Carotid imaging in cardiovascular risk assessment

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CHAPTER 8

Can and should carotid ultrasound be used in cardiovascular risk assessment? – the internist's perspective

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ABSTRACT

Cardiovascular risk management is a major and challenging task for internists. Risk scores using algorithms based on traditional risk factors are helpful in identifying patients in whom intensive prevention strategies are warranted or can be withheld. However there remains a need for more accurate screening tools to allow clinicians to individualize the primary prevention programs to their patients.

Approximately 40-80% of apparently healthy, asymptomatic subjects exhibit increased thickness of the lamina intima-media of the carotid artery or have atherosclerotic carotid plaques. These abnormalities can be measured safely and at low cost by ultrasound. Subclinical carotid lesions are strongly associated with generalized atherosclerotic burden and the risk of future cardiovascular events. Although many cardiovascular risk management guidelines recommend the use of these parameters incorporation in clinical practice is still not commonplace.

Based on the current literature it seems that in high risk patients there is no additional value of the measurements because even in absence of carotid lesions these patients should receive an intensive risk reduction regime. In the large low-intermediate risk group however carotid ultrasound findings seem to carry subtle but possibly clinically relevant information about cardiovascular risk profile. The effect of treatment decisions based on carotid ultrasound parameters has not been studied and they should only be made in conjunction with all other cardiovascular risk factors. Sequential measurements to monitor progression and evaluate treatment response on an individual basis are not sufficiently reproducible and are therefore not recommended.

INTRODUCTION

Case example

During your outpatient clinic you are visited by a 55 year old male. He has been under your care for cardiovascular risk management for the last 3 years. You are treating him for hypertension, with a thiazide diuretic and an ACE inhibitor; his blood pressure is relatively well regulated with values around 140/85 mmHg. His BMI is 32 kg/m^2 with predominantly visceral adiposity. Fasting blood glucose levels are slightly elevated but HbA1c is normal and stable. His LDL-C is 3.2 mmol/L with an HDL of 0.9 mmol/L, fasting triglycerides are 2.2 mmol/L. He has no specific complaints, leads a sedentary lifestyle which makes it difficult for you to determine whether he has angina on exertion. You have advised him to stop smoking and two months ago he quit after 35 packyears.

Your Framingham risk calculator tells you that he is currently at intermediate risk for suffering a heart attack in the next 10 years (15.3%). This does not warrant more aggressive management of his cardiovascular risk factors. However your clinical intuition gives you an uneasy feeling about your patient partly because had he not quit smoking his risk score would be significantly higher (28.4%) and the impending diabetes is not taken into account in the prediction model. All your efforts during his visits are aimed at determining whether the obviously present risk factors have led to the development of atherosclerosis. If so, you feel it is justifiable to aim for secondary prevention targets for blood pressure and lipids and are considering adding a statin and aspirin to his treatment regimen.

Could ultrasound examination of the carotid arteries of your patient help you decide? Although many guidelines on cardiovascular disease prevention recommend using cIMT and carotid plaque detection in risk assessment strategies its implementation in clinical practice is still not commonplace. This may partly be explained by conflicting data on the additional value of IMT above risk assessment tools such as the Framingham (40) PROCAM (41) and SCORE (42) algorithms among others.

The current review will summarize the pathophysiological and epidemiological basis for the use of IMT measurement and carotid plaque detection as possible predictors of future cardiovascular events. Technical and methodological considerations important for the interpretation of results will be addressed first.

Three main issues considering clinical applicability in individual patients will be discussed:

- Is the presence of subclinical carotid atherosclerosis representative of generalized and particularly coronary atherosclerosis?
- Does the presence of subclinical carotid atherosclerosis increase the risk of suffering a cardiovascular event?
- Can progression of subclinical carotid atherosclerosis be used to monitor the efficacy of cardiovascular risk management in individual patients?

The review will conclude with recommendations on implementation of carotid ultrasound in individual risk stratification.

Technical and methodological considerations

B-mode ultrasound imaging is able to visualize the intima-media complex of large arteries. The thickness of these vascular structures can be measured offline. Several autopsy studies have validated these measurements and found them to be highly accurate when compared with histological findings in the same arterial segment (43) (14). Early atherosclerotic changes in these arteries (smooth muscle cell proliferation, fatty streaks and non-stenotic plaques) can be detected by thickening of these vascular structures (figure 1). Carotid ultrasound is able to visualize morphological changes in the arterial wall, before the advanced stages of atherosclerosis are reached. It is therefore possible to identify vascular damage in patients before they develop clinical signs and symptoms.

In a substantial percentage of asymptomatic adults this form of subclinical atherosclerosis is present. Salonen et. al. observed lesions in 80% of male subjects in the general population by the age of 60 years. (44) Carotid ultrasound is a non-invasive, safe and inexpensive imaging modality. However, there is as of yet no standardized international imaging protocol dictating how to perform IMT measurements and plaque detection. In general, all current ultrasound devices provide sufficient resolution to assure accurate measurement, figure 2 shows a representative example.

