Carotid imaging in cardiovascular risk assessment

Ray, A.

Author: Ray, A.
Title: Carotid imaging in cardiovascular risk assessment
Issue Date: 2018-05-15

CHAPTER 2

Accuracy of Carotid Plaque Detection and Intima-Media Thickness Measurement with Ultrasonography in Routine Clinical Practice

A. Ray MD, J.T. Tamsma MD PhD, M.M.C. Hovens MD,
J. op 't Roodt, M.V. Huisman MD PhD

ABSTRACT

Background

Current guidelines in cardiovascular disease prevention advocate the use of carotid ultrasound measurements for risk stratification. Carotid abnormalities (plaques or increased intima-media thickness (IMT)) are associated with high risk of coronary and peripheral artery disease. An office-based measurement by clinicians would considerably broaden the clinical applicability of carotid ultrasound. In the present study we have assessed the accuracy of ultrasound detection of carotid plaques and intima-media thickness by trained internists in a routine outpatient setting.

Methods & Results

Carotid ultrasound was performed in 112 vascular outpatients by internists, after a six week training period. The internists' results were independently compared to the reference standard, consisting of carotid ultrasound performed in a specialized vascular laboratory. Sensitivity and specificity were calculated for plaque detection and IMT determination. The mean time required to perform the scans on the outpatient department was 7.3 minutes (range 4.5 to 16.7 minutes). A high level of accuracy for detecting plaques (sensitivity 78.5%; specificity 93.6%) was achieved. Identifying abnormal IMT had lower sensitivity but adequate specificity of 46.7% and 87.6%, respectively.

Conclusions

In conclusion, our findings demonstrate that clinicians can be trained well enough in six weeks to accurately and efficiently detect carotid plaques in an outpatient setting. As IMT abnormalities were less accurately detected, this may require a follow-up IMT, for instance in a specialized vascular laboratory. Incorporating vascular imaging results in treatment decisions may improve clinicians' ability to provide individualized patient care.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality. Identifying patients at high risk for future cardiovascular events and peripheral artery disease is an important challenge for clinicians, as the presence of traditional risk factors predicts only 60-65% of incident events [1]. It has repeatedly been established in longitudinal studies that increased intima-media thickness (IMT), as well as the presence of atherosclerotic plaques in the carotid artery, is associated with increased risk of future myocardial infarction and stroke [2-6]. Reported increases in relative risk for cardiovascular events vary between 1.2 and 3.6, in subjects with abnormal compared with normal IMT [3,6,7]. Furthermore it has been shown that IMT is independently associated with a host of cardiovascular risk factors [8,9], and with atherosclerotic changes in other vascular beds, including the coronary and femoral arteries [10-14]. The presence of plaque in the carotid artery increases cardiovascular risk by approximately three- to six-fold compared to plaque-free controls, depending on plaque severity [2,6,8,13]. Therefore carotid IMT measurement and plaque detection has been proposed as a means to improve risk stratification by identifying patients that may require more aggressive preventive interventions [2,7,15,16]. The European Society of Cardiology advises the use of carotid plaque detection and IMT measurement in risk assessment in hypertensive patients [17] and the American Society of Echocardiography as well as the American Heart Association concluded that carefully performed IMT measurement and plaque detection may add incremental information over traditional risk factors in selected patients [18,19]. However the ultrasound protocols of a vascular laboratory are time consuming, generally taking around 40-45 minutes. Furthermore, most general hospitals lack the specialized equipment needed for quantitative analysis of the scans. Recently, it has been demonstrated that IMT measured in normal clinical practice by trained sonographers was sufficiently reproducible with intra- and interobserver variability of 4.2% and 7.3% respectively [20]. Importantly, in this study the measurements were not compared with a reference standard which is a critical step in the evaluation of a diagnostic test [21].

