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Chapter 7

Measurement of carotid intima–media thickness to assess progression and regression of atherosclerosis

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Abstract

Imaging modalities have been developed to assess atherosclerosis in vivo in the arterial wall because large clinical end-point studies are time-consuming and costly. Historically, in-hospital angiography and Doppler ultrasonography have been used to assess atherosclerosis development. Investigations of the arterial lumen are, however, increasingly being replaced by modalities that can measure changes in the arterial wall itself—intravascular ultrasonography, MRI and multislice CT. The fact that intravascular ultrasonography is invasive, CT involves substantial radiation exposure and requires contrast agents, and that MRI is time-consuming and technically challenging all limit the widespread use of these techniques. Moreover, all modalities have high associated costs. B-mode ultrasonographic imaging of the carotid arterial walls occupies a unique position in atherosclerosis research. This method enables sensitive, reproducible and noninvasive assessment of intima-media thickness (IMT) as a continuous variable. Epidemiological and clinical trial evidence as well as digitization and standardization have made carotid IMT a validated and accepted marker for generalized atherosclerosis burden and vascular disease risk. Here we describe the application of carotid IMT measurements as a tool in risk evaluation of individuals and in studies of atherosclerosis progression and regression.
Introduction

Atherosclerosis is an inflammatory disease that often begins early in life with impairment of endothelial function, which leads to the formation of lesions in large and medium elastic and muscular arteries.\(^1\)\(^2\) The disease process is dynamic and is associated with remodeling of the arterial wall. In the early stages of arterial wall thickening and plaque formation, no luminal changes are seen, because the arterial wall expands to compensate. This process, known as the Glagov effect, can ensure the size of the arterial lumen is preserved until plaque formation becomes extensive. This compensatory mechanism is considered the best explanation for the fact that the early stages of atherosclerosis are clinically asymptomatic.\(^3\)

Although atherosclerosis can remain below the clinical horizon for a long time, it can manifest clinically as acute vascular disease at almost any stage of the disease process. Evaluation of atherosclerosis by means of clinical end points—morbidity and mortality—requires large study populations and necessitates considerable human and financial resources.\(^4\)\(^5\) As atherosclerosis is a slow process, collecting clinical end-point data takes a long time and provides information mainly on the late stages of vascular disease, which makes cause and effect relationships difficult to unravel. New insights into the disease process are, therefore, difficult to obtain and rapid evaluation of novel therapies can prove difficult—unless techniques to assess early atherosclerotic changes are used.

The use of surrogate markers to measure atherosclerosis burden in vivo has become widespread. To be useful as a validated tool for risk assessment in cardiovascular disease the method needs to be technically sound, but must also meet a number of methodological requirements. Disease risk and effects of treatment need to be identified with greater sensitivity and speed than clinical end points.\(^6\) The method must be widely available and preferably noninvasive. Furthermore, the association between risk and the disease marker must have been established statistically and be relevant...
to the study question. The surrogate marker should also model pathophysiological information. Finally, for clinical research in humans, regulatory requirements must be met.

As atherosclerosis is a multifactorial disease with distinct progression and regression behavior, cause and disease progression might not always be straightforward. A standardized and validated method is crucial for generating reproducible results that are predictive in nature. Brightness or 'B-mode' ultrasonography can depict all stages of atherosclerotic arterial wall changes as a continuous variable. The entire continuum of ultrasound-derived atherosclerosis measurements (arterial wall thickness, including the plaque) is referred to as intima–media thickness (IMT), although, strictly speaking, this nomenclature is incorrect from a histological perspective. IMT is a surrogate marker for atherosclerosis burden as well as cardiovascular disease risk assessment. It could be argued, however, that rather than being a surrogate marker, IMT is part of the disease process itself. Notably, the FDA has approved IMT as a surrogate marker of atherosclerotic disease for application in clinical trials; however, the addition of IMT assessment to prevention guidelines is still under discussion.

In this review we discuss the role of carotid IMT as a marker for progression and regression of atherosclerosis. We explore how the measurements can be used to assist clinical management and to advance atherosclerosis research.