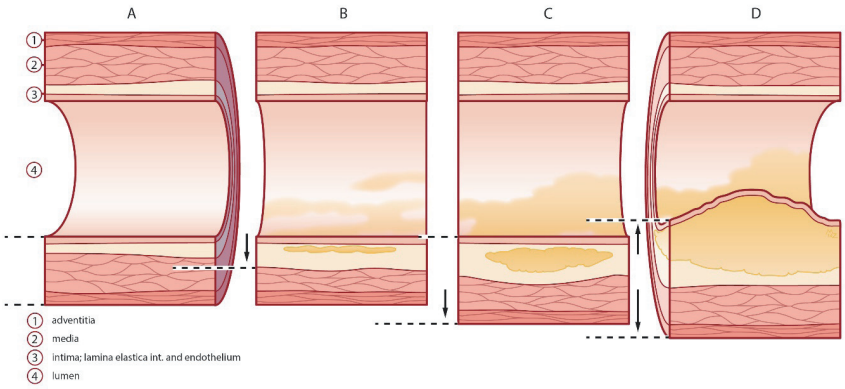

Figure 1 | Schematic representation of the progression of arterial atherosclerosis over a period of decades.

A) Normal arterial architecture as seen in healthy young subjects. B) Formation of fatty streaks in de arterial wall can be seen in post-mortem microscopy as early as in adolescence and represents a physiological vascular response to injury. Although these arterial changes can be a precursor of manifest atherosclerosis, absence of or adequate management of vascular risk factors can keep progression in check. Current imaging techniques are unable to objectify or quantify these subtle changes. C) With advancing age and under the influence of vascular risk factors the fatty streaks can progress to overt intimal thickening. In this stage of the atherosclerotic process the artery responds by an outward remodelling. The artery hereby preserves its lumen diameter and flow. Imaging studies with angiography and Doppler duplex will therefore not detect this early stage of atherosclerosis. Ultrasound measurement of intima media thickness however is sensitive enough to identify these lesions. D) Finally the atherosclerotic plaque starts encroaching into the lumen causing flow changes and stenosis which lead to tissue dysfunctions downstream. In this stage all imaging modalities are useful in diagnosing and evaluating the lesions, however a window for early intervention has passed.

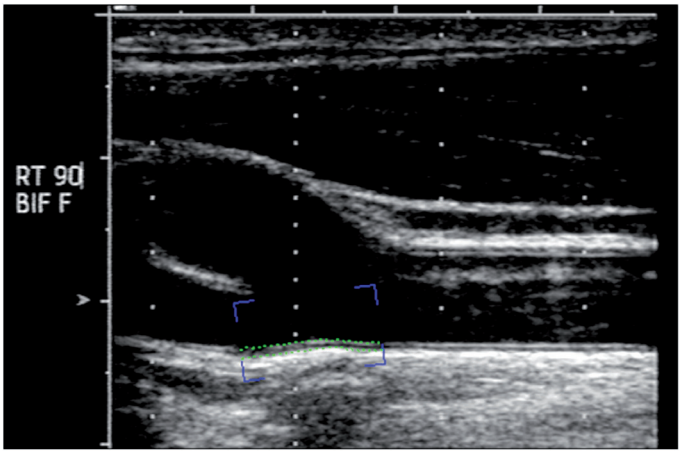

Figure 2 | Representative example of a longitudinal, cross-sectional carotid ultrasound image of a 62-year old male patient (a). The blue box shows an example of a region of interest for computer aided edge detection (green dotted lines). The distance between the green lines represents the IMT.

Ultrasound investigations are prone to operator variability, but several studies show excellent inter- and intra-observer reproducibility in the case of IMT measurement (45) (46) (47). The most frequently used location for the measurement is the most cranial one centimeter of the common carotid artery, but the carotid bifurcation and the internal carotid artery are other possible sites for measurement. Further differences in protocols arise because most authors calculate the mean IMT over one centimeter whereas others use the maximum value. As atherosclerosis is an asymmetrical process the angle at which the artery is approached by the operator can vastly influence the end results. Some authors try to limit the variance this causes by measuring IMT at several angles and using the mean value. Unilateral versus the average of bilateral measurements is another factor limiting uniformity. Due to these and other factors it remains unclear how to define normal IMT values. In healthy young adults IMT will be approximately 0.5mm slowly increasing with age. It is unclear where the threshold for higher cardiovascular risk lies and if this threshold is comparable in different populations (diabetics vs. non-diabetics; men vs. women; CKD vs. non-CKD; ethnic differences etc.). cIMT values exceeding 0.9mm are thought to imply increased cardiovascular risk. Atherosclerotic plaque is defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding cIMT value or demonstrates a thickness >1.5 mm.

Association with atherosclerotic burden

Increased IMT or the presence of plaque in the carotid artery has been directly correlated to coronary artery and overall atherosclerotic burden in several autopsy studies (48) (49). Iwakiri et al. recently published findings in 111 autopsy studies in which they found a positive association between cIMT and coronary intima media thickening ($R=0.31$, $p>0.001$). Although the correlation is statistically significant the strength of the association is modest. Abnormal cIMT in these subjects was also linked to the presence of a necrotic core in the atherosclerotic lesions. Fifty percent of subjects in the lowest tertile of cIMT demonstrated vulnerable plaques at various vascular beds. This increased to 80% in subjects with increased IMT. The cutoff point for the lowest tertile was <1,091mm. A cIMT value of <0.9mm is generally seen as the clinical threshold for higher cardiovascular risk. It would be of interest to know whether subjects

under this clinical cut-off point had less plaque burden or histologically less vulnerable plaques but these data were not published. The findings of this autopsy study support the hypothesis that carotid atherosclerosis represents more generalized vasculopathy but also suggest that the absence of carotid atherosclerosis does not necessarily exclude coronary pathology.

