Intima–media thickness: a new tool for diagnosis and treatment of cardiovascular risk

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Increased intima–media thickness (IMT) is a non-invasive marker of early arterial wall alteration, which is easily assessed in the carotid artery by B-mode ultrasound, and more and more widely used in clinical research. Methods of IMT measurement can be categorized by two approaches: (i) measurement at multiple extracranial carotid sites in near and far walls and (ii) computerized measurement restricted to the far wall of the distal common carotid artery. Because IMT reflects global cardiovascular risk, its normal value might be better defined in terms of increased risk rather than in terms of statistical distribution within a healthy population. The available epidemiological data indicate that increased IMT (at or above 1 mm) represents a risk of myocardial infarction and/or cerebrovascular disease. Close relationships have been shown between: (i) most traditional cardiovascular risk factors; (ii) certain emerging risk factors such as lipoproteins, psychosocial status, plasma viscosity, or hyperhomocysteinemia; and (iii) various cardiovascular or organ damages such as white matter lesion of the brain, left ventricular hypertrophy, microalbuminuria or decreased ankle to brachial systolic pressure index. Thus, IMT gives a comprehensive picture of the alterations caused by multiple risk factors over time on arterial walls. Prospective primary and secondary prevention studies have also shown that increased IMT is a powerful predictor of coronary and cerebrovascular complications (risk ratio from 2 to 6) with a higher predictive value when IMT is measured at multiple extracranial carotid sites than solely in the distal common carotid artery. Therapeutic double-blind trials have shown that lipid-lowering drugs, such as resin and overall statines, and to a lesser extent antihypertensive drugs, such as calcium antagonists, may have a beneficial effect on IMT progression in asymptomatic or in coronary patients. However, methodological standardization of IMT measurement still needs to be implemented before routine measurement of IMT can be proposed in clinical practice as a diagnostic tool for stratifying cardiovascular risk in primary prevention and for aggressive treatment decision. It can be anticipated however, that the presence of increased carotid IMT in one individual with intermediate cardiovascular risk would lead to his classification into the high-risk category and thus influence the aggressiveness of risk factor modifications. *J Hypertens* 20:159–169 © 2002 Lippincott Williams & Wilkins.

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Introduction

Various non-invasive markers of early arterial wall alteration are currently available, such as arterial wall thickening and stiffening, endothelial dysfunction and coronary artery calcification [1]. Of them, intima–media thickness (IMT) of large artery walls, especially carotid, can be assessed by B-mode ultrasound in a relatively simple way and represents a safe, inexpensive, precise and reproducible measure [2]. This explains why IMT is more and more widely used in clinical research: (i) to test the value of new or emerging risk factors by means of observational or epidemiological studies in groups of patients or in general populations [3] and (ii) to evaluate effects of risk factor modifications by various drugs on the progression of early arterial wall alteration in therapeutic trials [4]. In clinical practice, the measurement of IMT is not yet performed as a routine investigation but the predictive value of IMT with regards to cardiovascular complications has been established in several prospective studies, suggesting that IMT measurement might participate in the future in the stratification of cardiovascular risk of asymptomatic patients in primary prevention [5]. The present review describes the methods of measurement and 'normal' values of IMT, the relationship of IMT with atherosclerotic risk factors, cardiovascular damages and clinical events, and the effects of treatments (i.e. antihypertensive and lipid-lowering drugs) on IMT progression over time.

Methods of measurement

There are important differences in B-mode measurement of carotid IMT between laboratories [6]. These

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might concern IMT image acquisition (in relation to the segment and/or the wall of measure) as well as IMT image analysis with regards to the type of measure (mean maximum, mean random, mean over 1 cm). They also involve the determination of the echo boundary defining the IMT interfaces [7] which may be a manual cursor placement or an automated computerized edge detection (Table 1). Two main approaches are used for measuring IMT according to the above criteria: (i) measurement at multiple extracranial carotid sites in both near and far walls [8] and (ii) automated computerized measurement restricted to the far wall of the distal common carotid artery [9].