**Imaging atherosclerosis**

Techniques to visualize atherosclerosis in humans originate from the refinement of available clinical imaging techniques such as Doppler ultrasonography and coronary angiography. Doppler ultrasonography can only identify arterial stenosis if the lumen area is reduced by at least 40–50%. Traditionally, quantitative coronary angiography was the predominant imaging modality to assess the progression or regression of atherosclerosis. With quantitative coronary angiography, the cross-sectional coronary anatomy is depicted as a planar silhouette of a contrast-filled vessel lumen.
Both modalities are highly relevant in a clinical setting, but do not provide useful information on the early stages of arterial wall thickening before lesion formation.\textsuperscript{27,28}

Multislice CT is rapidly outgrowing its angiographic heritage and is being developed into a completely noninvasive technique. This method will undoubtedly replace coronary angiography for assessment of coronary stenosis and calcification. Electron-beam CT is also noninvasive, but is not widely available. This technique also predominantly highlights calcified tissue,\textsuperscript{29} which makes it unsuitable for the evaluation of the early stages of atherosclerosis. High-resolution MRI is also being used for volumetric and spectrometric measurement of the carotid arterial wall. That these modalities hold promise is undisputed; however, prospective epidemiologic and human trial data validating these techniques are not yet available. Moreover, an expensive infrastructure will be required to implement these techniques.

Intravascular ultrasonography (IVUS) depicts the arterial lumen and, most importantly, the arterial wall. This modality can, therefore, provide information on both plaque burden and coronary atheroma volume.\textsuperscript{30,31} IVUS is now increasingly used in conjunction with noninvasive B-mode ultrasonographic imaging of the carotid artery to assess the treatment effects of antiatherosclerotic therapies.\textsuperscript{32-34}

**Measurement of carotid intima–media thickness**

In essence, B-mode ultrasound IMT measurement involves a simple distance measurement between the leading edges of the lumen–intima and media–adventitia ultrasound interfaces (Figure 1). With this imaging method, the typical ‘double-line’ pattern of the normal arterial wall of the large peripheral arteries can be seen. Pignoli et al. investigated the double-line pattern in depth, and established the relationship between the leading edges of the ultrasound interfaces and the boundaries of the intima-media seen in an aorta specimen.\textsuperscript{35} This relationship formed the basis of the present ultrasonographic carotid IMT measurements. Initially, B-mode images were used to guide the Doppler sound beam for investigating blood velocity. With the
availability of computerized technology, B-mode ultrasonography was developed to produce real-time, high-resolution images. In the late 1980s, the assessment of small-vessel wall structures throughout the different stages of atherosclerosis became feasible. The technique can be used to monitor atherosclerosis by measurement of IMT as a continuous variable from the healthy and thin arterial wall to total occlusion. As a reference, the lumen of the common carotid artery in healthy individuals measures 6–9 mm in diameter with an average IMT of 0.4 mm at birth and 0.8 mm by the age of 80 years, if no risk factors are present. With an increased number of cardiovascular risk factors, IMT grows more rapidly over a lifetime and the probability of emerging lesions increases.

It should be realized that noninvasive assessment of atherosclerosis in humans investigates submillimeter structures and structural changes measured in hundredths of millimeters. These small changes are clinically significant; a meta-analysis of statin intervention studies using IMT as a surrogate marker indicated that a reduction in IMT thickening of 0.012 mm per year is congruent with a significant odds ratio of 0.48 for the reduction of cardiovascular events.

Practical considerations
The use of imaging techniques to visualize small structures of the peripheral arterial wall poses major technical challenges. First, the accuracy of measurements must be as high as possible. Although an increase in the ultrasound frequency can improve axial resolution, it must be noted that the measurement of IMT is a distance measurement in which the structure measured (approximately 0.55–0.95 mm) is much larger than the wavelength of the ultrasound produced by the commonly used near-field linear array transducer (approximately 0.12 mm). As the signal sampling rate is much higher than the wavelength, accurate measurement of IMT is not dependent on the frequency used but on the pixel resolution of the digitized image. As a consequence, digital representation of the imaged structures depends, in part, on pixel resolution. To visualize small structures such as the intima and media layers, the digital images
should be spread out over as many pixels as possible. Although this issue of accuracy is similar for every imaging technique, understanding how the ultrasonographic instrument displays information on the monitor and optimization of the image is particularly important when submillimeter-sized structures and even smaller changes in size are evaluated.