The association has also been studied in vivo. Increased cIMT and/or carotid plaque predicted coronary pathology in quantitative coronary angiography studies (50) (21), intravascular ultrasound examination (20), coronary calcification scores (51) and myocardial scintigraphy studies (22). The strength of the correlations are yet again modest at best (R=0.23-0.44) but all the findings were statistically significant and consistent. Most authors conclude that cIMT measurement and plaque detection may be useful as a non-invasive tool to approximate the presence of coronary artery disease. Whether asymptomatic patients with abnormal carotid ultrasound findings therefore require a more intensive CVD risk management strategies remains unclear.

Epidemiological evidence

Table 1 lists the population-based studies examining the association of cIMT with cardiovascular risk. It can be concluded that all current prospective data confirm the correlation between abnormal carotid ultrasound findings and elevated risk for future cardio- or cerebrovascular events. After correction for traditional risk factors the strength of association attenuates but cIMT and carotid plaque presence appear to be independent predictors. The strength of the association varies between a 20% and a 5-fold risk increase depending on the outcome parameter studied (MI, stroke and/or death), carotid scanning protocol segment used (internal carotid, external carotid, bifurcation, inclusion of plaque) and the level of statistical correction.

Whether this justifies its use in a routine cardiovascular screening setting is dependent on the additional predictive power of carotid ultrasound above the current standard risk prediction models. Analyses of the Framingham offspring and MESA studies as well as a recent meta-analysis have addressed this issue. In 2011 Polak et al. published data from the Framingham offspring study. A subset of 2965 members of this cohort underwent cIMT measurements. During the 7.2 years of follow-up 296 participants suffered a cardiovascular event. The same

Table 1 | Summary of population-based studies on the association between carotid ultrasound abnormalities and cardiovascular risk.

Author	n	Follow-up	Carotid parameter	Outcome parameter	Correction for traditional risk factors	HR [95% CI;p-value]]
Salonen et al 1991 (52)	1288	1m-2.5y	Bilateral CCA & BIF	Coronary artery event	none	6.71 [1.33-33.91;p<0.01] stenotic plaque 4.51 [1.51-11.47;p<0.01] minor plaque 2.17 [0.70-6.76;p=NS] increased cIMT
Belcaro et al 1996 (53)	2322	6y	Bilateral CCA, BIF, ICA	Cardiovascular event or death	none	*No formal HR; incident event distribution:* 0% events with normal ultrasound 5.5 % with increased cIMT (p<0.05) 18.4% with minor plaque (p<0.025) 42% with stenotic plaque (p<0.025)
Chambless et al 1997 (54)	14054	10.2y	Bilateral CCA, BIF, ICA	Cardiovascular events or death	Age, gender	5.07 [3.08-8.36;p<0.01] MI in women 8.54 [3.52-20.74;p<0.01] stroke in women 1.87 [1.28-2.69];p<0.01] MI in men 3.62 [1.45-9.15;p<0.01] stroke in men
Bots et al 1997 (55)	7983	2.7y	CCA	Cardiovascular events or death	Age, gender, BMI, smoking BP, lipids, diabetes, prior cardiovascular event	1.38[1.21-1.58;p<0.01] MI 2.23 [1.48-3.36;p<0.01] stroke
O'Leary et al 1999 (56)	5858	6.2y	CCA, ICA	MI, stroke	Age, gender, BP, presence of atrial fibrillation, smoking, diabetes	3.15[2.19-4.52;p<0.01] MI or stroke
Kitamura et al 2004 (57)	1289	4.5y	CCA, BIF, ICA	stroke	Age, BP, BMI	4.8 [1.9-12.0;p<0.01] stroke
Rosvall et al 2005 (58) (59)	5163	7y	CCA	MI, stroke	Age, gender, physical activity, smoking, BP, diabetes, lipids, waist circumference	1.23 [1.07-1.41;p<0.01] MI 1.21 [1.02-1.44;p<0.01] stroke
Lorentz et al 2006 (60)	5056	4.2y	CCA, BIF, ICA	MI, stroke	Age, gender, BMI, BP, lipids, smoking, diabetes	1.85 [1.09-3.15;P<0.01] combined stroke, MI or death
Polak et al 2011 (61)	2965	7.2y	CCA, BIF, ICA	Cardiovascular events or death	Age, gender, BP, lipids, smoking	1.21 [1.13-1.29;p<0.01] per 1SD increase in cIMT 1.92 [1.49-2.47;p<0.01] plaque
Polak et al 2013 (62)	6562	7.8y	CCA, ICA	Cardiovascular events or death	Age, gender, BP, lipids, smoking	1.45 [1.20-1.76;p<0.01] minor plaque 1.65 [1.34-2.03;p<0.01] stenotic plaque 1.33 [1.18-1.49;p<0.01] increased cIMT

Abbreviations: HR: Hazard ratio; CCA: common carotid artery; BIF: bifurcation; ICA: internal carotid artery; BP: blood pressure

authors recently reported their findings in het MESA-study population. A total of 6562 subjects were followed for an average of 7.8 years. A base prediction model was able to predict 74,3% of all CVD events [95% CI: 72.4-76.2], 72.9% of coronary events [95% CI: 70.5-75.2] and 77.4% of cerebrovascular events [95% CI: 73.9-80.9]. Presence of subclinical carotid atherosclerosis (plaque or increased cIMT) was significantly and independently associated with future events with hazard ratios ranging from 1.21 [95% CI: 1.13-1.30] for maximum cIMT in the internal carotid artery to 1.65 [95% CI: 1.34-2.03] for stenotic plaque. The predictive power of a model containing ultrasound parameters was slightly better than the base model. The increase in C-statistic regarding all cardiovascular events was marginal (0.46%-0.65%) but statistically significant. Looking at cerebrovascular events alone, the addition of carotid ultrasound findings did not significantly impact the performance of the baseline model. For coronary events cIMT and plaque presence appeared to be more relevant in this population. Including these parameters improved predictive ability of the base model by 0.89%-1.31%. Perhaps a more clinically relevant parameter is the net reclassification improvement (NRI) (63). This statistic quantifies in how many subjects the risk classification (low, intermediate, high) was rightly changed by taking cIMT and plaque presence into account. For coronary artery events the NRI was statistically significant for all ultrasound parameters and strongest for maximum IMT in the internal carotid artery (7%) and presence of stenotic plaque (5%).

