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Assessment and Relevance of Carotid Intima-Media Thickness (C-IMT) in Primary and Secondary Cardiovascular Prevention

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Abstract: Interventions aimed to prevent cardiovascular diseases (CVD) are more effective if administered to subjects carefully selected according to their CVD risk. Usually, this risk is evaluated on the basis of the presence and severity of conventional vascular risk factors (VRFs); however, atherosclerosis, the main pathologic substrate of CVD, is not directly revealed by VRFs. The measurement of the arterial wall, using imaging techniques, has increased the early identification of individuals prone to develop atherosclerosis and to quantify its changes over time.

B-mode ultrasound is a technique which allows a non-invasive assessment of the arterial wall of peripheral arteries (e.g. extracranial carotid arteries), and provides measures of the intima-media thickness complex (C-IMT) and additional data on the occurrence, localization and morphology of plaques.

Being an independent predictor of vascular events, C-IMT has been considered as a tool to optimize the estimation of CVD risk but this application is still a matter of debate. Though the technique is innocuous, relatively inexpensive and repeatable, its use in the clinical practice is limited by the lack of standardized protocols and clear guidelines.

This review outlines the rationale for the potential use of C-IMT in the stratification of cardio- and cerebro-vascular risk and discusses several topics related to the measurement of this variable, which are still controversial among experts of the field.

Keywords: Atherosclerosis, carotid ultrasound, carotid intima-media thickness (C-IMT), cardiovascular disease, cardiovascular risk prediction.

INTRODUCTION

Most patients with overt cardiovascular disease (CVD) have one or more vascular risk factors (VRFs) for atherosclerosis [1]; yet, experimental evidences raise doubts about the real possibility to discriminate subjects at high risk from normal individuals based solely on VRFs [2]. Indeed, studies indicate that traditional VRFs explain only 60-65% of CVD risk [3] and that the exposure to one or more of these VRFs is common even in subjects who will not develop overt clinical disease. In addition, many acute clinical events occur in patients at intermediate-risk [4] or even in subjects without any VRF [3]. Most algorithms used to estimate the global CVD risk take into account VRFs such as: gender, age, smoking, blood pressure, total cholesterol, HDL-cholesterol, and diabetes [5-9]. However, a myriad of other risk factors, not included in these algorithms (e.g. the family history of early coronary artery disease (CAD), insulin resistance, obesity, physical inactivity, depression, social isolation, etc.) can contribute to the development of atherosclerosis and CVD [10, 11].

It is also worth mentioning that CVD risk may be higher than the estimated risk due to a cumulative effect of borderline VRFs [10]. On the contrary, a single VRF such as age, for example, may yield high CVD risk estimates in older subjects regardless of their real atherosclerotic burden [12]. All these limitations have been early recognized by both the "American Heart Association" and the expert group of the "National Cholesterol Education Program" [10, 13].

Since atherosclerosis is one of the driving forces of CVD, one of the approaches currently proposed to increase the ability to identify individuals at high CVD risk is to integrate the information derived from VRFs with that derived from non-invasive imaging techniques which allow the direct detection of subclinical atherosclerosis and its change over time (progression, regression) [14, 15].

Among different diagnostic methods, B-mode ultrasonography of the supra-aortic trunks (carotids), aimed at measuring atherosclerotic plaques and intima media thickness (C-IMT) is one of the most interesting. The availability of ultrasound equipments with relatively affordable costs and the apparent ease of execution of ultrasonographic scans have encouraged many research groups to work in this area in the last years. As a result, thousands of studies have been published. Yet, many of them were carried out with poorly-standardized methods and debatable approaches, and nowadays even experts in the field struggle to disentangle this maze of information. Not less complex is this field for physicians who approach C-IMT for clinical reasons.

In particular, strong debate still continues about the usefulness of C-IMT to improve individual risk estimation. In this regard, the most recent ACC/AHA Cardiovascular Risk Guidelines questioned the contribution of C-IMT to risk assessment over and above the traditional risk scores [16].

This paper is an opinion article, written by a group of researchers working in this field since more than 20 years, and not a comprehensive review. Herein we will consider relevant data from the literature and direct personal experience that may be of help to define the role of this diagnostic technique in primary and secondary CVD prevention.

Given that no universally accepted guideline is available, in this paper we will discuss: 1) the rationale for using C-IMT for CVD risk stratification, 2) how to perform ultrasonic scans for the evaluation of C-IMT, 3) what, where and how C-IMT should be measured, 4) when, why and in which patient is it useful to perform a C-IMT interrogation, 5) what information should be included in an

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ultrasonic report for clinical use, 6) what C-IMT values should be considered abnormal and, finally, 7) whether it is appropriate to use C-IMT data to decide or modify the patient's therapy.

