#### A useful, extremely safe technique for the evaluation of vascular anatomy

# Carotid ultrasonography in the assessment of cardiovascular risk

#### Aldo Pende, Nathan Artom, Giovanni Pistocchi, Livia Pisciotta, Franco Dallegri

Clinic of Internal Medicine 1, Department of Internal Medicine, University of Genoa School of Medicine, IRCCS AOU San Martino - IST, Genoa, Italy

#### Summary

Carotid ultrasound is one of the most accessible examinations in daily clinical practice for the evaluation of the arterial status. However, the clinical implications of the presence, the extension and the morphology of carotid damage are not entirely clear. Aim of this narrative review is to discuss the role of carotid ultrasound in the assessment of cardiovascular risk through the examination of the updated evidence in the literature. We describe the technical aspects of the procedure and the possible correlations between the imaging results and the assessment of the cardiovascular risk. Some insights about new, more sophisticated techniques for carotid evaluation, such as carotid three-dimensional and contrast-enhanced ultrasound, are also presented.

Key words: carotid ultrasound; carotid intima-media thickness; carotid plaque; cardiovascular risk; cardiovascular events

#### Carotid ultrasound evaluation

B-mode ultrasound carotid evaluation is a high-resolution, noninvasive and widely available technique for the direct visualisation of the arterial anatomy (fig. 1) [1]. The examination determines the carotid intima-media thickness (CIMT), defined as the thickness, measured in the far wall of the common carotid artery (CCA), from the media-adventitia interface to the intima-lumen interface (with a threshold value for subclinical vascular damage >0.9 mm) (fig. 2), and the possible presence of atherosclerotic plaques, defined as CIMT >1.5 mm or as focal lesions encroaching into the vascular lumen by at least 0.5 mm or 50% of the surrounding IMT value [2]. From a pathophysiological point of view it is important to stress that an increase in CIMT and a carotid plaque are different phenomena. The main predictors of increased CIMT, which is specifically an expression of hypertrophy of the media and adequately evaluated at the level of the CCA, are age and hypertension [3]. In contrast, plaque, which is an expression of endothelial dysfunction, recruitment of inflammatory cells, accumulation of cholesterol and cellular debris (i.e., of the atherosclerotic process), is located in the intima and is more strongly predicted by the traditional athero-

An article from the series "Atherosclerosis and inflammation" sclerotic risk factors [4-7]. It occurs in sites with turbulent flow, such as the carotid bulb and the proximal internal carotid artery, with the CCA involved in very advanced damage only [8]. The carotid plaque can be characterised in terms of various features: degree of stenosis (mild <50%, moderate 50%-69%, severe 70%-99%), surface regularity, and echogenicity. For the degree of stenosis, Schulte-Altedorneburg et al. showed a good correlation between in vivo ultrasound findings and evaluation of postmortem carotid specimens in the same critical patients [9]. The degree of carotid stenosis is weakly related to the traditional atherosclerotic risk factors [10]. In addition, irregularities of the carotid plaque surface may represent a good marker of its vulnerability, which translates into increased risk of thromboembolic cerebral events [11-13]. With regards to plaque echogenicity, several studies clearly showed that echolucent carotid plaques were more related to cardiovascular events (CVEs) than were echogenic ones [14-16]: in fact, echolucent plaques histologically demonstrate a higher lipid content and a reduced fibrous and calcium content, which represent important features of advanced and/or unstable atherosclerotic disease [17]. Different methods exist for the quantitative assessment of the ultrasonographic properties of



**Figure 1**: Longitudinal B-mode image of the left carotid bifurcation with the internal carotid artery (ACI SN) and the external carotid artery (ACE SN) seen in the same plane. At the beginning of the external carotid artery the superior thyroid artery (AT) is observed.



Figure 2: Longitudinal B-mode image of the distal tract of the common carotid artery with the intima-media thickness.

the carotid plaques: the Gray Scale Median score, a measure of plaque brightness, and the integrated backscatter, which is able to differentiate lipids from other components [18].

# Two-dimensional carotid ultrasound for the prediction of cardiovascular events

#### Assessment of cardiovascular risk

Several scoring systems are used for cardiovascular risk (CVR) prediction in clinical practice: the American Framingham Risk Score (FRS) and the European Systematic Coronary Risk Evaluation (SCORE) charts have been proposed and validated [19, 20], and recently the American College of Cardiology and the American Heart Association released a new 10-year cardiovascular disease (CVD) calculator [21]. The Reynolds Risk Score uses, in addition to traditional risk factors, information from high sensitivity C-reactive protein (hs-CRP) and parental history of premature CVD [22, 23], which stresses the role of subclinical inflammation and of the genetic background in the pathogenesis of atherosclerosis; this score reclassified 30% of women estimated to be in the intermediate-risk group with the traditional FRS into a higher or lower risk category with improved accuracy [22].