Multiple carotid sites measurement

This approach usually consists in measuring IMT in the near and far walls of the three main segments of extracranial carotid arteries (common carotid, bifurcation, internal carotid) on both sides [8]. For each segment, ultrasound scan is performed in more than one direction, the maximal value of IMT is selected, and the final IMT considered is the average of IMT values at the 12 sites examined [8]. Alternatively the IMT considered may be the average of maximum IMT values at only six, four or even two carotid segments, or the average of randomly selected IMT measures in three to five carotid segments (Table 1). Measurements are usually performed on the basis of a video image by visual assessment of the leading edges (i.e. the upper demarcation line of the echogenic zone) of the blood–intima and media–adventitia interfaces defining IMT [7]. The analysis of IMT interfaces is performed off-line, manually or semi-automatically with the assistance of a computerized program, by placing a cursor on the interfaces in the digitized video image of the initial scan. Measurement of IMT at multiple carotid sites frequently incorporates plaque thickness because plaques are common in the carotid bifurcation and internal carotid artery of subjects with increased risk for cardiovascular disease. This explains why the measured IMT can be considered as a marker of early carotid atherosclerosis.

Far wall common carotid computerized measurement

Another methodology is to restrict IMT measurement to the far wall of the distal segment of the common carotid artery [9,10]. This superficial and straight segment offers the best geometric conditions for obtaining a high precision and reproducibility rate of ultrasound IMT measurement [10]. First, IMT is not measured at a single point but averaged on approximately 100 points of measure along at least 1 cm of longitudinal length of the vessel. Second, the distal carotid provides an optimal ultrasound image clearly defining IMT (i.e. the double line pattern); this image consists of two parallel echogenic interfaces: the first one between the blood and the intima and the other between the media and the adventitia [7]. Finally, IMT image is frozen in telediastole by means of electrocardiogram triggering to avoid a confounding effect of pulsatile deformation of wall thickness and transferred to a computer [9]. Then, a program of analysis based on the determination of gray-level density and special recognition tissular algorithms allows an automated measurement of IMT to be performed without reader-dependence. Furthermore, when a second measurement of IMT is performed subsequently within a longitudinal investigation, the computerized analysis program allows the 'anatomic profile' of the vessel obtained at the first examination to be generated and stored in the computer memory [9]. The anatomic profile helps the sonographer to adjust the probe in the same position as the first examination [9]. These computerized procedures improve the precision and reproducibility rate of the IMT measurement, providing approximately 3% of relative difference between two successive measures [11]. However, the measurement of IMT in the distal common carotid artery suffers from the inability to assess whether IMT does represent atherosclerosis (intimal thickening) or vascular hypertrophy (medial thickening), or both. The reason is that ultrasonography cannot distinguish between intimal thickness and medial thickness in the IMT measurement because of insufficient axial resolution. Therefore IMT, when measured in the distal common carotid artery free from intrusive atherosclerotic plaque, should be considered as a marker of early arterial wall change rather than as a surrogate for atherosclerosis. This premise actually applies to all the segments including the distal common carotid artery. The common carotid is less likely to have intrusive plaque than the bifurcation and internal segments and therefore it may be not the most appropriate segment to study if the objective is a specific investigation of atherosclerosis.

Table 1 **Methodological criteria taken into account for measuring carotid IMT**

Image acquisition	Segment: CCA, bulb, ICA, right/left
	Wall: far, near
Type of measure	Mean of several maximum measures (from 2 to 12)
	Mean of randomly selected measures (from 3 to 5)
	Mean of measures over 1 cm (≥ 100)
Methods of analysis	Manual cursor placement
	Automated computerized edge-detection

CCA, Common carotid artery; ICA: internal carotid artery.

Precision and reproducibility

Experimental studies

Several studies have used phantoms to test experimentally the precision and the capacity of ultrasonography for measuring the distance between two echogenic interfaces which are similar in dimension to that existing between carotid IMT interfaces [10–12]. Wedge lucite phantoms have been used, allowing distances to

be measured between interfaces ranging from 0.3–1.5 mm. The phantoms also allowed measurement of gradual changes of approximately 0.03 mm in the distance between these interfaces [10–12]. A computerized program to detect echogenic interfaces incorporating subpixel interpolation has been used to analyse the ultrasound image and to measure this distance between the two interfaces [10–12]. Compared with an optical method of measurement of interface distance, the computerized ultrasound method had a high reliability coefficient (R) of 0.99 [11]. The absolute difference between optical and ultrasound measurements varied from 0.03–0.05 mm without any systematic error [10,12]. Thus, the computerized ultrasound method allows the assessment of changes in distance between echogenic interfaces that are 10 times smaller than the axial resolution of the ultrasound transducers (0.2–0.4 mm) [12].