Whether carotid ultrasound can be adequately performed by internists and incorporated in a normal clinical setting has not been studied extensively. Office-based measurement by internists would considerably broaden the clinical applicability of carotid IMT and plaque detection. Results of a multicenter study showed that non-sonographer clinicians (doctors, nurses, etc) can accurately measure carotid IMT and plaques using a handheld ultrasound device [22]. Moreover, ultrasound screening for carotid plaque in an office setting has been shown to potentially alter treatment plans [23,24]. Therefore, the aim of the current study was to assess the level of accuracy that can be achieved by trained internists in identifying atherosclerotic plaque and increased IMT in a routine vascular outpatient setting.

MATERIALS & METHODS

Patients

Patients were recruited from the vascular outpatient department (OPD) at the Leiden University Medical Center. Oral and written informed consent was obtained from all patients; the study protocol was approved by the Institutional Review Board. To ensure the inclusion of a broad clinical spectrum, both patients with a history of CVD (prior myocardial infarction or stroke, coronary revascularization or known peripheral vascular disease) as well as subjects free of clinically manifest CVD were recruited. There were no predefined exclusion criteria. The presence of hypertension was defined as an average of 3 measurements over 140/90 mmHg or the use of anti-hypertensive medication. Subjects were designated as having a positive family history if at least one first degree relative had a cardiovascular event or revascularization intervention before the age of 60 years. Smoking habits were recorded, and patients who had not smoked in the last 12 months were designated as ex-smokers.

Study design

Two trained internists performed the carotid ultrasound scans on the OPD (see below for ultrasound protocol). After the scans on the OPD, carotid ultrasound examination was performed in a specialized vascular laboratory within two weeks, by a single blinded sonographer. The ultrasound on the vascular OPD always preceded the scans in the vascular laboratory. Relevant medical history was recorded and physical examination and blood sampling were performed only after the IMT scans to minimize pre-scan bias on the part of the sonographers. Quantitative analysis of IMT was performed on the scans made in the vascular laboratory as described below. As per design, the OPD scans were not quantitatively analyzed but rather evaluated in real-time as described below. However in a look-back at the false positive and false negative OPD scans these were analyzed in a quantitative manner. This allowed for a secondary analysis of the reasons for false adjudication on the OPD.

Ultrasound training

Two internists specialized in vascular medicine were trained over a 6 week period of by a certified sonographer with specific experience in vascular ultrasonography. On average, approximately 4 hours per week were spent learning and practicing the ultrasound protocol, leading to a total of 24 hours of training time in patients. In addition the internists were given a set of 25 frozen images of previously performed scans to become visually skilled in distinguishing normal IMT thickness from increased thickness, as well as plaque recognition. Initially the scans were performed on young healthy volunteers to get accustomed to adhering to the protocol. When the instructor was satisfied about the ability of the physicians to adequately visualize and recognize the vascular wall and anatomical structures such as the carotid bifurcation, older patients were included in the practice sample. Vascular abnormalities such as plaques and increased IMT were more prevalent in the older patients. The internists performed all the practice scans under supervision of the instructor. The ultrasound protocol was practiced 10 times in healthy volunteers and 20 times on older patients.