Second, the emphasis should be on high-end equipment that enables maximal spatial resolution at the time of image acquisition, and can scan with a low signal: noise ratio (a high dynamic range) and high tissue differentiation (i.e. relatively high frequencies, if depth allows). The latter element is of particular importance if early atherosclerosis and soft plaques are to be discriminated from signal noise in the vessel wall (Figure 1).

![Figure 1. Brightness-mode ultrasound images of carotid artery wall segments](image.png)

**Figure 1. Brightness-mode ultrasound images of carotid artery wall segments**

Brightness-mode ultrasound images of carotid artery wall segments from a 35-year-old asymptomatic male with a 14-year history of type 1 diabetes mellitus. (A) The sonographer selects the region of interest from an overview image of the carotid artery. (B) The expanded high-resolution 1.2 × 1.2 cm image of the region of interest is used for intima–media thickness measurements. The sonographer selects the best per-protocol image possible as a high resolution DICOM still. The distance between the arrows from the lumen–intima interface to the media–adventitia interface indicates an intima–media thickness of 1.12 mm. Abbreviation: DICOM, Digital Imaging and Communications in Medicine.
Another technical challenge involves the reproducibility of measurements, which should be as high as possible and, according to methodological and good clinical practice guidelines, must be reported for every specific study, in order to prove a priori that the measurements meet predefined protocol requirements. For this purpose, sonographers should undergo training specific to each new trial protocol, followed by certification and quality control to guarantee quality-assured data. The aim of standardized scan protocols is to ensure that comparable and reproducible IMT measurements are acquired within and throughout studies.

**Imaging protocol**

Different protocols do exist, but essentially all comprise the following elements. At the start of a carotid ultrasound scan, the individual being assessed is placed in a comfortable reclining position. As during writing, the sonographer should support the elbow of the arm holding the ultrasound transducer. The transducer angles for each of the cross-sections at which images are obtained have to be predefined. Arterial wall segments are defined anatomically by the anatomic landmarks of carotid dilatation and the carotid flow divider (Figure 2).

For each cross-section, the best image obtained from the segment is selected by the sonographer at the time of the scan. The selected images and metafile information, as well as the corresponding digital clip for dynamic information, are then saved in the Digital Imaging and Communications in Medicine (DICOM) file format.

Most large vascular clinics have ultrasonography equipment and trained vascular sonographers. For clinical purposes, when relatively large arterial wall structures are imaged, extensive plaques and symptomatic stenosis can be evaluated by Doppler flow and ‘onscreen’ measurements. For study purposes, however, particularly for pharmaceutical trials, the ‘onscreen’ method is inadequate, because measurement is inaccurate, administratively cumbersome, and hence difficult, if not impossible, to quality-control.
Figure 2. A composite ultrasonographic image of the carotid artery.

A composite ultrasonographic image of the carotid artery. For each arterial segment a high-resolution still image, as indicated by the dashed boxes, is selected by the sonographer. The carotid dilatation (arrowhead) and the carotid flow divider (arrow) are indicated. The following anatomical features are indicated: the common carotid artery 1 cm proximal to the dilatation; the carotid bulb between the dilatation and flow divider; and the internal carotid artery 1 cm distal to the flow divider. The scan protocol includes Doppler signal analysis to distinguish the external from the internal carotid artery and to exclude clinically relevant vascular stenoses. A bilateral carotid scan will, therefore, provide six DICOM stills and, to provide the image analysts with dynamic information, six associated DICOM clips. Abbreviations: CB, carotid bulb; CCA, common carotid artery; DICOM, Digital Imaging and Communications in Medicine; ECA, external carotid artery; ICA, internal carotid artery.

Taking the approach of analyzing DICOM-structured files in a core lab has the advantage that the source file cannot be altered once the image is saved by the sonographer, and an audit trail is recorded that includes traceability and change.
control. In multicenter trials, in order to meet the necessary quality, administrative and regulatory requirements, images are handled and IMT measurements recorded off-line in a core ultrasound laboratory.\textsuperscript{42}

**Variability**

Even though this modality is technically optimized and sonographers are trained, measurements in biological systems are always subject to a certain degree of variability. Variability can be introduced through the population studied, by the sonographer and image analyst, and by random error.\textsuperscript{43} Once the images have been acquired, however, the contribution of the on-line and off-line IMT measurements to variability is minor, since the image is fixed.