Clinical studies

These have shown that the reproducibility of IMT measurement is dependent of the site of measurement and the method of reading (automatic or manual). Estimates of reproducibility have been provided in detail, especially in the context of controlled clinical trials. For example, the ELSA study has performed a careful and complete analysis of the reproducibility according to the site of measurement [13].

It has been shown that the absolute difference between two repeated measurements ranged, on average, from 0.165 mm for the internal carotid to 0.069 mm for the common carotid segment [13]. In addition, the difference between repeated measurements was greater in the near wall (0.102 mm) than in the far wall (0.097 mm), but the difference between repeated measurements at 12 different sites was relatively low (0.077 mm). However, the use of the dimension of the value of the difference between repeated measures to compare reproducibility between choosing the common carotid alone and including more segments may be not appropriate because the value of IMT for the common carotid is smaller than that of more sites. This problem may be overcome by expressing variability as a percentage of the IMT value at the site of measurement, and the ELSA data show that the percentage variability between two repeated measurements is similar (approximately 7%) for the common carotid and for the 12 multiple sites measurement.

The type of reading of IMT, i.e. automatic versus manual, also influences reproducibility. It is obvious that the automatic measurement has better reproducibility than operator-dependent manual measurement. This has led many investigators to develop a new and high-performance method of automatic measurement, such as use of Fourier shape descriptions [14], or an anatomic mask procedure allowing superimposition of the image obtained at subsequent serial investigations and that of the initial investigation [9,11]. Such methods have demonstrated an absolute difference between repeated measures as low as 0.02 mm at the common carotid site [6], i.e. a percentage variability of less than 4%. However, the automatic methods are appropriate for the common carotid segment and totally automatic methods have not been reported for bifurcation and for internal segments. This results in better reproducibility for the common carotid IMT [6].

