensionless
	Wei et al. (Chinese community) [40]	583	56	15.5 (10.2)	Dimensionless
Circumferential strain	Yang et al. (ARIC) [36]	10,407	56	5.1 (1.6)	%
	Catalano et al. [30]	47	57	3.6 (2.0)	%
	Park et al. [42]	1057	53	3.3 (1.3)	%

and radiotherapy (RT) [55]. Toprak et al. found in irradiated patients as soon as 6 weeks after RT a new plaque formation and increased CIMT compared to controls (0.68 ± 0.11 versus 0.87 ± 0.16, $p < 0.001$) [56]. In a traditional meta-analysis, patients treated with statins showed a significant benefit with a reduced mean CIMT of − 0.17 mm compared with the "no statin groups" (95% CI − 0.22 to − 0.12, $p < 0.001$) [57].

There is a well-documented association between CIMT and cerebrovascular events [7]. Several longitudinal studies have validated the relationship between finding an abnormal CIMT and risk of stroke. Van den Oord et al. reported in their meta-analysis that a 1-SD increase in CCA-CIMT increases the risk of stroke by 31% [7]. Kumar et al. suggested a strong association between increased CCA-IMT with risk of ischemic stroke as compared to control subjects (1.46, 95% CI 0.90–2.02) [58]. Sun et al. demonstrated that an SD increase in mean CIMT was positively associated with the risk of first ischemic stroke (1.10, 95% CI 1.01–1.20) [59]. Silent brain ischemic events in stroke-free individuals were also

Table 3 Summary of the studies reporting the association of CIMT with future stroke

Author (study)	n	Age (years)	Mean CIMT (SD)	FU (years)	Stroke	Stroke HR (95% CI)
O'Leary et al. (CHS) [61]	4476	72	1.03 (0.20)	6.2	NR	1.36 (1.25–2.28)
Chambless et al. (ARIC) [62]	14,214	45–64	0.84 (0.40) male	7.2	199	1.21 (1.05–1.39) male
			0.81 (0.30) female			1.36 (1.16–1.59) female
Hollander et al. (Rotterdam) [63]	6913	69	0.80 (0.16)	6.1	378	1.28 (1.15–1.44)
Lorenz et al. (CAPS) [64]	5056	50	0.71 (0.17) right	4.2	107	1.11 (0.97–1.28)
			0.74 (0.20) left			
Price et al. (EAS) [65]	1007	69	0.82 (0.10)	12.0	65	1.59 (1.07–2.37)*
Prabhakaran et al. (NOMAS) [66]	1118	68	0.65 (0.15)	2.7	20	1.60 (0.80–3.20)*
Folsom et al. (MESA) [67]	6698	45–84	0.87 (0.19)	3.9	59	1.40 (1.20–1.80)*
Polak et al. (FHS) [68]	2965	58	0.66 (0.15)	7.2	74	1.13 (1.02–1.24)*
Anderson et al. (FATE) [69]	1574	49	0.70 (0.17)	7.2	12	1.86 (1.53–2.28)
Mathiesen et al. (Tromsø) [70]	6584	60	0.89 (0.19) male	9.6	397	1.08 (0.95–1.22) male
			0.83 (0.17) female			1.24 (1.05–1.48) female
Lorenz et al. (PROG-IMT) [71]	36,984	NR	NR	7.0	1339	1.21 (1.09–1.35)
Ruijter et al. (USE-IMT) [72]	45,828	58	0.73 (0.16)	11.0	1971	1.12 (1.10–1.15)
Elias-Smale et al. (Rotterdam) [73]	3580	64	0.82 (0.14) male	12.2	207	1.33 (1.18–1.50)
			0.77 (0.12) female			

FU follow-up, *NR* not reported

*Includes HR of both myocardial infarction and stroke

associated with increased CIMT [60]. A total of 13 follow-up studies showed a significant association between CIMT with the onset of a stroke (Table 3) [61–73]. In accordance with these studies, CIMT can be used as a diagnostic marker for predicting the risk of future stroke events [58, 74].