RATIONALE FOR USING C-IMT FOR CARDIOVASCULAR RISK STRATIFICATION

The rationale derives from two main sources of data: first, a huge number of clinical and epidemiological studies showing evidence of an association between this variable and the prevalence of clinical and instrumental signs of CAD and cerebrovascular disease; second, a series of cohort studies showing the ability of C-IMT to predict coronary and cerebrovascular events in a way completely independent from VRFs [17-22]. A meta-analysis of 8 large population studies, conducted on 37,000 patients, has shown that an absolute difference in C-IMT equal to 0.1 mm is associated with an increased risk of myocardial infarction (10-15%), and stroke (13-18%) [23].

The ACC/AHA Work Group, instead, recommended against measuring C-IMT in clinical practice for risk assessment, based on concerns regarding measurement quality, method standardization and level of evidence reported in three reviewed articles [24-26]. The ACC/AHA Work group considered that the first article [24], a systematic review of studies published before 2009, does not provide enough data in terms of C-IMT related reclassification, discrimination, calibration, and cost-effectiveness. Though the second article reported that, based on measures of reclassification, C-IMT actually improved risk assessment in two out of the three studies therein reviewed [25], the group judged that these improvements were modest. The analysis of the third article, an individual level meta-analysis of 14 population-based cohorts [26], lead the group to a similar conclusion. We believe that two important issues should be considered before reaching a definite verdict about this topic. First, in most of the studies reviewed in the guidelines, IMT was assessed only in the common carotid artery, i.e. the carotid segment with the lowest occurrence of atherosclerosis. Second, further pertinent studies not examined in the guidelines were recently published [27-29], and their positive results might warrant revision of the ACC/AHA recommendation.

HOW TO PERFORM ULTRASONIC SCANS FOR THE EVALUATION OF C-IMT?

A Consensus Statement for the use of carotid ultrasound has been delineated by the American Society of Echocardiography (ASE) [30], but is not universally accepted. Among its recommendations, the measurement of C-IMT should be carried out by expert sonographists, using last generation ultrasonic devices with linear array probes with frequency $\geq$ 7 MHz, and B-mode images should be preferred to those in M-mode. Moreover, the guidelines recommend measuring C-IMT only in the far wall of the first centimeters of the distal common carotid arteries using specific software able to detect echogenic lines of the intima-media complex. The C-IMT measures, captured in this way, should be compared with normal values defined on the basis of distribution curves for specific sex and age classes obtained from general healthy populations [19] and integrated with information about the presence of carotid plaques. To assess plaques, the ultrasonic scan should be performed considering both the "near wall" and the "far wall" of all the carotid segments: the common carotid artery (CC), the bifurcation (Bif) and the internal carotid artery (ICA). The scan should be performed longitudinally in three different angles and cross-sectionally on each segment (from the proximal centimeter of CC to the first centimeter of the ICA). Recent studies indicate that the systolic expansion of the lumen vessel, during the cardiac cycle, causes a reduction in C-IMT measures; therefore, to standardize the procedure, the images should be acquired during the final part of the diastolic phase [31]. Some of these guideline recommendations deserve further consideration and will be discussed below.

WHAT, WHERE AND HOW C-IMT SHOULD BE MEASURED?

Although C-IMT is formally the distance between the blood-intima and media-adventitia interfaces of a carotid segment (Fig. **1**), measurements on specific segments, specific walls or angles, with or without a specific software and, more importantly, incorporating or not the plaques, result in a series of very different variables, all of which, have been referred to as C-IMT. The problem is that each of these measures may reflect a different phenotype. Each of these points will be discussed to describe what might be, to our view, the minimum scanning protocol that allows collecting C-IMT variables of proved clinical utility with the least use of resources.

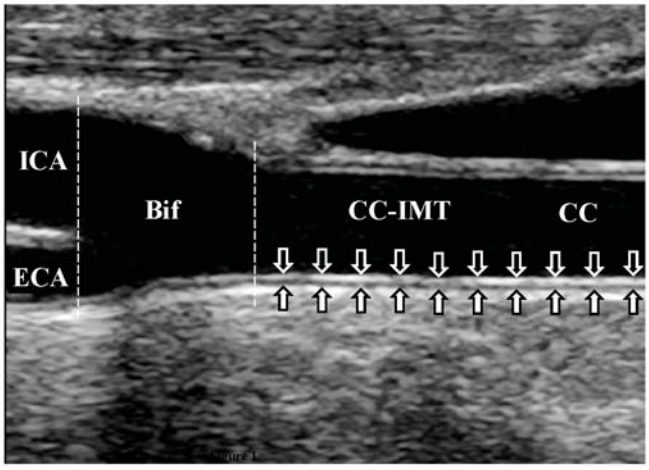

Fig. (1). Typical ultrasound image of an extracranial carotid artery where the common carotid artery (CC), the bifurcation (Bif), the internal carotid artery (ICA) and the external carotid artery (ECA) are easily recognizable. The intima-media thickness (C-IMT) is delimited by black and white arrows.