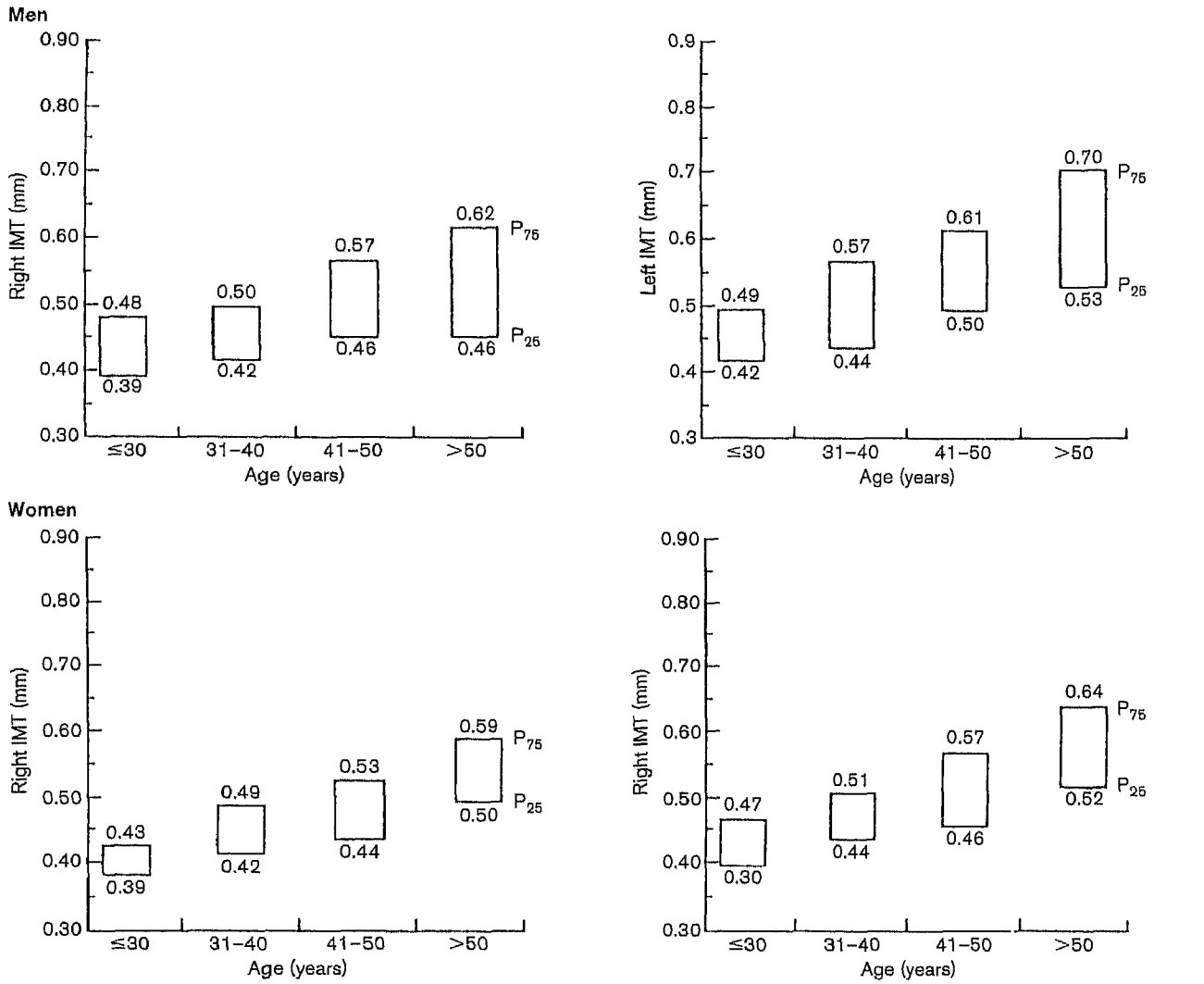
Normal values

Since increased IMT has increasingly become a target for detecting early alteration of the arterial walls, it is of major clinical relevance to define the threshold values beyond which IMT may be considered as abnormally high [5]. Thus, the ultrasonography diagnosis of 'increased' IMT in one individual at risk for atherosclerosis might help to better stratify the risk of the patient [5]. The normal values of carotid IMT are highly dependent on the methodology used for its measurement. They have generally been established on the basis of the distribution of IMT values (histogram) within a general healthy population [8,15]. The normal IMT values strongly influenced by age and sex should be considered by gender (men or women) or by range of age (e.g. decades) [8,9]. The definition of the upper normal limit used for defining normal range of IMT is arbitrary and is frequently set at the 75th upper percentile of the IMT distribution (Fig. 1). However, since IMT is considered as a candidate marker of cardiovascular risk [2], the normal value should be interpreted in terms of increased risk rather than in terms of statistical distribution within a population. Epidemiological studies should contribute toward defining the threshold of IMT above which the cardiovascular risk begins to increase sharply. The epidemiological data currently available indicate that a value of IMT at or above 1 mm at any age is associated with a significantly increased risk of myocardial infarction and/or cerebrovascular disease.

Relationship to cardiovascular risk

A close relationship of IMT has been found with a number of cardiovascular risk factors [3,16–20]. Traditional risk factors, such as male sex [9], ageing [9], being overweight [9], an elevated blood pressure [21–26], high blood cholesterol [27–29], diabetes and insulin resistance [30–32] and cigarette smoking [33,34] are positively associated with carotid IMT in observational and epidemiological studies in patients at cardiovascular risk and in the general population. Of all traditional risk factors, hypertension appears to have the greatest effect on IMT, probably via medial hypertrophy, which is a process specifically related to this disease [27–29]. Cumulative effects of classical risk

Fig. 1



Distribution of 'normal' values of common carotid artery far wall intima–media thickness (IMT) (both scales) in a population of healthy men and women by age range; AXA Study [9]. Upper and lower limits of bars are 75th upper (P_{75}) and 25th lower percentiles (P_{25}) of IMT distribution within the age range indicated in the *x*-axis. Abnormal increased IMT are values above the 75th upper percentile in each category of age.

factors also exist on IMT, as shown by the positive relationship found between the multifactorial risk score of Framingham and carotid IMT [34]. New or emerging risk factors have also been tested with regards to their relationship to carotid IMT [35–71] (Table 2). Some of these studies have demonstrated a consistent association with increased IMT, such as various lipoproteins [35–38], psychosocial status [39,40], plasma viscosity [41–42] and hyperhomocysteinemia [59,60, 62,63] (Table 2). Carotid IMT has also been found to be associated with cardiovascular alterations or organ damages [72–93] and specifically: (i) in the brain with white matter lesions assessed by magnetic resonance imaging [87]; (ii) in the heart with angiographically assessed coronary artery disease [93], electron beam computed tomographically assessed coronary artery calcification [92] and echocardiographic left ventricular hypertrophy [80–82]; (iii) in the kidneys with microalbuminuria in diabetic patients [91]; (iv) in the lower limb arteries with decreased ankle to arm systolic pressure index [76]; and (v) in the brachial artery with endothelial dysfunction attested by decreased vasodilatory response after reactive hyperemia after arterial occlusion [75]. All the relations of IMT with cardiovascular risk factors and organ damages indicate that increased IMT may be considered as a comprehensive picture of the alterations caused by multiple risk factors over time on the arterial walls. The extensive use of IMT in the literature for testing its relationship with various new or emerging cardiovascular risk factors