Furthermore, a recent meta-analysis showed that interventions reducing CIMT progression are also likely to reduce cardiovascular event rates and estimated a relative risk for CVD of 0.91 (95% CI 0.87–0.94) per 10 μm/year reduction of CIMT progression [75].

Besides CIMT, stiffness is another parameter used to detect mechanical changes in the arterial wall during arteriosclerotic progression. This finding can theoretically occur earlier than any structural change [76]. Both CIMT and various indices of arterial stiffness are associated with coronary atherosclerosis, stroke, and cardiovascular mortality [30, 77].

Carotid distensibility was also found to be significantly associated with a higher prevalence of a previous transient ischemic attack (TIA) or ischemic stroke in patients with at least 50% carotid stenosis. Patients in the quartile with the lowest distension had a 2.1 times (95% CI 1.1–4.1) higher prevalence of a previous TIA or ischemic stroke compared with the patients in the quartile with the highest distension [78, 79]. Moreover, carotid distensibility has also been associated with increased risk of ischemic stroke in a population free from cerebrovascular disease [80]. Van Sloten et al. demonstrated that a 1-SD greater carotid distensibility significantly predicted stroke with an HR 1.18 (95% CI 1.05–1.33). When Young's elastic modulus is used instead of distensibility, the HR was 1.08 (95% CI 0.96–1.22) for a 1-SD decrease [37].

Growing evidence indicates that PWV is a strong predictor of stroke [9, 28, 29, 36, 38]. The Rotterdam Study estimated that those in the upper tertile of PWV index had an age- and gender-adjusted hazard ratio of stroke of 2.34 (1.13–4.82; $p < 0.03$) when compared with the reference category with an estimated HR of 1.28 for stroke for a 1-SD increase in PWV [38]. In addition, carotid-cerebral PWV reflects cerebral arterial stiffness and it is also associated with atherosclerosis. Carotid-cerebral PWV was positively correlated with the number of lesions and the degree of stenosis and it showed the vascular structure change in acute ischemic stroke [81].

The ARIC (Atherosclerosis Risk in Communities) study indicated an independent association between carotid stiffness and stroke. This study showed that all arterial stiffness parameters were significantly associated with an increased incidence of stroke. They reported that individuals with stroke had lower baseline value for arterial compliance (7.10 mm^3/kPa versus 7.92 mm^3/kPa, $P < 0.03$), arterial distensibility (1.41%/kPa versus 1.75%/kPa, $p < 0.0001$), carotid arterial strain (7.10 mm^3/kPa versus 7.92 mm^3/kPa, $p = 0.03$), higher values for stiffness index (0.13 versus 0.11, $p < 0.0001$), Ep (175.76 kPa versus 137.54 kPa, $p < 0.0001$), and Young's elastic modulus (1028.09 kPa versus 851.66 kPa, $p < 0.0001$) when compared with those individuals without stroke. After adjustments for age, gender, race, and vascular risk factors, arterial distensibility (HR 1.19 [95% CI 1.02–1.38]), carotid arterial strain (HR 1.13 [95% CI 1.01–1.27]), stiffness index (HR 1.14 [95% CI 1.04–1.25]), Ep (HR 1.15 [95% CI 1.05–1.27]), and Young's elastic modulus (HR 1.15 [95% CI 1.05–1.28]) continued to have a significant association with incident stroke [36].

CIMT AND ARTERIAL STIFFNESS ASSESSMENT IN CARDIOVASCULAR RISK PREDICTION

To date, cardiovascular risk prediction has been based on assessing traditional cardiovascular risk factors such as age, gender, lipid levels, smoking status, diabetes, and elevated blood pressure [7, 82]. Individuals were classified as having low cardiovascular risk, intermediate, and high risk using a 10-year cardiovascular risk estimation tool. The European Guidelines on cardiovascular disease prevention in clinical practice recommend the use of the SCORE (Systematic Coronary Risk Estimation) which can be recalibrated for use in different populations by adjusting for secular changes in

mortality and risk factor prevalence. Subjects with low risk should reduce their risk factors and high-risk subjects are also given medical therapy [83].

