

# Mannheim Intima-Media Thickness Consensus

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## Abstract

Intima-media thickness (IMT) is increasingly used in clinical trials as a surrogate end point for determining the success of interventions that lower risk factors for atherosclerosis. The necessity for unified criteria to distinguish early atherosclerotic plaque formation from thickening of IMT and to standardize IMT measurements is addressed in this consensus statement. Plaque is defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness of  $\geq 1.5$  mm as measured from the media-adventitia interface to the intima-lumen interface. Standard use of IMT measurements is recommended in all epidemiological and interventional trials dealing with vascular diseases to improve characterization of the population investigated. The consensus concludes that there is no need to 'treat IMT values' nor to monitor IMT values in individual patients apart from few exceptions. Although IMT has been suggested to represent an important risk marker, it does not fulfill the

characteristics of an accepted risk factor. Standardized methods recommended in this consensus statement will foster homogenous data collection and analysis. This will help to improve the power of studies incorporating IMT measurements and to facilitate the merging of large databases for meta-analyses.

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## Introduction

Decades of silent arterial wall alterations precede cardiovascular clinical events, which then reflect advanced atherosclerotic disease. The first morphological abnormalities of arterial walls can be imaged by B-mode ultrasonography. This high-resolution, noninvasive technique is one of the best methods for detection of early stages of atherosclerotic disease, because it is easily applicable, readily available, and demonstrates the wall structure with better resolution than magnetic resonance angiography or conventional angiography. Accordingly, ultrasound has been used in a number of studies to monitor the intima-media thickness (IMT) of the carotid arteries, a measurement which has consequently been shown to be associated with cardiovascular risk factors and the inci-

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dence of cardiovascular disease. Surprisingly, however, there are diverse approaches for measuring IMT, and some of these may lead to divergent results. Moreover, there are no unified criteria for distinguishing atherosclerosis as seen in early plaque formation from thickening of the intimal-medial complex. This is because IMT reflects not only early atherosclerosis, but also nonatherosclerotic intimal reactions such as intimal hyperplasia and intimal fibrocellular hypertrophy. This differentiation is important because epidemiological studies have shown that wall thickening as depicted by ultrasonographic measurements of IMT is different from atherosclerotic plaque regarding localization, risk factors and predictive value on cardiovascular events. As IMT is being increasingly used in clinical trials to serve as a surrogate end point for determining the success of interventions that lower risk factors for atherosclerosis, it is imperative that standardized methods be used to allow homogenous data collection and analysis. This would help to improve the power of such studies and to facilitate the merging of large databases for meta-analyses. This consensus statement therefore addresses the important issue of standardization of IMT measurements and seeks to clarify problems related to the classification of early atherosclerotic lesions.

### **IMT and Early Plaque**

In the absence of atherosclerotic plaque, B-mode ultrasound displays the vascular wall as a regular pattern that correlates with anatomical layers. The intima-media portion of this pattern is represented by the area of tissue starting at the luminal edge of the artery and ending at the boundary between the media and the adventitia. This interface is well depicted by ultrasound. With increasing age, this pattern has been shown to thicken in a uniform way in straight arterial segments. Thickening of the intima-media is accelerated and enhanced in the presence of risk factors of atherosclerosis, particularly high blood pressure. As a mirror of these processes, IMT was identified as a tool to investigate normal aging and preclinical atherosclerosis. Later stages of atherosclerosis (plaque, stenosis, occlusion) can also be identified by ultrasound imaging either in the absence of or coincident with increasing IMT. However, there are intermediate stages between increased IMT and atherosclerotic plaque formation that are impossible to differentiate even on histological examination. Such conditions are common at the bifurcation and the origin of the internal carotid artery, but occur only occasionally in the common carotid artery.

Epidemiological and intervention studies have shown that although both share some common atherosclerosis risk factors, the natural history, patterns of risk factors and the prediction of cardiac and cerebral events are different for IMT and plaque. The consensus recommends the following definitions for ultrasound characterization of IMT and atherosclerotic plaque.

(1) IMT is a double-line pattern visualized by echotomography on both walls of the common carotid arteries in a longitudinal image. It is formed by two parallel lines, which consist of the leading edges of two anatomical boundaries: the lumen-intima and media-adventitia interfaces. (2) Plaque is a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness of  $\geq 1.5$  mm as measured from the media-adventitia interface to the intima-lumen interface. These definitions will allow classification of the great majority of the carotid lesions observed with ultrasound.

### **Where to Measure?**

The common carotid artery can be assessed in nearly every patient. Successful examination of the internal carotid artery and of the carotid bulb depends both upon the anatomical topography of the patient and on sonographer expertise.

(1) Measurement of IMT is most simply performed in a region free of plaque where the double-line pattern is observed – this is advantageous as measurements are easier, more accurate, reproducible and can be standardized by computerized analyses. (2) IMT can be measured in the common carotid artery, at the bulb and the origin of the internal carotid artery. (3) In study designs that include wall thickness, values obtained from different sites of the carotid arteries should be documented separately.

### **Whom to Assess?**

Standard and regular use of IMT measurements are recommended in all epidemiological and interventional trials dealing with vascular diseases to better characterize the population investigated (similarly to the documentation of other risk factors).

There is no need to 'treat IMT values' nor to monitor IMT values in individual patients apart from few exceptions (e.g. familial hypercholesterolemia).