Ultrasound protocol on the outpatient department

On the OPD all scans were performed using an Aloka SSD-1400 high-resolution ultrasound device with a 7.5MHz linear transducer. Subjects were examined in prone position with the head tilted to the side counter lateral to the site of examination. The left and right carotids were both scanned. First, a transverse scan was performed for orientation, starting at the clavicle and moving cranially up to the mandible, hereby locating the height of the carotid bifurcation. Subsequently, longitudinal images were obtained. This technique allows visualization of two echogenic lines, separated by an anechoic space. It has previously been established that these lines indicate the blood-intima and the media-adventitia interfaces, and that the distance between the lines represents a histologically reliable measure for the thickness of the lamina intima and media [25]. The caudal tip of the flow divider (i.e. the wall structures between the internal and external carotid arteries) was used as the anatomical landmark to localize the most distal 1cm of the common carotid artery. The artery was visualized at four angles (anterior, two antero-lateral projections and lateral). The internists estimated the IMT of the common carotid artery in real time by placing electronic callipers around the intima-media complex. Subsequently, the presence of plaques was assessed both in the common carotid artery and the bifurcation, defined as focal thickening of >1.5mm or >1.5 times the surrounding IMT. The presence, at any angle, of either a maximum IMT of >1mm or atherosclerotic plaque resulted in a categorization of the scan as abnormal. If no plaques were detected and the maximum IMT was <1mm at all angles, the scan was considered normal. Designating a scan 'normal' or 'abnormal' was done by the internists in writing, immediately after performing the scan. On the scan result-forms the internists could illustrate their findings on a schematic diagram of the carotid artery (pre-printed on the form) and add comments. It has been recently shown that a similar ultrasound protocol, limited to plaque detection and IMT measurement in the common carotid artery, produces the same results as more comprehensive protocols that include quantification of IMT in the carotid bifurcation and internal carotid artery [26]. All scans were recorded on sVHS videotapes for independent analysis of the outpatient scans at a later point in time. In addition, in order to identify the factors leading to discrepancies between OPD and vascular laboratory findings, all false positive and false negative scans were retrospectively reviewed by a blinded observer, who was not involved with the scanning of the patients. Practical feasibility was determined subjectively by evaluating the ability of the internists to incorporate the measurement in their outpatient work and quantifying the time spent performing the scans.

Ultrasound protocol in the vascular laboratory

In the vascular laboratory the identical ultrasound protocol was performed using an Acuson Sequoia 512 (Siemens Medical AG, Munich, Germany) high-resolution ultrasound machine with an 8LS (8MHz) linear transducer. This transducer frequency was 0.5MHz higher than the one used on the OPD but this minor difference resulted in similar screen resolution and image quality.

One sonographer (4 years of experience) who has been certified to implement this ultrasound protocol for clinical trials performed and analysed the scans. The within-subject reproducibility achieved by the sonographer, performing the same scanning protocol in a previous trial was >95% [27]. At the time of scan and analysis the observer was blinded for both the clinical data of the patient and the result of the OPD scan. The scans from the vascular laboratory were quantitatively analysed off-line with computer-aided automatic boundary detection where possible and manual adjustment where necessary, using the ASM II software package version 1.1364 (Gustavson, Chalmers, Sweden). The use of automatic boundary detection has been shown to be accurate and is advised in the recent Mannheim consensus on IMT measurement [28]. The overall gain settings during scanning were kept at 0dB when possible. The sonographer was free to adjust the gain levels if necessary, but within the limits of -7dB to 7 dB to avoid possible influences of extreme gain settings on IMT quantification. Mean IMT was defined as the average of the mean values of the far and near walls of the common carotid artery at all four angles. Mean maximum IMT was calculated from the mean of the maximum values at these sites. All quantifications were performed in cardiac diastole.

The definition of plaque was identical to the one used on the OPD (focal thickening of >1.5mm thickness or >1.5 times the surrounding IMT). In the vascular laboratory plaques were further classified as described earlier [6,28]. They were classified to be mild if only the aforementioned criteria were met. Moderate plaques were defined as lesions encroaching into the lumen. If the lesion caused stenosis the plaque was classified as severe.

Statistical analysis

All data were analyzed using the SPSS 12.0 software package. Data are expressed in means [95% confidence intervals] unless indicated otherwise. Differences between groups were analyzed with a student T-test, categorical data were compared using a Chi-squared test. P-values of <0.05 were considered statistically significant. Calculation of sensitivity, specificity, positive and negative predictive values as well as likelihood ratios for the internists to identify plaque and abnormal IMT was done as described earlier [21,29]. The retrospective analyses of the false negative and false positive OPD scans were compared to the reference standard by a Bland-Altman plot [30].