Den Ruijter et al. combined the data from 14 large population based cohorts resulting in a database of 45.828 individuals without know cardiovascular disease (64). During a median follow-up of 11 years 4007 first time myocardial infarctions or strokes occurred. A model based on the Framingham Risk Score performed reasonably well in predicting the clinical events (75.7% [95% CI: 74.9-76.4]). Adding common carotid IMT to this model did not significantly improve performance of the model (75.9% [95% CI: 75.2-76.6]). In the entire cohort more than 90% of subjects stayed in the same risk category after adding cIMT values. Therefore the net reclassification improvement was marginal (0.8% [95% CI 0.1%-1.6%). The added value of cIMT improved slightly when subjects at intermediate risk alone were analyzed. In this subset the net reclassification improvement was approximately 4%. In patients with diabetes there was no effect on the area under the ROC or net reclassification improvement observable. The authors conclude that although cIMT improves risk prediction, especially in intermediate

risk patients, the additional value is too marginal to warrant its use.

Carotid atherosclerosis progression and cardiovascular risk

Several randomized intervention studies have shown that pharmacological interventions (statins, niacin, anti-hypertensive drugs, etc.) can slow cIMT progression when compared to a placebo control group. The suggestion in these trials is that limiting progression may lead to fewer future cardiovascular events. To clinicians it may therefore seem that sequential measurements of IMT to monitor progression can serve as a tool in evaluating the efficacy of individual cardiovascular risk management strategies. However there are no clear long-term data supporting this assumption. Several studies have looked at carotid atherosclerosis progression and its association with future events.

Results from the Multiethnic Study of Atherosclerosis suggested that cIMT progression is associated with risk of myocardial infarction and stroke. A recent meta-analysis evaluated this correlation on a larger scale. Pooled data from 10 cohort studies provided results from 36.984 primary prevention patients with 257.067 person-years of follow up. The robust, independent and significant correlation between cIMT and subsequent clinical end-point is confirmed in this analysis. By contrast a consistent null result is found for cIMT progression. Overall hazard ratios were found to be approaching 1.0 in unadjusted models as well as after adjustment for cardiovascular risk factors and baseline cIMT.

In a meta-analysis the relationship between changes in cIMT and the occurrence of major vascular events was analyzed (65). Data from 41 intervention studies were included. Most studies examined the effect of statins on cIMT progression but the dataset also included trials with antihypertensive drugs, lifestyle interventions, estradiol and anti-oxidants. The main finding was that progression or regression of cIMT was not correlated with more or fewer events in these trials. This does not detract from the beneficial effect of the interventions in the trials but demonstrates that cIMT changes do not accurately reflect these effects.

The recently published results from the IMPROVE study confirm the lack of predictive value of standard cIMT progression parameters for future events (66). A cohort of 3482 subjects with three or more vascular risk factors was included in the study. A novel parameter, the fastest progression of maximum IMT, was postulated by the authors. There was a significant and independent association

between this new value and the occurrence of CV events during a mean follow-up time of 21.5 months

Wannarong et al. compared changes in carotid IMT, plaque area and plaque volume in 349 subjects as predictors of myocardial infarction, stroke, transient ischemic attacks and death (67) . During the median follow-up time of 3.17 years only progression of plaque volume independently predicted future events.

DISCUSSION

It remains a challenge for clinician involved in primary prevention of cardiovascular disease to correctly identify patients at elevated risk. Assessment tools using models based on traditional risk factors have aided clinical decision-making tremendously. However, especially for patients at intermediate risk the need for more accurate risk markers persists. It is specifically this group of patients in which under- or overtreatment may occur. The vast majority of published data on the correlation of carotid atherosclerosis and coronary atherosclerosis demonstrates a close association. Carotid ultrasound provides a safe, patient-friendly and affordable means to objectify and quantify carotid atherosclerosis. In 1996 Belcaro et al. estimated the cost of one carotid-femoral IMT examination to be around 12 euros or approximately 15 US dollars, including training, equipment and staff expenses. (53) Long-term follow up studies with large sample sizes consistently confirm that elevated IMT and the presence of carotid plaques lead to higher risk of suffering coronary and cerebrovascular events. When adjusted for traditional cardiovascular risk factors the additional risk appears to be approximately 20-30%, suggesting that cIMT is an independent risk factor. Unadjusted odds ratios far exceed these figures.