Table 2 **Association between emerging or new cardiovascular risk markers and carotid intima–media thickness**

Risk marker	Population (study)	Association
Lipids		
Lipoprotein (a)	Healthy adults (ARIC)/type II diabetics [37]	Yes/yes
LDL particle size	Healthy adult (ARIC) [35]	Yes
Apolipoprotein E polymorphism	Subjects with and without coronary artery disease [36]	Yes
Oxidized LDL antibodies	Healthy adults [38]	Yes
Insulin		
Insulin resistance	Vasospastic angina [67]	Yes
Insulin sensitivity	Hypertension subjects (ICARUS) [32]	Yes
Plasma insulin	Healthy subjects (IRAS) [68]	No
Proinsulin	Healthy subjects (IRAS) [88]	Yes
Gene polymorphism		
Lipoprotein lipase	Dyslipidemic (ARIC) [51]/healthy adults (STANISLAS) [53]	Yes/no
Apolipoprotein E4	Healthy adults (STANISLAS) [53]	No
Angiotensin converting enzyme	Healthy adults/low risk subjects/diabetics [54–57]	Yes/no/yes
MTHFR	Healthy adults (CUDAS) [59]	No
Homocysteine		
Mild hyperhomocysteinemia	Healthy subjects (CUDAS/ARIC/Rotterdam) [60,61,63]	Yes
Severe homocysteinemia	Homocysteinuria [62]	Yes
Infection		
Chlamidia pneunomiae	Healthy adults [64]	No
Cystomegalo virus	Healthy adults (ARIC) [65]	Yes
Herpes virus	Healthy adults (ARIC) [66]	No
Other factors		
Hostility	Healthy post-menopause women [39]	Yes
Social inequality	Healthy adults (ARIC) [40]	Yes
Alcohol consumption	Healthy adults (ARIC) [44]	No
Birth weight	Healthy adults [46]	Yes
Physical activity	Healthy men [50]	No
Family history of coronary artery disease	Healthy adults [49]	Yes
Blood and plasma viscosity	Healthy subjects (AXA/Edinburgh) [42,41]	Yes/Yes
Serum sialic acid	Healthy adults (ARIC) [43]	Yes
Cell adhesion molecules	Outpatients [45]	Yes
Von Willebrand factor	Cerebrovascular disease patients [48]	Yes
Serum elastase activity	Older adults [47]	No

LDL, low density lipoprotein.

emphasizes the major role currently played by this biomarker in clinical research.

Relation to clinical events

Several prospective studies of asymptomatic subjects in primary prevention have tested the predictive value of IMT with regards to clinical cardiovascular complications [94–99], such as myocardial infarction or stroke (Table 3). The KIHD Study in middle-aged healthy Finnish men has shown that a carotid IMT = 1 mm was associated with a two-fold greater risk for acute myocardial infarction over 3 years [94]. The ARIC study in several US communities has shown that a carotid IMT = 1 mm was associated with an increased risk ratio of coronary event over a period of 4–7 years (risk ratio of approximately 2 and 5 in 45–64-year-old men and women, respectively) [95,96]. The CHS Study in US elderly subjects has shown that a carotid IMT = 1.18 mm was associated with a four-fold greater risk for combined acute myocardial infarction and

Table 3 **Relation of carotid intima–media thickness (IMT) with cardiovascular events in asymptomatic subjects**