## How to Analyze?

Standard equipment includes a high-resolution B-mode system operating with preferentially linear ultrasound transducers at frequencies above 7 MHz. Appropriate depth of focus (e.g. 30–40 mm), frame rate (>15 Hz), and gain settings (minimal intraluminal artifacts) are recommended to obtain the best image quality.

Various scanning procedures are used.

(1) The arterial wall segments should be assessed in a longitudinal view, perpendicular to the ultrasound beam, with both walls clearly visualized in order to achieve diameter measurements. Lateral probe incidence is recommended as it offers the best view in the middle field where the resolution is known to be greater than in the near or far field.

(2) IMT should be measured preferably on the far wall. This is because IMT values from the near wall depend in part on gain settings and are less reliable.

(3) Along a minimum of 10 mm length of an arterial segment, a high-quality image acquisition is required for serial reproducible measurements. (a) Edge detection systems that are properly calibrated provide accurate measurements of IMT. Observations made by readers are no less valid, but they need to be controlled and are time consuming compared to automated systems, which can provide the mean maximal value of 150 measurements performed on 10 mm of common carotid artery in a very short time (< 0.1 s). (b) Interadventitial and lumen diameter measurement must be obtained as IMT is significantly correlated with the arterial diameter.

(4) Intraclass correlation coefficient should be evaluated for intra- and interobserver variability in each ultrasound lab, both for IMT and plaque measurements.

## Who Should Analyze?

In clinical trials, several additional requirements are recommended to assure data harmonization. They can be performed through an expert IMT panel – represented in the Steering Committee – to address:

- (1) study design,
  - (2) study control,
  - (3) full image monitoring,
  - (4) statistical plan analysis,
  - (5) data monitoring (from CRO and Core Lab),
  - (6) result analysis
- and define:

- (1) inclusion criteria of the centers,
- (2) equipment installation if necessary,
- (3) sonographers' training performance quality control,
- (4) certification of the centers (equipment and sonographers),
- (5) quality assurance and quality control,
- (6) central reading facilities,
- (7) evaluation of data variability through intraclass correlation coefficient.

All these procedures can reduce measurement variability, which is a key parameter for sample size evaluation.

## Which End Point to Analyze?

In studies where clinical outcome parameters are defined, IMT and plaque measurements should be included as secondary end points. In studies without clinical end points, measurements of IMT and plaque may represent primary outcome.

Optimal choices of primary outcome should be defined according to the design of the study and should address IMT and plaque measurements: maximal thickness, areas, scores and volume may all be useful if evaluated.

## Conclusions

Recent studies have shown that reduction of IMT values are significantly correlated with risk reduction and improvement of risk factor profiles in a large population. However, neither positive nor negative predictive values on ischemic risk reduction are known in individual subjects treated successfully for specific risk factors. Thus, although IMT has been suggested to represent an important risk marker, it does not fulfill the characteristics of an accepted risk factor. Evidence-based study results demonstrating the efficacy of treatment through significantly improved outcome are needed.

## Additional References

- Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, Dhanjil S, Griffin M, Belcaro G, Rumley A, Lowe GD: Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: The British Regional Heart Study. *Stroke* 1999;30:841–850.
- Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ: Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;1316:1371–1375.
- Magyar MT, Szikszai Z, Balla J, Valikovics A, Kappelmayer J, Imre S, Balla G, Jeney V, Csiba L, Bereczki D: Early-onset carotid atherosclerosis is associated with increased intima-media thickness and elevated serum levels of inflammatory markers. *Stroke* 2003;34:58–63.
- van der Meer IM, Iglesias del Sol A, Hak AE, Bots ML, Hofman A, Witteman JCM: Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: The Rotterdam Study. *Stroke* 2003;34:2374–2379.
- Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R: Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. *Circulation* 1986;74:1399–1406.
- Rundek T, Elkind MS, Pittman J, et al: Carotid intima-media thickness is associated with allelic variants of stromelysin-1, interleukin-6, and hepatic lipase genes: The Northern Manhattan Prospective Cohort Study. *Stroke* 2002;33:1420–1423.
- Steinke W, Els T, Hennerici M: Compensatory carotid artery dilatation in early atherosclerosis. *Circulation* 1994;89:2578–2581.
- Taylor AJ, Burke AP, O'Malley PG, Farb A, Malcom GT, Smialek J, Virmani R: A comparison of the Framingham risk index, coronary artery calcification, and culprit plaque morphology in sudden cardiac death. *Circulation* 2000;101:1243–1248.
- Touboul PJ, Elbaz A, Koller C, Lucas C, Adrai V, Chedru F, Amarenco P: Common carotid artery intima-media thickness and brain infarction: The Etude du Profil Génétique de l'Infarctus Cérébral (GENIC) case-control study. The GENIC Investigators. *Circulation* 2000;102:313–318.
- Touboul PJ, Hennerici M: Epaisseur intima media AVC et traitements médicamenteux 'IMT, Drugs and Stroke'. Paris, Datebe, 2002, p 108.
- Touboul PJ, Prati P, Scarabin PY, Adrai V, Thibout E, Ducimetiere P: Use of monitoring software to improve the measurement of carotid wall thickness by B-mode imaging. *J Hypertens Suppl* 1992;10:S37–S41.
- Woo KS, Chook P, Raitakari OT, McQuillan B, Feng, Celermajer DS: Westernization of Chinese adults and increased subclinical atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999;19:2487–2493.