Whereas observing the change of population variability can be the goal of some IMT measurements, the sources of measurement variability should be reduced as much as possible. If thin artery walls, such as those in children, are imaged (Figure 3A), population and measurement variability is small. When imaging thicker structures (Figure 3B and C), total measurement variability increases because of the difficulty of reproducing a slice through extensive plaque structures (Figure 4). In follow-up studies, measurement variability is, therefore, mostly sonographer-dependent. Intrasonographer variability (expressed as SD of the mean absolute difference of paired replicate scans) of IMT measurements is around 0.04 mm in children,\textsuperscript{44} and 0.2 mm in older patients with peripheral vascular disease.\textsuperscript{45,46}

In controlled clinical trials, measurement variability is decreasing. This decrease is most likely to be a result of technical improvements, standardization and training. In studies carried out between 1985 and 1990, the measurement SD as calculated above was 0.2 mm in patients with coronary artery disease,\textsuperscript{45,47} whereas currently this figure is approximately 0.09 mm.\textsuperscript{48} Moreover, two decades ago intraclass correlations of 0.60-0.75 mm were reported, whereas currently they are often 0.90 mm or higher.\textsuperscript{49} The sources of variability of IMT measurements have been described extensively elsewhere.\textsuperscript{43}
Figure 3. Examples of images of the arterial wall of the common carotid artery

The arterial wall of the common carotid artery of an asymptomatic individual throughout life and the various stages of arterial wall thickening. (A) Double lines in the common carotid artery during childhood (age 8 years). (B) Slight arterial wall thickening at the carotid bulb during middle age (age 52 years). (C) Extensive plaque formation at the carotid bulb at old age (age 85 years). The white lines delineate the lumen–intima and the media–adventitia interfaces drawn along the wall for approximately 10 mm.
The main sources of variability are differing features between patients, and between-sonographer and within-sonography variability in measurements. (A) Variation in measurements caused by plaque differences in the longitudinal plane. (B) Variation in measurements caused by plaque area differences in the transverse plane. Lack of adherence to predefined transducer angulations and landmark identification can influence results in comparative and follow-up studies. The dotted lines represent the transducer axis. $\delta$ indicates the distance between the lumen–intima and media–adventitial interfaces.

**Carotid intima-media thickness: observational studies**

Large follow-up studies such as the Rotterdam Study\textsuperscript{10,11} and the Atherosclerosis Risk in Communities Study (ARIC)\textsuperscript{12-15} have used B-mode ultrasonography to measure IMT to investigate the determinants of atherosclerotic disease in the general population.\textsuperscript{9} The Rotterdam Study was a single-center, prospective, follow-up study of 7,983 individuals older than 55 years. The main objective of this study was to identify the determinants of atherosclerosis progression in the carotid artery wall. This ultrasound study provided solid evidence that IMT measurements can be used to indicate the degree of existing generalized atherosclerosis and future cardiovascular...
disease risk. The investigation also provided evidence for associations between carotid IMT and stroke, angina pectoris, myocardial infarction, intermittent claudication and essential hypertension. In ARIC, a US-based study that involved 15,800 adults, high-resolution B-mode ultrasonography was able to identify atherosclerotic lesions at all stages of development. A seemingly small increase in mean carotid IMT of 0.2 mm was associated with an increase in relative risk for myocardial infarction and stroke of 33% and 28%, respectively—a link that has been confirmed subsequently by many other studies.

Studies that used multiple measurements of carotid IMT to investigate the determinants of disease progression showed that risk factors such as age, smoking, dyslipidemia and hypertension are the main predictors of increased carotid IMT. Furthermore, carotid IMT measurements have predictive value not only for adverse cerebral events, but also for cardiac and peripheral vascular events. The presence of plaques or stenoses in the carotid artery tree drastically increases this cardiovascular event risk. At present, vascular clinics are increasingly using IMT to define an individual’s cardiovascular risk. Although more standardized evaluation is necessary, results from recent studies indicate that individual risk-profile assessment might improve with the addition of this noninvasive parameter.