Should C-IMT be Measured in Common Carotid Artery only or in the Whole Carotid Tree?

The choice to measure C-IMT only in CC (or even only in the first distal centimeter of CC), is often justified by the easier accurate measurements on this segment compared to the Bif or the ICA. However, though somewhat less simple to carry out, a protocol based on measurements on the whole carotid tree has several advantages [27]. First, as plaques are preferentially localized at the level of Bif and ICA, measurements of C-IMT in these sites may reflect atherosclerosis better than those obtained exclusively on the CC. Second, while C-IMT of each carotid segment is affected by VRFs which are rather specific for that particular segment [32], composite variables derived from measurements taken on the whole carotid tree may provide more consistent associations. For example, in a recent study [27], composite variables (e.g. IMT_{mean} or $IMT_{mean\text{-}max}$) were better predictors of combined cardiovascular events or cerebrovascular events than CC-IMT. Moreover, the addition of $IMT_{mean\text{-}max}$ lead to correctly reclassify 14.5% of subjects considered at intermediate risk by the Framingham risk equation to the high risk category. Improving the predictability for this group, which represents the real gray decision area for clinicians, would have significant clinical implications by shifting at-risk subjects to the risk category qualified for pharmacological treatment. Third, C-IMT of Bif and ICA are more influenced by flow turbulence (another important mechanism for the development of atherosclerotic plaque) than C-IMT of the CC. Finally, as exemplified in (Fig. **2**), the choice of measuring C-IMT only in the first centimeter of the distal vessel, rather than in the whole length of the CC, may provide misleading results.

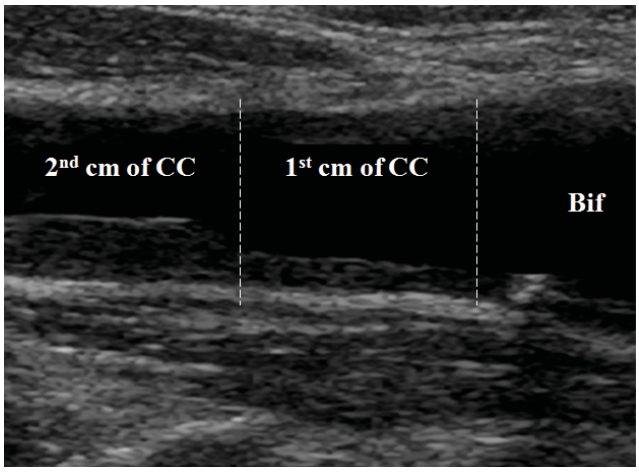

Fig. (2). Ultrasonographic image of a common carotid which shows the importance of evaluating the artery in its entire length. Note the chance of underestimation of atherosclerosis burden if only the first distal centimeter of the common carotid artery is considered (as actually is in several clinical and epidemiological studies).

Should C-IMT be Measured in the Far Wall only or also in the Near Wall? Should C-IMT be Measured with a Single Scan Angle or with More than One?

In an ultrasonographic scan of the extracranial carotid arteries, the ultrasound beam crosses the two arterial walls (near and far) by encountering a different sequence of interfaces: adventitia → media → intima of the near wall, and intima → media → adventitia of the far wall. According to some authors, this determines a higher accuracy in the measurement of the far wall, due to physical reasons [33]. Beyond these technical aspects, measuring only the far wall (may be even with a single scan angle) saves time and resources. However, this choice often leads to misclassification of the patient, which often reveals patent plaques on the near walls or when explored using different angles. An example of this situation is shown in (Fig. **3**).