RESULTS

A total of 112 patients were included in the study. The clinical and demographic characteristics of the study population are summarized in table 1. Mean age was 53.8 yrs [51.6-56.6], 11.6% of patients had type 2 diabetes mellitus and 21.4% had a history of CVD. There was a high prevalence of hypertension and hypercholesterolemia of 49.0% and 67.6% respectively. Of our patients 52.5% was either a current smoker or had smoked in the past, and 30.4% had a family history of CVD. Mean IMT in our sample was 0.743 [0.719-0.768] and the mean of the maximum IMT was 0.847 [0.817-0.877], quantified in the vascular laboratory. Of the 112 patients 65 (58.0%) had atherosclerotic plaque in the carotid artery. Of these plaques 50% were classified in the vascular laboratory as severe, 26% as moderate and 24% as mild.

Feasibility

On average the scans on the outpatient department took 7.3 minutes to perform (range 4.5 to 16.7 minutes). This was the effective scanning time and did not include the preparation time etc. Typically, if a patient was already in supine position for blood pressure measurement or physical examination the ultrasound could be easily incorporated. In cases where the patients had to lie down specifically for the ultrasound the internists subjectively found including the scan more intrusive in their normal routine. In a half-day session on the OPD, during which time a total of approximately 15 patients were seen, the clinicians were able to include an average of 2-3 patients.

Accuracy of plaque detection

Data on plaque detection are summarized in table 2. Of the 65 plaques identified in the vascular laboratory, 51 were recognized by the internists on the outpatient and 14 were not seen, for a sensitivity of 78.5% [69.9%-86.1%]. In 3 patients the internists on the outpatient indicated the presence of a plaque where no plaques were seen in the vascular laboratory for a specificity of 93.6% [89.1%-98.1%]. The positive predictive value for plaque detection was 83.1% and the negative predictive value was 75.9%. The likelihood ratios of positive and negative tests on the OPD were 12.2 and 0.23, respectively for plaque detection.

Table 1 | Patient characteristics. CVD: cardiovascular disease; BMI: body mass index; IMT: intima-media thickness.

Variable	Total group (n=112)
Age (yrs)	53.8 [51.6-56.6]
% Diabetes	11.6%
% CVD	21.4%
% Hypertension	49.0%
% Hypercholesterolemia	67.6%
% Family History of CVD	30.4%
Smoking	
% Current smokers	21.8%
% Ex-smokers	30.7%
BMI (kg/m^2)	27.3 [26.4]
Systolic BP (mmHg)	133.1 [129.0-137.3]
Diastolic BP (mmHg)	81.9 [79.8-84.1]
Anti-platelet therapy	22.0%
Statin therapy	54.3%
Antihypertensive therapy	46.7%
Mean IMT (mm)	0.743 [0.719-0.768]
Mean max IMT (mm)	0.847 [0.817-0.877]
Plaques	65 (58.0%)
Mild	23.7%
Moderate	26.2%
Severe	50.1%

CVD: cardiovascular disease; BMI: body mass index; IMT: intima-media thickness

Table 2 | Comparison of plaque findings on the outpatient department and the vascular laboratory.

	Vascular lab plaque +	Vascular lab plaque -	total
OPD plaque +	51	3	54
OPD plaque -	14	44	58
Total	65	47	112

OPD: outpatient department. Sensitivity: 78.5% [95% CI: 69.9%-86.1%]. Specificity: 93.6% [95% CI: 89.1%-98.1%]. Plaque prevalence: of 58.0%. Positive predictive value: 94.4%. Negative predictive value: 75.9%. Likelihood ratio of a positive test: 12.2. Likelihood ratio of a negative test: 0.23

Accuracy of IMT measurement

Data regarding the measurement of IMT are summarized in table 3. Sensitivity of the internists for recognizing IMT ≥ 1mm was 46.7% [37.5%-55.9%], with a specificity of 87.6% [81.5%-93.7%]. The positive and the negative predictive values were 36.8% and 91.4% respectively. Likelihood ratios for positive and negative tests for the IMT estimation on the OPD were found to be 3.7 and 0.69, respectively.