Carotid intima–media thickness: Assessing success of therapy

Studies have used measurement of IMT has to assess the efficacy of drugs designed to lower lipid concentrations, antihypertensive agents, hormone replacement therapy, antioxidant supplements and lifestyle interventions. An early study that used ultrasound-derived IMT was the 4-year, placebo-controlled Cholesterol Lowering Atherosclerosis Study (CLAS), which assessed the effects of therapy with colestipol and nicotinic acid in men who had previously undergone CABG surgery. The investigators found that drug treatment had beneficial effects and reduced carotid IMT after 2 and 4 years of therapy (p < 0.0001). The Asymptomatic Carotid Artery Progression Study (ACAPS) was a 3-year trial in which the effects of therapy with a
daily dose of 20–40 mg lovastatin was compared with placebo in asymptomatic men and women aged between 40 and 79 years who had early carotid atherosclerosis. The IMTs of 12 carotid artery wall segments were recorded per patient. Lovastatin significantly reduced IMT over the trial period compared with placebo (p < 0.001).

The Kuopio Atherosclerosis Prevention Study (KAPS) investigated the 3-year efficacy of pravastatin in hypercholesterolemic men aged between 44 and 65 years. In this trial, the primary outcome measure of disease progression (increase in IMT) in both carotid and femoral artery segments was significantly lower in pravastatin-treated patients than in those who received placebo (p = 0.02).

In the Regression Growth Evaluation Statin Study (REGRESS), the effects of 40 mg pravastatin were assessed in men with angiographically proven coronary artery disease and a total cholesterol level in the range 4.0-8.0 mmol/l (154-309 mg/dL). In this 2-year atherosclerosis regression trial, the efficacy of pravastatin was demonstrated by coronary angiography and B-mode ultrasonography of the peripheral arteries. The ultrasonography substudies were conducted at three trial sites and included 255 of the 885 patients enrolled in REGRESS. Interestingly, the ultrasonography findings showing regression of IMT with treatment were highly significant (p < 0.0001), a significance level not obtained using coronary angiography in the overall REGRESS study.

In the 2-year Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial, the effects of 80 mg atorvastatin and 40 mg simvastatin once daily were investigated in 325 patients with familial hypercholesterolemia. Aggressive cholesterol lowering was found to be more effective than conventional statin therapy. Specifically, the study showed an actual decrease in carotid IMT in the more-aggressive therapy group (who achieved an average LDL cholesterol reduction of 51%), whereas the less-aggressive treatment (resulting in a 41% reduction) was associated only with inhibition of atherosclerosis progression. The outcome of the 1-year Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study...
in 161 patients with cardiovascular disease is in line with the ASAP trial findings. To investigate whether lowering LDL cholesterol to below the National Cholesterol Education Program Adult Treatment Panel III criterion of 2.6 mmol/L (100 mg/dL) for secondary prevention would further reduce the burden of atherosclerotic disease, the effects on carotid IMT of 80 mg atorvastatin and 40 mg pravastatin once daily were compared. Atorvastatin reduced LDL cholesterol levels by an average of 49.0% to 2.0 (± 0.6) mmol/l (76 (± 23) mg/dL); pravastatin by 27% to 2.8 (± 0.7) mmol/L (110 (± 30) mg/dL). In the pravastatin group, IMT stabilized; in the atorvastatin group, IMT decreased, demonstrating atherosclerosis regression (p = 0.03).

The 2-year Long-term Intervention with Pravastatin in Ischaemic Disease Study (LIPIDS) also investigated whether lipid lowering to below the guideline threshold was beneficial. In this study, 214 children aged between 8 and 18 years who had familial hypercholesterolemia were randomized to either 20 mg or 40 mg pravastatin or placebo once daily. Carotid IMT showed a reduction of 0.014 mm (± 0.046 mm; p = 0.02) in the pravastatin arm relative to placebo. Cross-sectional baseline data showed significant differences in IMT between children with familial hypercholesterolemia and unaffected siblings, even at a young age (Figure 5). Long-term follow-up showed that ultrasound imaging allows observation of atherosclerosis progression even in thin arterial walls (average 0.49 mm (± 0.06 mm)). These results indicate that the observation of treatment effects depends on the difference in IMT change between treatment groups, regardless of the stage and extent of the disease. The efficacy of antiatherosclerotic agents is, therefore, best tested in populations with a high atherosclerosis progression rate, but not necessarily in a population with a high burden of atherosclerosis.
Intima–media thickness data from unaffected siblings and children with familial hypercholesterolemia