Several studies investigated risk prediction models with and without CIMT [24, 44, 45]. The British Regional Heart Study found that CCA-IMT was strongly associated with risk for stroke, whereas bulb IMT and plaque were more directly associated with ischemic heart disease [84]. Nambi et al. evaluated whether the Framingham risk score (FRS) had a significant improvement by using CIMT measurement. Their analyses suggested that plaque formation was a more effective finding than CIMT in predicting future CV events [24]. Furthermore, Inaba et al. estimated that plaque assessment is 35% better than CIMT in predicting cardiovascular events [85]. Although the improved risk prediction model using CIMT was small, some authors recommend taking into consideration the clinical relevance of this increase in populations at intermediate risk [7, 68, 73, 86]. On the other hand, Lorenz et al. found CIMT derived from the CCA, the bulb, and the internal carotid artery to be less predictive than the traditional Framingham and SCORE risk models [21]. This controversy surrounding the usefulness of CIMT measurement in risk stratification appears to result from the inconsistent methodology used in CIMT studies.

Regarding the assessment of vascular stiffness, patients at intermediate risk could be reclassified into a higher or lower cardiovascular risk category when arterial stiffness was measured [38, 87, 88]. Up to 15% of the patients at intermediate risk in the Framingham heart study could be reclassified into a higher (14.3%) or lower (1.4%) risk category when arterial stiffness was assessed [88].

Carotid distensibility is a significant predictor for future CVD and all-cause mortality. The predictive value, however, is not as strong as is PWV [89, 90]. Van Sloten et al. demonstrated that greater carotid stiffness is associated with a higher incidence of stroke independently of PWV and improved risk prediction of stroke, thus identifying carotid stiffness as a potential separate target for stroke prevention strategies [91]. Circumferential strain can be used as a screening tool for subclinical atherosclerosis. Vascular mechanics and the number of risk factors for vascular disease have been shown to correlate significantly [15, 42]. Park et al. showed that as the number of risk factors for atherosclerosis increased from 0 to at least 4, circumferential strain decreased accordingly. Patients with a high Framingham risk score also showed lower circumferential strain (5.01 ± 2.19; 3.46 ± 1.34, 3.08 ± 1.38; $p < 0.001$) for FRS less than 5%, 5–15%, and greater than 15% [42]. The addition of carotid strain to CIMT significantly improved the ability to detect patients at high cardiovascular risk [15, 42].

IMPLICATIONS FOR CLINICAL MANAGEMENT

Current guidelines from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) recommend lifestyle advice in primary prevention in low and intermediate cardiovascular risk, including smoking cessation, healthy diet low in saturated fat, and physical activity. In high risk cases, pharmacologic intervention adding low-dose aspirin among people less than 70 years of age who are not at increased bleeding risk and statin is suggested. In intermediate risk cases, adding statins depends on a function of cardiovascular risk uncontrolled after lifestyle modifications and low-density lipoprotein (LDL) level [83].

The addition of a surrogate marker for atherosclerosis for asymptomatic people at intermediate risk could further suggest reclassifying them into a higher risk group and providing earlier and better medical and lifestyle management. In young people, CIMT provides a reliable marker for early atherosclerotic disease where vascular events will likely not occur for decades and where plaque formation or calcification is not yet established [86].

Ruijter et al. demonstrated that CIMT had a small, yet significant potential for reclassification in intermediate risk individuals, with a clinical net reclassification index (NRI) of 3.2% in men and 3.9% in women [46]. Romanens et al. showed how carotid ultrasound can be

used to better detect higher-risk subjects defined as being at low risk by SCORE. Subjects were shifted in 7–34% of cases from low to a higher risk category. Those shifted were treated with 20 mg rosuvastatin per day and the relative risk reduction per 1 mmol/l LDL reduction was 35% (primary care patient with cardiovascular risk less than 20%) in 10 years. This approach allowed them to calculate the maximum cost per ultrasound examination that would allow cost-efficiency. Using these assumptions, they found a high cost-efficiency when carotid ultrasound was added to the clinical workup in low-risk patients [92]. As the interest in risk prediction is currently shifting from a 10-year risk to lifetime risk, the added value of a CIMT measurement and its cost-effectiveness using a horizon of 20–30 years may be worthwhile to explore [46].