Table 3 | Comparison of IMT findings on the outpatient department and the vascular laboratory.

	Vascular lab IMT ≥ 1mm	Vascular lab IMT < 1mm	total
OPD IMT ≥ 1mm	7	12	19
OPD IMT < 1mm	8	85	93
Total	15	97	112

OPD: outpatient department. Sensitivity: 46.7% [95% CI: 37.5%-55.9%]; Specificity: 87.6% [95% CI: 81.5%-93.7%]; Prevalence of increased IMT: 13.4%; Positive predictive value: 36.8%; Negative predictive value: 91.4%; Likelihood ratio of a positive test: 3.7; Likelihood ratio of a negative test: 0.69.

Look back at false negative and false positive findings

The distribution of false negative scans was constant over the study period and equal between the two internists. In the case of plaque detection there were two main factors that led to incorrect findings on the OPD as compared to the vascular laboratory. First, in several instances the carotid bifurcation was cranially located making it difficult for the clinicians to visualize it due to obstruction of the ultrasound transducer by the patient's mandible. In these cases, the sonographer in the vascular laboratory was better able to detect plaques by helping patients to hyperextend their neck using foam rolls or pillows. Second, due to the curvilinear anatomy of the carotid bifurcation the clinicians were not always able to adequately visualize the intima-media complex. The sonographer, having no time restraints was able to meticulously examine the curved surface.

Regarding IMT, the 20 false negative and false positive cases had a mean maximum IMT of 0.970mm [range: 0.723mm-1.380mm]. Retrospective analysis revealed that, in all cases the internists adequately visualized the intima-media complex and the image quality was sufficient to allow off-line analysis. Quantitative analysis of the OPD scans resulted in identical values as were found in the vascular laboratory (mean difference 0.001mm; p=0.939), illustrated in the Bland & Altman plot in figure 1. The main factor leading to incorrect designation

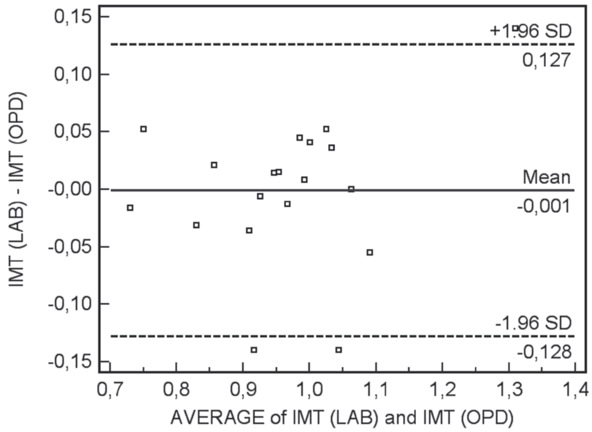

Figure 1 | Bland & Altman plot of retrospective quantitative IMT measurements of false negative and false positives.

IMT: intima-media thickness; LAB: vascular laboratory; OPD: outpatient department.

of IMT as being normal or abnormal by the internists was lack of precision of the manual calliper placement.

DISCUSSION

This study has assessed the accuracy of plaque detection and IMT measurement by internists in a routine outpatient setting. The most important finding is that internists can achieve acceptable sensitivity and high specificity for carotid plaque detection after a six-week training period, resulting in high positive and negative predictive values. We believe that the external validity of our data is strengthened by the fact that the 58% overall plaque prevalence in our patients was comparable to previous reports: Rosvall et al. [5] found 43% carotid plaques in 5163 subjects with and average age of 58 years and van der Meer et al. [31] reported 58% plaques in 6389 subjects of >55 years of age. Both these study samples were recruited from the general population and showed similar patterns of co-morbidity, although our patients were slightly younger. Our data show that 20% of plaques were not identified by the internists on the outpatient department. The look back at these false negatives revealed that it was due to high anatomical location and curvilinear anatomy of the carotid bifurcation, making it difficult to visualize. In a normal clinical situation these patients, in whom the carotid bifurcation was not optimally visualized, could still be referred to a specialized vascular laboratory or radiology department. The high specificity of outpatient plaque detection demonstrates that when carotid abnormalities are seen using this simple test it represents true presence of plaque.