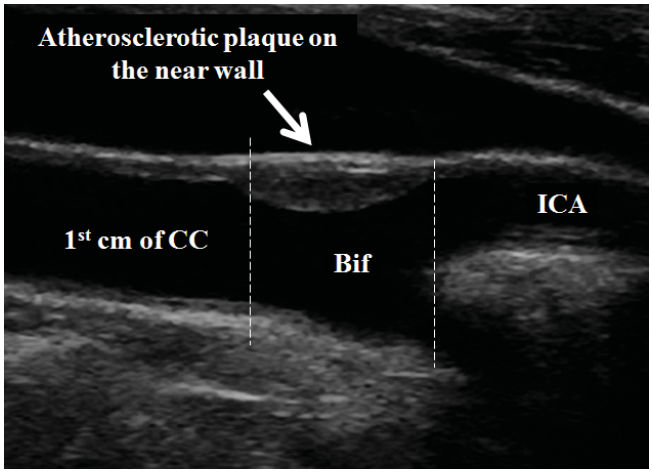

Fig. (3). Ultrasound image of an extracranial carotid with an atherosclerotic lesion in the near wall of bifurcation. If only C-IMT of the far wall of the common carotid artery is considered, this patient would be classified as normal.

Is it Mandatory to use Dedicated Software for Measuring C-IMT?

The answer largely depends on whether C-IMT is measured for a one-time assessment of atherosclerosis burden or for assessing C-IMT changes over time. In the first case, C-IMT measurements performed directly with the electronic caliper of the ultrasonic device itself are accurate enough and allow to detect associations with VRFs or, possibly, to perform individual CV risk stratification [34, 35]. In the second case, (e.g. to monitor disease progression or the effect of therapeutic interventions), highly accurate measurements with dedicated software become crucial to reduce error, inasmuch as the expected changes are always in the order of a few hundredths of a millimeter even if the second measurement is performed after years.

Should Plaques be Included in the C-IMT Measurements or Should they be Computed Independently of C-IMT?

The formation of atherosclerotic lesions is a continuous process that, especially in specific carotid sites (such as Bif and ICA), transforms slowly C-IMT into a plaque. C-IMT is therefore a continuous variable with values that range from completely normal (normal C-IMT) to overt pathological (plaque). Moreover, criteria utilized for definition of plaque on ultrasound images are arbitrary and, consequently, different definitions lead to different results. Several definitions of plaque have been proposed over the years: a) a specific area of mineralization in the vessel wall or focal protrusion into the lumen [36], b) a localized thickening of increased density with a C-IMT value greater than 2 mm [37], c) a focal structure that encroaches into the lumen at least 0.5 mm or at least 50% compared to the surrounding IMT values, or a thickness > 1.5 mm as measured from the media-adventitia to the intima-lumen interfaces [38], d) a focal thickening greater than 50% compared to the contiguous walls [39], e) a localized area of thickening of > 1 mm [40] or f) a localized area of thickening of > 1.2 mm [41, 42]. In addition, regardless of the definition used, most authors categorize plaques only in terms of presence/absence. Therefore, the distinction between C-IMT and plaques as two different entities is, in general, only an issue of statistical management. It is well known that the relationship between wall thickness and CVD risk is continuous and that a dichotomization of an originally continuous variable leads to a reduction of the predictive power of the variable itself [27]. The predictive power of plaques is undeniably higher than the predictive power of C-IMT in plaque-free areas because while plaque is atherosclerosis itself, C-IMT in plaque-free areas is just a marker of atherosclerosis. However, in several of our studies we found that when plaques are incorporated into C-IMT measurements, the predictive power of C-IMT is greater compared with the information derived from plaques (regardless of the definition used) or from C-IMT measured in plaque-free areas [27, 35]. Although several studies indicate that another index of plaques, namely Total Plaque Area, predicts myocardial infarction [43] and stroke [44] better than C-IMT, preliminary results from our group suggest, similarly to what happens when plaque thickness is considered, that this is the case only when total plaque area is compared with "CC-IMT_{mean} measured in plaque free areas" but not when compared with composite variables incorporating plaques (e.g. $IMT_{mean\text{-}max}$). Further analyses are ongoing to corroborate these data.

In summary, we believe that for the purpose of CVD risk stratification in single individuals, measurement of C-IMT in all segments (CC, Bif and ICA) of both right and left carotid arteries is recommended. For each segment, the maximum value of C-IMT (C-IMT_{max}) obtained incorporating the plaques and detected by considering both near and far walls of three scan angles (lateral, anterior and posterior) should be determined. The C-IMT_{max} value measured in each segment should then be averaged in order to obtain the C-$IMT_{mean\text{-}max}$, which is the variable with the highest predictive power [27].

This type of protocol is much less difficult and faster to carry out than it may appear. A well-trained sonographer is able to perform this type of scan in about 15-20 minutes, an acceptable time

even in the clinic, especially in view of the importance of the information obtained.

WHEN, WHY AND IN WHICH PATIENT IS IT USEFUL TO PERFORM A C-IMT INTERROGATION?