Herein lies a problem in the interpretation of the studies. Is the aim of carotid ultrasound to provide the clinician with another cardiovascular risk factor to take into account in treatment decisions or can it be seen as the sum result of all traditional and non-traditional risk factors in a specific patient? There are strong arguments for the latter. Over the last decades cIMT has been shown to independently correlate to a plethora of non-traditional risk factors for atherosclerosis, including lp(a), homocysteine levels, lymphocyte/neutrophil ratios, inflammatory markers, circulating endothelial progenitor cells, markers

of endothelial function, etc. Moreover it has been suggested that traditional risk factors are not the major contributors to cIMT variance. It would seem useful for clinicians to obtain a general idea about the atherosclerotic state of the patient before making treatment decisions. For most of the abovementioned non-traditional risk factors however there is no known or proven treatment. Finding subclinical atherosclerosis in the carotid arteries in non-smoking patients without diabetes, hypertension or hyperlipidemia therefore presents the clinician with a dilemma. It does not seem prudent to look for non-traditional risk factors if it has no treatment consequences. If there are treatable risk factors present it is still unclear whether intensifying prevention interventions, e.g. setting lower LDL-cholesterol, blood pressure and HbA1C targets or adding aspirin, will lead to better outcomes. Conversely there is no evidence that absence of carotid atherosclerosis justifies withholding or delaying treatment of traditional risk factors.

The meta-analysis of the largest dataset examining these issues concludes that cIMT measurement improves risk assessment to such a limited extent that it is not a useful tool. On a population level this conclusion is accurate. However on an individual patient level the discussion is more subtle. In approximately 5% of patients at intermediate cardiovascular risk the addition of cIMT would have rightly reclassified them as high risk patients. Plaque detection and cIMT measurements in the carotid bifurcation and the internal carotid artery were not included in this analysis. Adding these parameters is likely to have positively affected the contribution of carotid ultrasound to the prediction model as they were the strongest predictors of future coronary artery events in the MESA-study. Although the group of patients who may benefit from carotid ultrasound measurements will remain small the consequences are potentially profound. Initiating early risk reduction strategies could prevent or delay morbidity and mortality due to progression of atherosclerotic burden.

Evaluating the response to an implemented risk management strategy could greatly aide clinicians in decisions about intensifying treatment. Monitoring cIMT progression would be a relatively simple and low-cost method to this end. However the current data suggest that progression of cIMT is not correlated with risk of cardiovascular events. A possible explanation for this finding is that one-time cIMT measurements are highly reproducible but the progression of cIMT is prone to inter- and intra-observer variability. This is due to the fact

that cIMT varies between 0.5mm and 1.2mm whereas yearly cIMT progression is in the range of 0.001-0.030mm. Sequential measurements are therefore much more susceptible to changes in the exact location of the reading (angle of the transducer, position of the subjects head etc.). Although advances in ultrasound equipment and scanning protocols are increasingly minimizing these variations it appears that cIMT progression is too unreliable to use as a marker to individualize risk management strategies. The most recent studies suggest that focal changes in carotid atherosclerosis (increasing plaque volume and fastest progression of maximum IMT) may prove helpful in monitoring treatments. Both these longitudinal parameters were found to independently predict future events, however further studies confirming these initial findings are needed. In addition, these novel parameters are not routinely measured and validation and standardization are required before they can be utilized in clinical practice.

FUTURE PERSPECTIVES

To fully elucidate the value of carotid ultrasound a four-armed management study is needed in which subjects with and without carotid atherosclerosis are randomized for intensive versus standard risk prevention strategies based on the ultrasound findings. Promising work is being done in the area of plaque characterization with ultrasound. Detailed description was beyond the scope of this review but by utilizing gray scaling techniques it is possible to identify lipid-rich, vulnerable carotid plaques. (68) These appear to be even more strongly associated with future vascular events, particularly ischemic strokes. (25) (69) (70) Finally, newer ultrasound equipment can perform real-time quantification of cIMT instead of the time consuming off-line procedure employed at the moment. These portable ultrasound machines make quick office-based measurement of cIMT and plaque detection available without the need for a dedicated vascular laboratory or radiology department. Growing experience with and exposure to carotid ultrasound will likely help clinicians properly implement and interpret it in clinical practice.

Recommendations & Learning points

- In patients at high cardiovascular risk there is no additional value of carotid ultrasound
- In patients at low or intermediate risk carotid ultrasound can aide clinicians by giving an indication of overall atherosclerotic burden; presence of carotid plaque or increased cIMT should prompt reclassification of the patient to a higher risk category
- Sequential measurement of cIMT to monitor progression are unreliable and the predictive value of longitudinal changes in cIMT is uncertain; it cannot be used to individualize risk management strategies
- Bilateral examination of the common carotid artery, the carotid bulb and the internal carotid artery from several angles provide the optimum information on cIMT and plaque presence
- The effect of treatment decisions based on carotid ultrasound parameters has not been studied and they should only be made in conjunction with all other cardiovascular risk factors