The clinical implications of our study are underlined by the results from other studies relating the presence of carotid plaque to future cardiovascular events [2,6,8]. In particular, Griffin et al. in 2002 [32] demonstrated that with ultrasound plaque detection and characterization high-risk patients could be identified, independent of other cardiovascular risk factors. Our data strongly suggest that carotid plaque detection during routine clinical practice may be a useful tool in identifying high risk patients for CVD and peripheral artery disease.

In our study it was more difficult for internists to accurately identify increased IMT. The internists could only achieve 47% sensitivity with respect to identifying abnormal IMT but a high specificity (88%) was achieved. In our look back at the reasons for incorrect estimation of IMT we found that it was mainly due to inaccurate placement of the electronic callipers. Retrospective quantitative analysis of the twenty discrepant OPD and vascular laboratory scans showed excellent agreement suggesting that inaccurate manual measurement, and not insufficient image quality, caused the false results. Based on our findings we argue that manual normal IMT measurement in clinical practice is not suitable to exclude additional cardiovascular risk and it should be followed by an IMT performed in a specialized vascular laboratory. Moreover, using a dichotomous cut-off value for IMT is a relatively crude method. Although IMT values > 1mm are associated with elevated risk it would be more accurate to statistically correct the continuous value for IMT in individual patients to age, gender and ethnicity. Such calculations and corrections however are time consuming and may not be feasible in an office-based approach. Whether the use of more advanced ultrasound equipment, including real-time IMT quantification and automatic correction for these factors may facilitate the use of IMT values for risk assessment in an outpatient setting remains to be prospectively studied.

Our study had limitations. It is possible that longer and more intense training would have improved the results achieved by the internists. We achieved a high accuracy for plaque detection using training program that can be easily implemented. This is reflected by the constant distribution of false positive and false negative findings on the outpatient department during the inclusion period, indicating the absence of an additional learning curve during the study. Second, different ultrasound machines were used for the outpatient measurements and the scans in the vascular laboratory. The minor difference of 0.5 MHz in transducer frequency however did not lead to differences in image quality, which is supported by the high agreement in the retrospective quantitative analysis.

In conclusion, our findings demonstrate that internists can accurately detect carotid plaques using ultrasound, after a six-week training period. The limited amount of time required to perform the scans allowed the internists to incorporate the measurements in their normal clinical routine. Adequate recognition of increased IMT is more difficult and may require a specialized vascular laboratory or alternatively ultrasound equipment dedicated to IMT quantification.

Learning Points

- Internists are able to identify carotid plaques by ultrasound in routine clinical practice with high precision after a six-week training period
- In-office plaque detection may aide internists to individualize preventive cardiovascular strategies per patient
- Measurement of carotid intima-media thickness by internists is not recommended because it lacks accuracy when compared to measurement in a specialized vascular laboratory
- Errors in measuring intima-media thickness in an out-patient setting are mainly due to insufficient precision of manual estimations of thickness

BIBLIOGRAPHY

1 Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. *JAMA* 2004; 291(2):210-215.

2 Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study. Belcaro G, Nicolaides AN, Laurora G, Cesarone MR, De Sanctis M, Incandela L *et al. Arterioscler Thromb Vasc Biol* 1996; 16(7):851-856.

3 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. *Circulation* 1997; 96(5):1432-1437.

4 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. *N Engl J Med* 1999; 340(1):14-22.

5 Incidence of stroke is related to carotid IMT even in the absence of plaque. Rosvall M, Janzon L, Berglund G, Engstrom G, Hedblad B. *Atherosclerosis* 2005; 179(2):325-331.

6 Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Salonen JT, Salonen R. *Circulation* 1993; 87 (Suppl):II56-II65.