In year 2000, considering the above-mentioned limits of VRFs in risk stratification, the "*American Heart Association Prevention Conference V*" recommended the measurement of C-IMT to improve the stratification of CVD risk in the single individual [10]. Yet, who should undergo a C-IMT assessment is still quite controversial. According to the "SHAPE" (Screening for Heart Attack Prevention and Education) working group, all men aged between 45 and 75 years and all women aged between 55 and 75 years should be encouraged to undergo screening, unless they have a documented history of CVD or unless they are classified "at very low risk" on the basis of VRFs [4]. According to the ASE Consensus Statement, candidates for C-IMT screening are subjects without CAD classified at intermediate risk (6-20%) by the Framingham Risk Score (FRS), subjects with a family history of early CVD in first-degree relatives (parents, siblings), subjects younger than 60 years with at least one important VRF and women younger than 60 years with two or more VRFs. The C-IMT evaluation should be also proposed to tailor the aggressiveness of therapies aimed at controlling VRFs. According to the same document, the measurement of C-IMT is instead considered "inappropriate" when the information conveyed by C-IMT will not change the therapeutic approach to the patient such as, for example, in patients with overt CAD [30].

Taking into account that C-IMT measurement is non-invasive, relatively inexpensive, and rich in information, other authors consider that, regardless of age, each patient with a major risk factor, such as pre-diabetes, diabetes, metabolic syndrome, smoking habit, hyperlipidemia or family history of early cardiovascular disease, as well as all patients older than 45 years, would undergo C-IMT evaluation [45].

According to some studies the "additional" prognostic value of this variable and the appropriateness of its use may depend on the specific clinical features of each patient. This issue has been faced by The "Society of Atherosclerosis Imaging and Prevention (SAIP)", in collaboration with the "International Atherosclerosis Society", who carried out a critical review of the applicability of C-IMT in 33 different clinical scenarios in which this test could have an additional prognostic value, in the "presence" or "absence" of overt CAD [46]. In each scenario, the additional prognostic value of C-IMT was categorized by an independent clinical committee using a 1 to 9 scale as follows: appropriate use (score 7-9), uncertain use (score 4-6) or inappropriate use (score 1-3). The main concepts that we extract from a comprehensive table reported in this review are: 1) in individuals without CAD, CVD risk assessment using C-IMT is considered appropriate: a) in subjects with diabetes mellitus without a family history of premature CAD, b) in subjects with metabolic syndrome older than 30 years and c) in patients at intermediate risk (FRS 11-20%) regardless of whether they are carriers of two or more VRFs or whether the presence of coronary calcium or of a family history of premature CAD have already been ruled out. In all other clinical situations assessed, CVD risk evaluation using C-IMT was considered uncertain or even inappropriate; 2) in patients with CAD, the use of C-IMT to assess CVD risk was not considered appropriate in any of the clinical scenario considered.

WHAT INFORMATION SHOULD BE INCLUDED IN AN ULTRASONIC REPORT FOR CLINICAL USE?

The ultrasonographic reports often include generic sentences such as: "diffuse thickening of the carotid artery". This kind of expressions, being subjective and difficult to interpret, are of scarce clinical usefulness. To be objective and clinically useful, an ultrasonographic report should include all the numerical values of C-IMT measured in each segment of both right and left carotids. When measured in a segment with perfectly parallel interfaces, C-IMT_{max} corresponds to C-IMT_{mean}, instead, when a focal plaque is measured, the maximum value is always greater than the average value. In both cases it is therefore enough to report only the maximum value of each segment. In this way, C-IMT will range from normal to pathological values compatible with plaque's definition. Regardless of the dimension, already included in the numerical value of C-IMT, a focal thickening greater than 50% compared to the contiguous walls should be defined as "plaque" and described in the report. The carotid percentage of stenosis should not be calculated from cross-sectional images (because this approach would certainly lead to misleading data due to the process of vascular remodeling); instead, it should be evaluated in longitudinal images, as the ratio between the intima-intima distance of the area involved in the stenosis and the intima-intima distance of surrounding areas free of plaques. According to our experience, data obtained with this approach provide stenosis measures which are identical to those obtainable with angiography.

According to some authors [40], further improvement in risk estimation may be gained by considering not only the largest identified plaque (C-IMT_{max}) but also the total plaque burden in both carotid arteries. We consider that the average of all the C-IMT_{max} observed in each carotid segment (namely C-$IMT_{mean\text{-}max}$), is the variable that best describes the total plaque profile and which has the best predictive power [27]. It is worth saying that sonographers who anyway choose to measure C-IMT in plaque-free areas should provide information about the presence/absence of plaques, a variable that improves significantly the estimate of CVD risk regardless of the value of C-IMT [47].