Increase in IMT	Site of measure	Study (country)	Subject (sex, age)	Follow-up duration (years)	Outcome	Risk ratio (95% confidence interval)
At or above 1 mm	CCA	KIHD [94] (Finland)	M, 40–60	3	AMI	2.2 (0.07–6.7)
At or above 1 mm	Mean maximum 6 sites	ARIC [95,96] (USA)	M, 45–64	4–7	CHD	1.9 (1.3–2.7)*
			W, 45–64	4–7	CHD	5.1 (3.1–8.4)*
			M, 45–64	6–9	Stroke	3.6 (1.5–9.2)*
			W, 45–64	6–9	Stroke	5.5 (3.5–20.7)*
At or above 1.18 mm	CCA	CHS [97] (USA)	M-W, ≥ 64	6	AMI and stroke	2.9 (2–4)†
Per 0.16 mm	CCA	Rotterdam [98] (Holland)	M-W, ≥ 55	3	AMI	1.4 (1.2–1.8)†
			M-W, ≥ 55	3	Stroke	1.4 (1.3–1.8)†

KIHD, Kuopio Ischaemic Heart Disease; ARIC, Atherosclerosis Risk In Communities; CHS, Cardiovascular Health Study; CCA, common carotid artery; AMI, acute myocardial infarction; CHD, coronary heart disease. *Adjusted for age and race; †adjusted for age and sex.

stroke over 6 years [97]. The Rotterdam Study in elderly Dutch subjects has shown that each difference of 0.16 mm in IMT was accompanied by a risk ratio of 1.4 for acute myocardial or stroke over 3 years [98]. In addition, studies in secondary prevention, in particular the CLAS study [99] in patients with established coronary artery disease, has shown that for each 0.03 mm increase per year in common carotid IMT, the relative risk for any coronary event was 3.1. All these studies are concordant in demonstrating that increased IMT is a powerful predictor of coronary and cerebrovascular complications whatever the method and the site of measurement, including the distal common carotid far wall IMT. However, the predictive power appears less strong for IMT measured only in the distal common carotid than for IMT measured at multiple extracranial carotid sites. This supports the idea that the common carotid artery alone may not be the most appropriate segment to study if the objective is to predict atherosclerotic-related complications.

Therapeutic trials on IMT

Because of its quantitative value and its high precision and reproducibility rates, carotid IMT measurement is more and more frequently used in therapeutic trials to test the effects of drugs. We have restricted this review to randomized double-blind trials. However, the results and interpretation of these trials may be influenced by the site of measurement of IMT which, schematically, can be either multiple extracranial carotid segments or the far wall of the common carotid artery.

Multiple carotid sites measurement

A number of trials have tested the effects of lipid-lowering drugs (statins) on carotid IMT while other trials have tested the effects of various calcium antagonists [22,100–113] (Tables 4 and Table 5).

The KAPS [100] and CAIUS [101] studies have shown that pravastatin, compared to placebo, decreased significantly the progression of IMT in asymptomatic high-risk patients over 3 years of treatment (Table 4). In contrast, the PLAC II study [102] did not find that pravastatin, compared to placebo, had a different effect on IMT progression over 3 years in coronary patients (Table 4), although pravastatin significantly reduced IMT progression by approximately 35% in the common carotid segment possibly because the IMT variability associated with this segment was lower compared to other segments. The REGRESS study [103] has also shown that pravastatin, compared to placebo, significantly decreased the progression of IMT, assessed as the mean of carotid and femoral measurements, in coronary patients (Table 4). The ACAPS study [104] in asymptomatic patients showed that lovastatin, compared to placebo, significantly decreased IMT progression over 3 years. Finally, the recent ASAP study [105] in familial hypercholesterolemia showed that a high dose (80 mg) of atorvastatin, compared to 40 mg simvastatin, significantly decreased IMT progression over 2 years (Table 4).

The MIDAS [106] study in hypertensive patients did not find a difference in IMT effects for isradipine and hydrochlorothiazide over 3 years because there was no difference in the slope of IMT progression for both treatments (Table 5). However, when the data were analysed as IMT change from baseline after 3 years of treatment, a difference existed favouring isradipine. The VHAS study in hypertension [107] also concluded that there was a lack of any different effect for verapamil and chlorthalidone on IMT progression over 4 years (Table 5), but found a significant greater effect for verapamil to decrease IMT progression when the slope of IMT was corrected by the initial value of IMT. The PREVENT [108] study in coronary patients has shown that amlodipine, compared to placebo, over 3 years significantly decreased IMT progression (Table

Table 4 Effect of lipid-lowering drugs on carotid intima–media thickness (IMT) in randomized double-blind trials