A small change in CIMT (on the order of 0.01–0.1 mm) cannot be measured in individuals in clinically meaningful time frames, especially taking into consideration reader error and patient factors leading to variability. Follow-up measurement of CIMT is only recommended in large research studies in which standardized CIMT protocols including multiple angles, anatomic landmarks, and automated edge detection software technology are used to assess CIMT progression or regression on serial measurements in a large dataset [86].

Although the routine noninvasive evaluation of arterial stiffness and the CIMT may provide a more precise risk stratification factor compared with that achieved from the usual common risk score alone [30], measurements should not routinely be performed in the general population, as the overall added value may be too limited to result in health benefits. On the basis of this decision, the target patient population may be individuals classified as being at low or intermediate risk, in whom information on the CIMT measurements may improve the cardiovascular risk stratification and therefore the pharmacological intervention would be started or modified [46].

PWV adds value to the existing risk prediction based on standard Framingham risk factors. This was particularly true in younger individuals with intermediate CVD risk. Although PWV is also predictive in patients with preexisting CVD, there is little point in attempting to refine risk estimation in people who have known CVD or who are categorized as high risk based on established risk factors. Such individuals are going to be treated anyway, so addition of PWV would not alter management of these patients. The converse probably is true for individuals at very low risk. National thresholds vary but those with low risk and abnormal PWV would have a 10-year CVD risk of 5–15%. For people at intermediate risk, the addition of PWV to a model that includes standard risk factors yields a net reclassification of 15% (coronary heart disease events) to 27% (CVD death), underscoring the potential utility of PWV as a guide to early intervention [89].

One of the limitations of ultrasound is image quality, which depends highly on the sonographer's experience to use appropriate standardized carotid angles. In attempt to avoid it, the advances in software and hardware engineering have developed new automatic methods for the measurements of CIMT and arterial stiffness including novel artificial intelligence-based approaches.

FUTURE PERSPECTIVE

Diverse approaches for measuring CIMT and arterial stiffness are in use today. Standardization of acquisition and outcome measures are needed. Studies investigating the value of CIMT and stiffness should provide a uniform way to report their results. This would enable homogenous data collection and analysis to facilitate future data interpretation. Further advances in the development of these early biomarkers may help to improve the diagnosis of subclinical carotid atherosclerosis.

Ultrasonographic strain imaging with speckle tracking technique is a recent method for the assessment of carotid stiffness. This method has the potential to become a valuable noninvasive tool in the detection of early subclinical carotid artery disease [15, 19, 36, 42].

Recently, a combination of deep learning and machine learning was proposed for CIMT measurements showing up to 20%

improvement in CIMT readings for the artificial intelligence system compared to the conventional methods [93]. This new method may be useful to further characterize cardiovascular risk and identify earlier biomarkers in an asymptomatic population [94, 95].

CONCLUSIONS

CIMT is a well-accepted early surrogate marker for subclinical carotid atherosclerosis, predicting CVD and improving the cardiovascular risk prediction models. Arterial stiffening is one of the earliest manifestations of the structural and functional changes in the carotid artery wall. Assessment of carotid artery stiffness allows one to predict CVD and can be useful to refine risk stratification. This is particularly important in individuals classified as being at intermediate cardiovascular risk by the assessment of traditional risk factors alone, in whom CIMT and arterial stiffness measurements may reclassify them into a higher risk and therefore pharmacological therapy should be started.

A combination of multiple imaging markers will likely further improve imaging-based cardiovascular risk prediction. Further research is clearly needed to standardize and investigate the cardiovascular risk prognostication of CIMT and stiffness.

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