Finally, based on available evidence showing an additional predictive power of plaque echolucency [48] some authors propose that the report should include a description of the echogenic characteristics (soft, mixed, or calcified) of each detected plaque. Though qualified technicians may certainly recognize plaque ecostructure, to date the method is entirely subjective and at risk of mistakes.

WHAT C-IMT VALUES SHOULD BE CONSIDERED ABNORMAL?

According to the Consensus Statement outlined by ASE [30], C-IMT values equal or greater than the 75th percentile of the distribution of a healthy population entail a risk higher than that estimated by the FRS and thus should be considered abnormal [30]. C-IMT values between the 25th and the 75th percentile are considered in the normal range and should not influence the traditional risk estimation. Values $\leq$ 25th percentile have to be considered "low", suggesting a lower risk than that expected by the FRS. According to the same document, patients with carotid plaques should be considered automatically at high risk regardless of C-IMT values [30]. In fact, in all the studies in which both variables (C-IMT measured in areas free of plaques and plaques) were considered, the presence of carotid plaques was associated with an increased risk of CAD [37, 49].

As mentioned above, the variable obtained incorporating the plaques into C-IMT measurements, ranges from normal values up to pathological values. This continuous distribution raises the issue of determining the threshold value of normality [50]. A C-IMT of 1 mm has been used as the limit of normality in several epidemiological studies [19, 51]. Although this value, determined in general populations without taking into account patient's age and sex, is useful for epidemiological identification of groups at-risk, it seems inappropriate for the estimation of the CVD risk in a single individual. In fact, using this criterion, a patient with a C-IMT just above the threshold value (e.g. 1.1 mm) would have the same risk estimation of a patient with plaques of 4 mm or more. In addition, if a C-IMT value of 1 mm should be considered "abnormal" in a 30

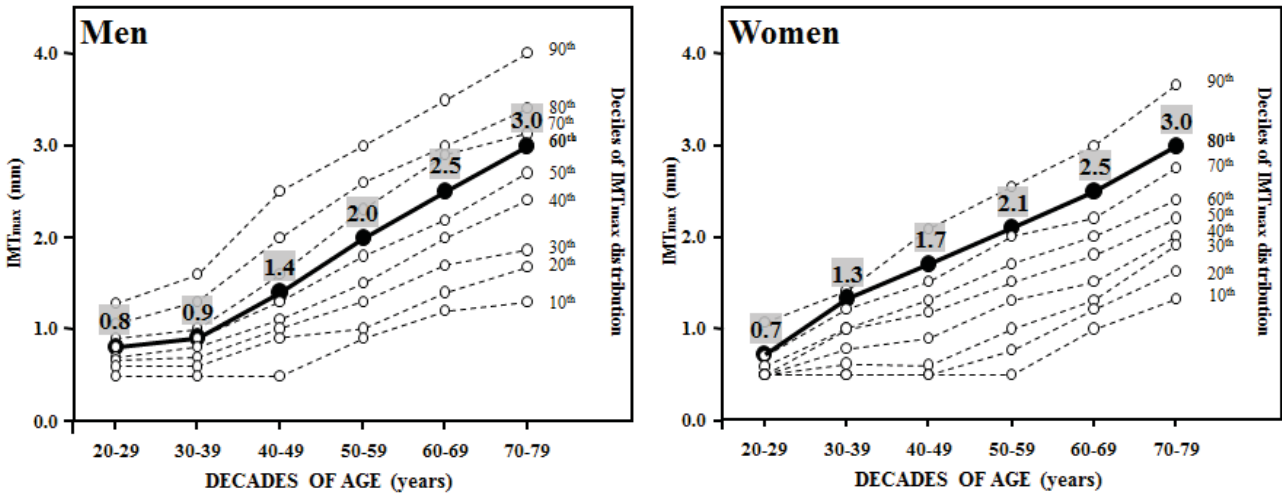

Fig. (4). Threshold values above which C-IMT$_{max}$ has to be considered as abnormally high. These values correspond to the 60th percentile for men and to the 80th percentile for women of the C-IMT$_{max}$ distributions obtained in different age decades in a group of about 2000 Italian dyslipidemic patients [35].

years old patient, the same value is within the range of normality in a subject older than 50 years.

The ASE Consensus Statement has attempted to face the problem by considering C-IMT percentiles and using the arbitrarily chosen 75th percentile as threshold of normality [30, 52]. Once again, this threshold value has been calculated in the entire population without taking into account sex and age. In this way, almost all the subjects with risk factors (for example with dyslipidemia or hypertension) would be certainly classified as pathological and C-IMT would poorly add to what is already obtainable according to the simple VRFs evaluation.