BIBLIOGRAPHY

1. *Design, baseline characteristics and carotid intima-media thickness reproducibility in the PARC study.* Touboul PJ, Vicaut E, Labreuche J, et al. 2005, Cerebrovasc Dis., pp. 57-63.
2. *Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study.* G. Burke, G. Evans, W. Riley, A. Sharrett, G. Howard, R. Barnes, et al. 1995, Stroke, pp. 386–391.
3. *Evaluation of the associations between carotidartery atherosclerosis and coronary artery stenosis: a case control study.* Craven TE, Ryu JE, Espeland MA, Kahl FR, McKinney WM, Toole JF, et al. 1990, Circulation, pp. 1230-42.
4. *The quantitation of atherosclerosis, III: the extent of correlaion of degrees of atherosclerosis within and between the coronary and cerebral vascular beds.* Young W, Gofman JW, Tandy R, Malamud N, Waters ESG. 1960, Am J Cardiol, pp. 300-8.
5. *Atherosclerotic changes of extracoronary arteries are associated with the extent of coronary atherosclerosis.* Lekakis JP, Papamichael CM, Cimponeriu AT, Stamatelopoulos KS, Papaioannou TG, Kanakakis J, et al. 2000, Am J Cardiol , pp. 949-52.
6. *Measurements of Carotid Intima-Media Thickness and of Interadventitia Common Carotid Diameter Improve Prediction of Cardiovascular Events : Results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events i.* Damiano Baldassarre, PhD , Anders Hamsten, MD, PhD, Fabrizio Veglia, PhD, Ulf de Faire, MD, PhD, Steve E. Humphries, PhD, Andries J. Smit, MD, Philippe Giral, MD, Sudhir Kurl, MD, Rainer Rauramaa, MD, PhD, Elmo Mannarino, MD, Enzo G. 2012, J Am Coll Cardiology.
7. *2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* Goff D., Lloyd-Jones D.M., Bennett G., Coady S., D'Agostino R.B., Gibbons R., Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW. 2014, J Am Coll Cardiology, pp. 2935-59.
8. *2013 ESH/ESC Guidelines for the management of arterial hypertension.* Mancia G., Fagard R., Narkiewicz K., Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sl. 2012, European Heart Journal, pp. 1635-1701.
9. *2016 European Guidelines on cardiovascular disease prevention in clinical practice.* Massimo F. Piepoli, Arno W. Hoes, Stefan Agewall, Christian Albus, Carlos Brotons, Alberico L. Catapano, Marie-Therese Cooney, Ugo Corrà, Bernard Cosyns, Christi Deaton, Ian Graham, Michael Stephen Hall, F. D. Richard Hobbs, Maja-Lisa Løchen, Herbert Löll. s.l. : Eur Heart J, 2016, European Heart Journal, pp. 1635-1701.
10. *Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. D.* Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels. 2012, JAMA, pp. 769-803.
11. *The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis.* Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, O'Leary DH. 2013, J Am Heart Assoc.
12. *Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities).* Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM. 2010, J Am Coll Cardiol, pp. 1600-1607.
13. *Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. .* Peters SA, den Ruijter HM, Bots ML, Moons KG. 2012, Heart, pp. 177-184.

14. *Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging.* Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. (6):1399-406., s.l. : Circulation, 1986, Circulation, Vol. 74, pp. 74:1399-1406.
15. *Reproducibility of carotid vessel wall thickness measurements. The Rotterdam Study.* Bots ML, Mulder PG, Hofman A, van Es GA, Grobbee DE. s.l. : J.Clin.Epidemiol.47(8):921-30, 1994.
16. *Precision and reproducibility of ultrasonographic measurement of progression of common carotid artery atherosclerosis.* Salonen JT, Korpela H, Salonen R, Nyyssonen K. s.l. : Lancet 1993;341(8853):1158-9.
17. *Reproducibility of In Vivo Carotid Intima-Media Thickness Measurements.* Suzan D.J.M. Kanters, Ale Algra, Maarten S. van Leeuwen and Jan-Dirk Banga. s.l. : Strokel 28 (3), 1997.
18. *Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force.* Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. s.l. : J Am Soc Echocardiograp 21:93-111, 2008.
19. *Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals.* Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. s.l. : JAMA; 291(2):210-5., 2004.
20. *Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings.* Amato M, Montorsi P, Ravani A, Oldani E, Galli S, Ravagnani PM, Tremoli E, Baldassarre D. (17):2094-101, s.l. : Eur Heart J, 2007, Eur Heart J, Vol. 28, pp. 28:2094-2101.
21. *The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease.* Geroulakos G, O'Gorman DJ, Kalodiki E, Sheridan DJ, Nicolaides AN. (6):781-5, s.l. : Eur Heart J, 1994, Eur Heart J, Vol. 15, pp. 15(6):781-5.
22. *Carotid atherosclerosis is correlated with extent and severity of coronary artery disease evaluated by myocardial perfusion scintigraphy.* Hallerstam S, Larsson PT, Zuber E, Rosfors S. 281-8, s.l. : Angiology, 2004, Angiology, Vol. 55, pp. 55:281-288.
23. *Prediction of major adverse cardiovascular events by age-normalized carotid intimal medial thickness. .* Ali YS, Rembold KE, Weaver B, Wills MB, Tatar S, Ayers CR et al. s.l. : Atherosclerosis;187(1):186-90, 2006.
24. *Effect of carotid atherosclerosis screening on risk stratification during primary cardiovascular disease prevention.* Bard RL, Kalsi H, Rubenfire M, Wakefield T, Fex B, Rajagopalan S et al. s.l. : Am.J.Cardiol.;93(8):1030-2, 2004.
25. *Cardiovascular risk assessment using ultrasound: the value of arterial wall changes including the presence, severity and character of plaques.* Griffin M, Nicolaides AN, Belcaro G, Shah E. s.l. : Pathophysiol Haemost Thromb, 2002, Vols. 32:367-370.
26. *Measurement of carotid artery intima-media thickness in dyslipidemic patients increases the power of traditional risk factors to predict cardiovascular events.* Baldassarre D, Amato M, Pustina L, Castelnuovo S, Sanvito S, Gerosa L et al. s.l. : Atherosclerosis 191(2): 403-8, 2007.
27. *Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: the Assessment of Prognostic Risk Observational Survey.* Cuspidi C, Ambrosioni E, Mancia G, Pessina AC, Trimarco B, Zanchetti A. s.l. : J.Hypertens. 20(7): 1307-14, 2002.
28. *Measuring subclinical atherosclerosis: is homocysteine relevant?* Sarwar AB, Sarwar A, Rosen BD, Nasir K. s.l. : Clin.Chem.Lab Med. 2007.
29. *Plasma lipoprotein(a) is an independent factor associated with carotid wall thickening in severely but not moderately hypercholesterolemic patients.* Baldassarre D, Tremoli E, Franceschini G, Michelagnoli S, Sirtori CR. s.l. : Stroke;27(6):1044-9, 1996.
30. *Carotid intima-media thickness and markers of inflammation, endothelial damage and hemostasis.* Baldassarre D, de Jong A, Amato M, Werba PJ, Castelnuovo S, Frigerio B et al. s.l. : Ann.Med. 2007:1-24.
31. *Ethnic differences in carotid wall thickness. The Insulin Resistance Atherosclerosis Study. .* D'Agostino RB, Jr., Burke G, O'Leary D, Rewers M, Selby J, Savage PJ et al. s.l. : Stroke;27(10):1744-9, 1996.