Treatment	Study	Outcome	Patients	Follow-up (years)	IMT progression rate (mm/year)		
					Drug	Control	*P*
Colestipol/niacin versus placebo	CLAS [110]	Mean CCA	Coronary	4	−0.012 ± 0.003	0.012 ± 0.003	< 0.001
Pravastatin versus placebo	PLAC II [102]	Mean maximum 12 sites	Coronary	3	0.059 ± 0.008	0.068 ± 0.008	NS
	REGRESS [103]	Mean CA-FE	Coronary	2	0.00 ± 0.20	0.05 ± 0.20	0.008
	KAPS [100]	Mean maximum 12 sites	Asymptomatic	3	0.017 ± 0.004	0.031 ± 0.003	0.005
	LIPID [112]	Mean CCA	Coronary	4	−0.003 ± 0.002	0.012 ± 0.002	< 0.001
	CAIUS [101]	Mean maximum 12 sites	Asymptomatic	3	−0.004 ± 0.003	0.009 ± 0.003	< 0.001
Lovastatin versus placebo	ACAPS [104]	Mean maximum 12 sites	Asymptomatic	3	−0.009 ± 0.003	0.006 ± 0.003	0.001
	MARS [111]	Mean CCA	Coronary	4	−0.028 ± 0.003	0.015 ± 0.005	< 0.001
Atorvastatin versus simvastatin	ASAP [105]	Mean maximum 12 sites	Familial Hypercholesterolemic	2	−0.015*	0.018*	< 0.001

Data are mean ± SE. CCA, Common carotid artery; CA, carotid; FE, femoral; NS, non significant. *Estimated from change in IMT after 2 years.

Table 5 **Effect of calcium antagonism and angiotensin-converting enzyme inhibition on carotid intima–media thickness (IMT) in randomized double-blind trials**

					IMT progression rate (mm/year)		
Treatment	Study	Outcome	Patients	Follow-up	Drug	Control	*P*
Isradipine versus hydrochlorothiazide	MIDAS [106]	Mean maximum 12 sites	Hypertensive	3	0.04 ± 0.002	0.05 ± 0.002	NS
Verapamil versus chlortalidone	VHAS [107]	Mean maximum 6 sites	Hypertensive	4	0.015 ± 0.005	0.016 ± 0.005	NS
Lacidipine versus atenolol	ELSA [22]	Mean maximum 4 sites	Hypertensive	4	–	–	
Nifedipine versus hydrochlorothiazide/amiloride	INSIGHT [113] IMT	Mean CCA	Hypertensive	4	−0.007 ± 0.002	0.0077 ± 0.002	0.002
Amlodipine versus placebo	PREVENT [108]	Mean maximum 12 sites	Coronary	3	−0.012 ± 0.012	0.033 ± 0.012	0.007
Ramipril versus placebo	SECURE [109]	Mean maximum 12 sites	High risk	4.5	0.014 ± 0.002	0.022 ± 0.003	0.03

5). Finally, the recent SECURE [109] study, a substudy of the HOPE trial conducted in patients at high cardiovascular risk, showed that ramipril, compared to placebo, over 4.5 years significantly decreased the progression of carotid IMT (Table 5).

The outcome of all the above trials (i.e. IMT measured at multiple carotid sites including frequently plaque in bifurcation or internal carotid) can be considered as a surrogate of atherosclerosis. Therefore, when a drug demonstrates a beneficial effect on IMT progression (such as pravastatin, atorvastatin, amlodipine or ramipril), it can be inferred that this drug exerts an antiatherosclerotic effect on the carotid walls. Moreover, it is noteworthy that all the trials (except PREVENT) showing a significant difference in IMT progression between both treatments, concomitantly demonstrated a significant difference in the incidence of cardiovascular complications. However, the PREVENT study showed that amlodipine was associated with fewer hospitalizations for unstable angina and revascularization. The concomitant effects of treatment on IMT progression and the incidence of cardiovascular complications has led to the consideration of IMT, when measured at multiple carotid sites, as a surrogate marker for cardiovascular complications.