Since the purpose of the C-IMT use is the optimization of CVD risk stratification, the values of normality should be calculated in terms of increased risk rather than statistical distribution of a population [53]. For example, we showed in a previous study that these limits correspond to the 60th percentile in men and the 80th percentile in women [35]. This increased risk is better assessed when the measurements obtained are compared with normality values, defined on the basis of specific distribution curves for classes of sex and age, which are main determinants of C-IMT [54]. Using this approach, we showed that C-IMT can be used to optimize the global CVD risk estimation in asymptomatic patients at intermediate risk [35]. In this category of patients, C-IMT values greater than the threshold values, calculated in specific sex and age classes (Fig. **4**), were associated with a three times greater risk to develop a new vascular event compared with the risk predicted by the FRS.

This approach results in the reclassification of many patients at intermediate risk into the high risk class [27], i.e. the class in which, according to the current guidelines, the use of appropriate pharmacological therapies is cost/effective. In addition, the distribution of C-IMT values may vary depending on the ultrasonographic equipment, the scanning protocol, and the population evaluated. A recent study from our group represents a good example of the latter factor [55]. Using the same equipment and protocol to avoid methodological confounders, significant differences in terms of C-IMT distribution were observed among European countries according to a north-to-south geographical gradient, strongly suggesting the need of region-specific nomograms to define thresholds of normality.

IS IT APPROPRIATE TO USE C-IMT DATA TO DECIDE OR MODIFY THE PATIENT'S THERAPY?

Serial assessment of C-IMT change over time is considered a good method to monitor the natural progression of atherosclerosis in epidemiological studies and/or to assess the average response to treatment in clinical trials. Conversely, according to the SAIP research group [46], the scientific bases for monitoring changes in single individuals are still not convincing.

However, a novel approach recently proposed by our group to assess carotid IMT progression might question this view [56]. The Fastest-IMT$_{max\text{-}progr}$ (i.e. the greatest value among the progressions of IMT$_{max}$ observed in the whole carotid tree), identifies focal increases of carotid IMT and, in contrast with other IMT progression variables, is associated with cardiovascular risk. Noticeably, in the cited study, the Fastest-IMT$_{max\text{-}progr}$ allowed the identification of "fast progressors" (i.e. patients with a Fastest-IMT$_{max\text{-}progr}$ above the median of the cohort) despite treatment with statins, who had an incidence of CV events comparable with that of Framingham Risk Score–matched subjects not treated with statins. If confirmed, this observation could have an impact on clinical decisions. In fact, the Fastest-IMT$_{max\text{-}progr}$ might be useful to identify, after only 15 months, those patients who need a more aggressive therapeutic approach.

ADVANTAGES OF USING C-IMT

Compared with other methods to detect the carotid anatomy, ultrasonographic assessment has several advantages: 1) it can be repeated several times in a reproducible manner, without any negative effect to the patient (e.g. the risk of radiation exposure associated with other techniques used to investigate arterial morphology such as angiography or angioTAC); 2) it is not focused on the arterial lumen but on the arterial wall, which is the real target organ of atherosclerosis; 3) it can be performed with equipment often already available for other purposes; 4) it is relatively inexpensive; 5) it is usually not hampered by patient's anatomy [57]; 6) it can be considered as a tool for the early diagnosis of accelerated atherosclerosis even in young adults and children [58]; 7) it provides a hint on the lifetime cumulative vascular effects of known and unknown risk factors; 8) it may alert about the need to search for emergent risk factors in subjects with unexplained early thickening of arterial wall and/or premature presence of atheroma; 9) it provides the physician the opportunity to individually tailor prevention therapies, even aggressive, before the occurrence of cardiovascular events that could lead to severe disability or death [56]; 10) finally, ultrasonographic assessement of C-IMT and plaques might allow a more efficient selection of patients at CVD risk and, consequently, could reduce the "number of subjects to be treated to prevent an

event (NNT)" and, ultimately, the cost/benefit ratio of prevention programs.

LIMITATIONS OF ULTRASONOGRAPHIC ASSESSEMENT OF C-IMT AND PLAQUES

A main limitation of ultrasonographic assessement of C-IMT and plaques is the lack of a standardized and univocally accepted scan protocol. Standardization is particularly critical when repeated measurements are used to determine the progression or the regression of disease. The recent development of ultrasonographic devices that allow the automatic detection of the blood-intima and media-adventitia interfaces, could greatly reduce the error performed by the observer and lead to a marked improvement in reproducibility within and between laboratories [59].