32. *The impact of ethnicity and sex on subclinical cardiovascular disease: the Diabetes Heart Study.* Freedman BI, Hsu FC, Langefeld CD, Rich SS, Herrington DM, Carr JJ et al. s.l. : Diabetologia 2005;48(12):2511-8.
33. *Yeboah J, Burke GL, Crouse JR, Herrington DM. Relationship between brachial flow-mediated dilation and carotid intima-media thickness in an elderly cohort: The Cardiovascular Health Study.* s.l. : Atherosclerosis, 2007.
34. *Alizadeh Dehnavi, R., Doornbos, J., Tamsma, J. T., Stuber, M., Putter, H., van der Geest, R. J., Lamb, H. J., and de Roos, A. Assessment of the Carotid Artery at 3T MRI Imaging: a Study on Reproducibility.* s.l. : Radiology, 2006.
35. *Carotid plaque MRI and stroke risk: a systematic review and meta-analysis.* Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, Dunning A, Mushlin AI, Sanelli PC. 2013, Stroke, pp. 3071-7.
36. *Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging.* Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Smith D et al. s.l. : Circulation;106(23):2, 2002.
37. *Effects of aggressive versus conventional lipid-lowering therapy by simvastatin on human atherosclerotic lesions: a prospective, randomized, double-blind trial with high-resolution MRI.* Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Chaplin WF et al. s.l. : JACC 46(1):106-12, 2005.
38. *Carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions.* Yuan C, Mitsumori LM, Beach KW, Maravilla KR. s.l. : Radiology;221(2):285-99, 2001.
39. *Glagov remodeling of the atherosclerotic aorta demonstrated by cardiovascular magnetic resonance: the CORDA asymptomatic subject plaque assessment research (CASPAR) project.* Mohiaddin RH, Burman ED, Prasad SK, Varghese A, Tan RS, Collins SA et al. s.l. : J.Cardiovasc. Magn Reson;6(2):517-25, 2004.
40. *Prediction of coronary heart disease using risk factor categories.* Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. 1837-1847, s.l. : Circulation, 1998.
41. *Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study.* Assmann G, Cullen P, Schulte H. 105(3):310-315., s.l. : Circulation, 2002.
42. *Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project.* Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM and group., SCORE project. 24(11):987-1003, s.l. : Eur Heart J, 2003.
43. *Ultrasound-determined intima-media thickness and atherosclerosis. Direct and indirect validation.* Persson J, Formgren J, Israelsson B, Berglund G. (2):261-4., s.l. : Arterioscler Thromb, 1994, Arterioscler Thromb, Vol. 14, pp. 14:261-4.
44. *Progression of carotid atherosclerosis and its determinants: a population-based ultrasonography study.* Salonen R, Salonen JT. s.l. : Atherosclerosis, 1990, Vols. 81:33-40.
45. *Common carotid intima-media thickness measurement. A method to improve accuracy and precision.* Baldassarre D, Werba JP, Tremoli E, Poli A, Pazzucconi F, Sirtori CR. 8; 1588-92, s.l. : Stroke, 1994, Vol. 25.
46. *Ultrasound assessment of atherosclerotic vessel wall changes: reproducibility of intima-media thickness measurements in carotid and femoral arteries.* Srámek A, Bosch JG, Reiber JH, Van Oostayen JA, Rosendaal FR. 12:699-706., s.l. : Invest Radiol, 2000, Vol. 35.
47. *Reproducibility of ultrasonographic measurements of different carotid and femoral artery segments in healthy subjects and in patients with increased intima-media thickness.* Smilde TJ, Wollersheim H, Van Langen H, Stalenhoef AF. 4:317-24, s.l. : Clin Sci (Lond), 1997, Vol. 93.
48. *Usefulness of carotid intima-media thickness measurement as an indicator of generalized atherosclerosis: findings from autopsy analysis.* Iwakiri T, Yano Y, Sato Y, Hatakeyama K, Marutsuka K, Fujimoto S, Kitamura K, Kario K, Asada Y. (2):359-62, s.l. : Atherosclerosis, 2012, Atherosclerosis., Vol. 224, pp. 225(2):359-62.