7 Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. Chambless LE, Folsom AR, Sharrett AR, Sorlie P, Couper D, Szklo M *et al. J Clin Epidemiol* 2003; 56(9):880-890.

8 Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *S*Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN *et al. troke* 1999; 30(4):841-850.

9 Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts. The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) investigators. Howard G, Manolio TA, Burke GL, Wolfson SK, O'Leary DH. *Stroke* 1997; 28(9):1693-1701.

10 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 *et al. Eur Heart J* 2007; 28(17):2094-2101.

11 Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW *et al. Stroke* 1995; 26(3):386-391.

12 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 *et al. Circulation* 1990; 82(4):1230-1242.

13 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. *Eur Heart J* 1994; 15(6):781-785.

14 Atherosclerotic changes in the femoral and carotid arteries in familial hypercholesterolemia. Ultrasonographic assessment of intima-media thickness and plaque occurrence. Wendelhag I, Wiklund O, Wikstrand J. *Arterioscler Thromb* 1993; 13(10):1404-1411.

15 Prediction of coronary heart disease in middle-aged adults with diabetes. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, Pankow JS. *Diabetes Care* 2003; 26(10):2777-2784.

16 Subclinical disease as an independent risk factor for cardiovascular disease. Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, Haan MN *et al. Circulation* 1995; 92(4):720-726.

17 European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R *et al.* *Eur Heart J* 2007; 28(19):2375-2414.

18 Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and non-invasive cardiovascular tests. Greenland P, Smith SC, Jr., Grundy SM. *Circulation* 2001; 104(15):1863-1867.

19 American society of echocardiography report. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E. *Vasc Med* 2006; 11(3):201-211.

20 Carotid artery intima-media thickness measured by ultrasonography in normal clinical practice correlates well with atherosclerosis risk factors. Baldassarre D, Amato M, Bondioli A, Sirtori CR, Tremoli E. *Stroke* 2000; 31(10):2426-2430.

21 Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. Jaeschke R, Guyatt GH, Sackett DL. *JAMA* 1994; 271(9):703-707.

22 Carotid intima-media thickness testing by non-sonographer clinicians: the office practice assessment of carotid atherosclerosis study. Korcarz CE, Hirsch AT, Bruce C, Decara JM, Mohler ER, Pogue B *et al.* *J Am Soc Echocardiogr* 2008; 21(2):117-122.

23 Ultrasound Detection of Increased Carotid Intima-Media Thickness and Carotid Plaque in an Office Practice Setting: Does It Affect Physician Behavior or Patient Motivation? Korcarz CE, Decara JM, Hirsch AT, Mohler ER, Pogue B, Postley J *et al.* *J Am Soc Echocardiogr* 2008.

24 Does detection of carotid plaque affect physician behaviour or motivate patients? Wyman RA, Gimelli G, McBride PE, Korcarz CE, Stein JH. *Am Heart J* 2007; 154(6):1072-1077.

25 Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. *Circulation* 1986; 74(6):1399-1406.

26 An Abbreviated Carotid Intima-Media Thickness Scanning Protocol to Facilitate Clinical Screening for Subclinical Atherosclerosis. Gepner AD, Wyman RA, Korcarz CE, Aeschlimann SE, Stein JH. *J Am Soc Echocardiogr* 2007.

27 Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ *et al.* *N Engl J Med* 2007; 356(16):1620-1630.

28 Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N *et al.* *Cerebrovasc Dis* 2007; 23(1):75-80.

29 How to appraise a diagnostic test. Bhandari M, Guyatt GH. *World J Surg* 2005; 29(5):561-566.

30 Statistical methods for assessing agreement between two methods of clinical measurement. Bland JM, Altman DG. *Lancet* 1986; 1(8476):307-310.

31 Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. van der Meer I, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. *Circulation* 2004; 109(9):1089-1094.

32 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. *Pathophysiol Haemost Thromb* 2002; 32(5-6):367-370.