Far wall common carotid measurement

The measurement of IMT in the distal common carotid artery far wall is used alternately, but less frequently, than multiple carotid measurements in intervention trials. Three lipid-lowering drug trials in coronary patients (CLAS [110] with colestipol/niacin, MARS [111] with lovastatin and LIPID [112] with pravastatin) have shown that the active drug, compared to placebo, over 4 years significantly decreased IMT progression (Table 4). A recent study in hypertension, the IMT-INSIGHT [113] study ancillary to the INSIGHT trial, has clearly shown that nifedipine GITS compared to a combination of hydrochlothiazide and amiloride significantly decreased IMT progression over 4 years (Table 5). These trials on the common carotid IMT highlight three main obsevations. First, the measurement of IMT in the far wall of the common carotid artery free of atherosclerotic plaque allows a perfect image to be obtained of the two echogenic lines defining IMT and therefore the automatic detection of these two lines using an automatic computerized edge detection program. This automatic measurement improves considerably the precision and reproducibility and so allows a significant difference in IMT progression to be demonstrated between both treatments using a relatively small sample size. Second, the physiological meaning of IMT measured in the common carotid artery is less clear than IMT measured at multiple carotid sites because far wall common carotid artery IMT cannot be considered as a surrogate of atherosclerosis. Indeed, the common carotid artery is the site of earlier lesions which are not necessarily atherosclerotic in nature compared to the more advanced ones in the bifurcation or internal carotid arteries. Third, there is no obligatory parallelism between IMT progression in the common carotid artery and the incidence of subsequent cardiovascular complications. The IMT-INSIGHT trial has found the same incidence of events on nifedipine and diuretic treatment whereas the IMT progression was different between both treatments. The reason is that common carotid IMT is a very early preintrusive lesion and its short-term change cannot be translated into atherothrombotic complications whose mechanisms involve advanced atherosclerotic lesions. Nevertheless, it is likely that a common carotid IMT change may indicate the incidence of clinical complications at long-term, but further trials of longer duration are required to demonstrate such an hypothesis.

Relation between IMT changes and diameter changes

When interpreting IMT changes in intervention studies it is important to know to what extent they are influenced by concomitant changes in the carotid artery diameter. The carotid diameter change may passively modify wall thickness by stretching more or less the artery wall because of the non-compressibility of the arterial wall mass (80). The lack of measurement of arterial diameter in a therapeutic trial of IMT may be therefore a problem when interpreting the treatment

effect on IMT. Thus, it is currently recommended to measure concomitantly IMT and diameter in therapeutic trials. One possibility to minimize a potential influence of diameter change on IMT change is to calculate the area of the circular section of IMT, i.e. the cross-sectional area of IMT or CSA-IMT [80,113]. Assuming that IMT remains constant around the circular section of the carotid artery, CSA-IMT can be estimated as:

$$\pi \times \text{IMT} \times (\text{IMT} + D)$$

where D is the lumen diameter of the carotid artery at the site of IMT measurement [80,113]. It is noteworthy that the measurement of the diameter is easier in the common carotid artery than in other carotid segments such as the bifurcation or the internal carotid. Using this methodology, the IMT-INSIGHT trial [113] has shown that the different IMT change between nifedipine and diuretic treatment was not influenced by diameter changes induced by both treatments.

Clinical perspective of IMT measurement

Since carotid IMT is a marker of early arterial wall change, including atherosclerosis and/or vascular hypertrophy, its detection by B-mode ultrasonography might participate in the diagnosis of high cardiovascular risk in primary prevention and in the decision to treat aggressively those patients at risk with drug treatments of modifiable risk factors [5]. Before proposing the routine measurement of IMT in clinical practice, several limitations have to be overcome, such as the standardization of methods of measurement (including the site and the analysis of the measurement) and a precise definition of the threshold of IMT above which the risk of cardiovascular event can be considered to substantially increase in one individual [114].

Conclusion

IMT assessed by B-mode ultrasound in superficial large arteries, especially the carotid, is of major relevance with regard to the following points: (i) reflection of multiple risk factors [22]; (ii) mirror of atherosclerotic burden and/or index of cardiovascular growth, particularly in hypertension [34]; (iii) predictor of subsequent events [99]; and (iv) end-point for therapeutic trials [115]. However, the role of IMT measurement as a screening tool in asymptomatic patients with conventional cardiovascular risk factors is not yet clearly defined, mainly because of methodological obstacles. However, it can be anticipated that identifying the presence of increased IMT in the carotid arteries of one individual with intermediate cardiovascular risk would lead to his classification in the high risk category and thus influence the aggressiveness with which risk factor modification is peformed [5].

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