Intima–media thickness data from 95 unaffected siblings and 214 children with familial hypercholesterolemia aged 13.0 years (SD 3.0; range 7.9–18.9). Intima–media thicknesses are 0.46 mm (SD 0.054 mm) and 0.48 mm (SD 0.054 mm), respectively (p = 0.004). Even at a young age, intima–media thickness measurements can detect early increases in arterial wall thickness in those at high cardiovascular disease risk. In the same children, using the same ultrasonography imaging protocol, statin therapy for 2 years yielded favorable effects when compared with placebo. The strength of the standardized intima–media measurement lies in its potential to noninvasively identify cardiovascular disease risk and show treatment effects in populations in need of atherosclerosis prevention before the outbreak of disease. Abbreviations: FH, familial hypercholesterolemia; IMT, intima–media thickness.

Carotid and coronary ultrasonography: complementary imaging modalities

The results of the previously mentioned studies underline the utility of carotid ultrasonography as a tool to assess cardiovascular drug effects. To be convincing clinically, a novel drug has to prove its antiatherosclerotic effects in the vascular bed that is directly related to its clinical symptoms—for cardiovascular disease this means the coronary arteries.
IVUS of the coronary arteries is a validated and standardized tool for observing the effects of novel antiatherosclerotic drugs on coronary atheroma volume.\textsuperscript{30-32} The findings of the ARBITER carotid IMT study,\textsuperscript{61} the IVUS-based Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial\textsuperscript{62} and the large outcome study Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22)\textsuperscript{63} in patients with acute coronary syndromes were similar, in that they all showed 80 mg atorvastatin (i.e. aggressive lipid lowering) to be superior to 40 mg pravastatin (i.e. moderate lipid lowering).

More recently, the results of the Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE) 1 trial\textsuperscript{64} in heterozygous patients with familial hypercholesterolemia and the RADIANCE 2 trial\textsuperscript{65} in patients with mixed dyslipidemia, in addition to the Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) IVUS-based trial,\textsuperscript{66} showed no benefit of 60 mg torcetrapib on arterial wall parameters despite impressive and beneficial lipoprotein changes. These findings indicated that this agent had off-target toxic effects and were corroborated by the results of the large morbidity and mortality study of this drug—the Investigation of Lipid Level to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial.\textsuperscript{67}

\textbf{Conclusions}

Surrogate markers of atherosclerosis such as carotid IMT can identify populations and individuals at increased cardiovascular disease risk and can guide future treatment in cardiovascular disease prevention. Observational studies and clinical trials have demonstrated the strong relationship between carotid IMT progression and regression, and cardiovascular events. With IMT data from many epidemiological studies and clinical trials accumulating, there is increasing evidence that IMT measurement can be used at individual level to refine cardiovascular disease risk scores. As B-mode ultrasonography is a relatively new technique and involves training and craftsmanship,
official acceptance of carotid IMT as a routine measurement in risk evaluation is still under discussion. Carotid IMT in fact meets the criteria of a validated marker for the assessment of atherosclerotic vascular disease and can evaluate novel agents in the true spirit of prevention before the emergence of clinical disease.

Key points

- In atherosclerosis research, surrogate markers are important in the early identification of disease, and in risk assessment and the evaluation of drug efficacy
- If imaging modalities are to be used in clinical studies and pharmaceutical trials, technical optimization and stringent standardization are required
- Carotid ultrasonography is a noninvasive method for measuring carotid intima–media thickness—a validated surrogate marker of atherosclerotic disease—that allows atherosclerosis assessment in individuals across the entire cardiovascular risk spectrum
- Carotid intima–media thickness measurements can be used to assess the consequences of cardiovascular disease risk reduction in patients and to investigate novel antiatherosclerotic strategies in clinical trials

References