A further limitation is that the visualized arteries are the carotids and not the coronaries. Indeed, most cardiovascular deaths are due to coronary events and the condition of the coronary arteries cannot be automatically inferred from that observed in the carotid tree. For example, in a systematic review of studies published between years 1999 and 2005 [60], the authors showed that, even if a positive relationship between CAD and C-IMT was observed in 29 of the 33 studies reviewed, the correlation coefficients were relatively low and ranged between 0.12 and 0.51. The authors concluded that the poor correlation between the two vascular beds was probably due to differences in the atherosclerotic progression between coronary and carotid districts [60-63]. Subsequent studies have shown that rather than a real lack of association between the two vascular beds, the poor correlation between carotid ultrasound and coronary angiography may be attributable to the limited capacity of angiography to identify atherosclerotic lesions not protruding into the lumen [64, 65]. Data from our group support this possibility by showing that the correlation between severity of carotid atherosclerosis and coronary atherosclerosis is much stronger and also in line with the results of post-mortem studies when both vascular districts are evaluated using the same methodology (ultrasound) and the same parameters of vascular wall (IMT vs IMT) [22]. Interestingly, in the same study we have also shown that, in patients with normal/intermediate coronary atherosclerosis, the presence of a carotid-IMT_{mean} greater than 1 mm (or carotid-IMT_{max} > 1.78 mm) multiplies by 18 the risk of having a coronary-IMT_{max} > 0.608 (i.e. the lowest coronary-IMT_{max} value observed in subjects with angiographic coronary stenosis), and by 7 the chance of having a flow-limiting coronary stenosis. These results indicate the usefulness of carotid ultrasound as a further screening tool to identify patients who may deserve consideration for a coronary Intravascular Ultrasound (IVUS) investigation among those with an angiographic diagnosis of intermediate lesions and even coronary normality.

FUTURE STRATEGIES

In view of the existing relationship between C-IMT and VRFs, it is important to know whether C-IMT provides prognostic information for individuals over and above that provided by VRFs. Most of the authors that used the ROC metric to address this topic [51, 66-71] concluded that the contribution of C-IMT variables to the overall risk discrimination based on VRFs alone is small and insufficient to change current clinical and public health efforts to reduce the burden of vascular diseases [16, 66, 68-70]. However, C-statistic may be insensitive to small changes in predictive accuracy and, using this method of analysis, even well-established VRFs may be discarded as non-significant in some circumstances [72, 73]. Consequently, there is general agreement that newer methods such as reclassification statistics (Integrated Discrimination Improvement; IDI and Net Reclassification Improvement; NRI) must be applied [72, 74]. To the best of our knowledge, only few studies have so far used reclassification analyses to evaluate whether ultrasound measures add prognostic information over and above traditional VRFs [75-78] and most of them concluded that models that include C-IMT measured in specific segments (i.e. CC or Bif or ICA) do not consistently improve the individual risk stratification over those including only traditional VRFs. More recent studies, however, have shown that substantial improvements over VRFs alone can be obtained when composite IMT variables (e.g. $IMT_{mean-max}$) are used instead of C-IMT variables measured in specific segments [35, 78]. Despite these new encouraging findings, the weight of C-IMT as a tool to improve risk stratification in comparison with other new emergent risk markers (e.g. coronary artery calcium [79], femoral arteries IMT [80, 81], C-reactive protein [82], genetic polymorphisms [83], etc.) remains to be clarified in prospective studies, whose results might help to optimize the clinical use of this type of measures. Finally, it is important to recognize that recommendations for the clinical use of C-IMT are mainly based on observational studies. The biggest challenge in the near future will be to demonstrate, with randomized trials, that the addition of information emerged from carotid imaging to the traditional strategies for risk stratification, indeed, leads to reduce the burden of myocardial infarction and stroke.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

ASE	=	American Society of Echocardiography
Bif	=	Carotid Bifurcation
CAD	=	Coronary Artery Disease
CC	=	Common Carotid
C-IMT	=	Intima-media thickness of the extracranial carotid artery
$C\text{-}IMT_{max}$	=	Maximum value of C-IMT of the whole carotid tree. Calculated incorporating the plaque, corresponds to the thickest plaque detected
$C\text{-}IMT_{mean\text{-}max}$	=	Average of the maximum values of C-IMT measured in all the carotid segments considered
CVD	=	Cardiovascular Disease
FRS	=	Framingham Risk Score: global algorithm for cardiovascular risk generated in the Framingham study
ICA	=	Internal Carotid Artery
SAIP	=	Society of Atherosclerosis Imaging and Prevention
SHAPE	=	Screening for Heart Attack Prevention and Education
VR	=	Vascular Risk
VRFs	=	Vascular Risk Factors

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