49. *Is plaque formation in the common carotid artery representative for plaque formation and luminal stenosis in other atherosclerotic peripheral arteries? A post mortem study.* Pasterkamp G, Schoneveld AH, Hillen B, Banga JD, Haudenschild CC, Borst C. 205-10, s.l. : Atherosclerosis, 1998, Atherosclerosis. , Vol. 137, pp. 137:205-210.
50. *Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis. A case-control study.* Craven TE, Ryu JE, Espeland MA, Kahl FR, McKinney WM, Toole JF, McMahan MR, Thompson CJ, Heiss G, Crouse JR 3rd. (4):1230-42., s.l. : Circulation, 1990, Circulation, Vol. 82, pp. 82(4):1230-42.
51. *Carotid Artery Plaque and Progression of Coronary Artery Calcium: The Multi-Ethnic Study of Atherosclerosis.* Polak JF, Tracy R, Harrington A, Zavodni AE, O'Leary DH. 26(5):548-55, s.l. : J Am Soc Echocardiogr, 2013.
52. *Ultrasonographically assessed carotid morphology and the risk of coronary heart disease.* Salonen, J T Salonen and R. 11:1245-1249, s.l. : Arteriosclerosis, Thrombosis, and Vascular Biology, 1991.
53. *Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study.* Belcaro G, Nicolaides AN, Laurora G et al. 851-56., s.l. : Arterioscler Thromb Vasc Biol, 1996, Vol. 16.
54. *Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993.* Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. 6:483-94, s.l. : Am J Epidemiol, 1997, Vol. 146.
55. *Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study.* Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. (5):1432-7., s.l. : Circulation, 1997, Vol. 96.
56. *Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group.* O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. (1):14-22., s.l. : N Engl J Med, 1999, Vol. 340.
57. *Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men.* Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, Kiyama M, Tanigawa T, Yamagishi K, Shimamoto T. s.l. : Stroke, 2004, Vols. 35(12):2788-94.
58. *Incidence of stroke is related to carotid IMT even in the absence of plaque.* Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. s.l. : Atherosclerosis, 2005, Vols. 179(2):325-31.
59. *Incident coronary events and case fatality in relation to common carotid intima-media thickness.* Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. s.l. : J Intern Med, 2005, Vols. 257(5):430-7.
60. *Carotid Intima-Media Thickening Indicates a Higher Vascular Risk Across a Wide Age Range : Prospective Data From the Carotid Atherosclerosis Progression Study (CAPS).* Lorenz MW, von Kegler S, Steinmetz H, Markus HS and Sitzer M. 87-92, s.l. : Stroke, 2006, Vol. 37.
61. *Carotid-Wall Intima–Media Thickness and Cardiovascular Events.* Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, and D'Agostino RB, Sr. s.l. : N Engl J Med, 2011, Vols. 365:213-21.
62. *The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis.* Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, O'Leary DH. 2, s.l. : J Am Heart Assoc, 2013, Vol. 2.
63. *Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. .* Pencina MJ, D'Agostino RB Sr, Steyerberg EW. (1):11-21, s.l. : Stat Med, 2011, Vol. 30.
64. *Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis.* Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels. (8):796-803., s.l. : JAMA, 2012, Vol. 308.
65. *Does Carotid Intima-Media Thickness Regression Predict Reduction of Cardiovascular Events?* Costanzo P, Perrone-Filardi P, Vassallo E. s.l. : JACC, 2010, Vols. 56 (24); 2006-20.

66. *Progression of Carotid Intima-Media Thickness as Predictor of Vascular Events : Results from the IMPROVE Study.* Baldassarre D, Veglia F, Hamsten A, Humphries SE, Rauramaa R, de Faire U, Smit AJ, Giral P, Kurl S, Mannarino E, Grossi E, Paoletti R and Tremoli E. s.l. : ATVB, 2013.

67. *Progression of Carotid Plaque Volume Predicts Cardiovascular Events.* Wannarong T, Parraga G, Buchanan D, Fenster A, House AA, Hackam DG and Spence JD. s.l. : Stroke, 2013, Vols. 44:1859-1865.

68. *Lipid-rich Carotid Artery Plaques Appear Echolucent on Ultrasound B-mode Images and may be Associated with Intraplaque Haemorrhage.* Gronholdt M-LM, Wiebe BM, Laursen H, Nielsen TG, Schroeder V and Sillesen H. s.l. : Eur J Vasc Endovasc Surg, 1997, Vols. 14; 439-445.

69. *Ultrasonic Echolucent Carotid Plaques Predict Future Strokes.* Grønholdt M-LM, Nordestgaard BG, Schroeder TV, Vorstrup S and Sillesen H. s.l. : Circulation, 2001, Vols. 104:68-73.

70. *Echolucent Plaques Are Associated With High Risk of Ischemic Cerebrovascular Events in Carotid Stenosis: The Tromsø Study.* Mathiesen EB, Bønaa KH and Joakimsen O. s.l. : Circulation, 2001, Vols. 103:2171-2175.

71. *Ultrasound B-mode imaging in observational studies of atherosclerotic progression.* Salonen JT, Salonen R. II56-65, s.l. : Circulation, 1993, Vol. 87.

72. *Common carotid intima-media thickness is predictive of all-cause and cardiovascular mortality in elderly community-dwelling people: Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study.* Murakami S, Otsuka K, Hotta N, Yamanaka G, Kubo Y, Matsuoka O, Yamanaka T, Shinagawa M, Nunoda S, Nishimura Y, Shibata K, Takasugi E, Nishinaga M, Ishine M, Wada T, Okumiya K, Matsubayashi K, Yano S, Ichihara K, Cornélissen G, Halberg F. Suppl 1:S49-53., s.l. : Biomed Pharmacother, 2005, Vol. 59.