These scores are simple to use in evaluating CVR; however, in some cases the estimate is suboptimal, particularly in subgroups of the general population (for example, those at low or intermediate risk), since they vary widely in terms of the background risk in study populations, predictors and outcomes considered [24–29]. Other limitations of these scores include a substantial underestimation of lifetime risk, with a potential misclassification of high-risk subjects at low or intermediate CVR [30]. Among healthy adults aged 20 to 79 years, risk scores classify 75% of the subjects as low or intermediate risk, but in these categories a substantial number of CVEs (about 60%) occurs [31]. The main goal for primary prevention seems to be the identification of low-risk or intermediate-risk subjects who have subclinical atherosclerosis, and therefore could be reclassified to a higher risk level [32]. To improve individual risk assessment, several studies investigated the role of CIMT and carotid plaque evaluation with a noninvasive and safe technique such as carotid ultrasound.

#### Role of the carotid intima-media thickness

Some years ago, Lorenz et al. published a systematic review and meta-analysis involving 37,197 subjects from the general population and showed that for an absolute CIMT difference of 0.1 mm the future risk of CVEs increased by more than 10%: this relationship was stronger for stroke than for myocardial infarction and was independent of traditional risk factors [33]. However, the incremental value of CIMT measurement for risk stratification in addition to those risk factors was less clear: a subsequent meta-analysis by Den Ruijter et al. involving 45,828 subjects showed that the addition of CIMT to FRS determination modestly improved 10-year risk prediction (net reclassification improvement of 0.8%), although a more evident influence could be seen in subjects at intermediate risk, with a net reclassification improvement of 3.6% [34]. Very recently, Bots et al. confirmed these conclusions in 17,254 subjects with elevated blood pressure, demonstrating the limited but significant utility of CIMT measurement in CVR prediction for individuals at intermediate risk [35].

# Role of carotid intima-media thickness progression or regression

Several studies evaluated the progression of CIMT as a predictor of CVD: although the MESA trial showed a significant association between CIMT progression and CVEs [36], a subsequent large meta-analysis showed that the progression of CIMT (detected through the changes between two ultrasound examinations 2–7 years apart) did not improve the CVR prediction [37]. In addition, the evaluation of treatment-induced regression of CIMT failed to demonstrate a predictive value for CVEs [38]. For these reasons, in recent European Society of Hypertension / European Society of Cardiology guidelines for management of arterial hypertension, CIMT evaluation was considered of limited value for the follow-up of hypertensive patients [39].

#### Recent statements of the guidelines

In 2013, a guideline from the American College of Cardiology and the American Heart Association reconsidered the role of CIMT, in conjunction with other biomarkers, in the assessment of CVR [40]: the conclusions of the panel's experts were that, after quantitative risk assessment with the usual tools, in the presence of uncertainties about treatment decisions family history of premature CVD, hs-CRP serum levels, coronary calcium score (CCS) or ankle-brachial index, but not CIMT, could be evaluated to reclassify



**Figure 3:** Longitudinal B-mode image of the carotid bifurcation with an echogenic irregular carotid plaque extended from the carotid bulb to the proximal internal carotid artery. Plaque area is measured in a longitudinal view in which the plaque has the largest extension, freezing the frame and tracing around the plaque perimeter with a cursor on the screen.

the risk. On the other hand, a previous guideline from the American College of Cardiology Foundation and the American Heart Association for the assessment of the CVR in asymptomatic adults evaluated as "reasonable" the measurement of CIMT in subjects at intermediate risk (Class IIa of recommendation, level of evidence B) [41].

### Role of carotid plaque in cardiovascular risk prediction: comparison with CIMT

The definition of CIMT is straightforward and allows adequate comparisons between studies. On the contrary, criteria for defining and assessing carotid plaque and, more generally, the global carotid damage, defined as carotid burden, can vary [42]. Some authors initially tried to evaluate the cardiovascular predictive value through a carotid plaque score, calculated as the sum of the maximum thickness of the plaques in the various segments of both carotid arteries. Several studies showed that, compared with CIMT, plaque score was a stronger predictor of CVEs and correlated with the complexity of coronary lesions [43-45]. However, Spence et al. suggested that the best method for assessing the carotid burden was to calculate the carotid plaque area (CPA), defined as the sum of the areas of all the plaques in the carotid tree evaluated in a longitudinal view: subjects with high values of CPA at baseline (patients in the highest quartile for CPA) presented a significant increase in CVEs (figs 3 and 4) [46]. With consecutive measure-



**Figure 4**: Longitudinal **(A)** and transverse **(B)** image of an echogenic calcified carotid plaque, located in the carotid bulb. No ultrasound waves penetrated beyond calcium, resulting in a dark cone of shadow.

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ments of CPA, the progression of the atherosclerotic damage was linked to increased CVR, something not demonstrated with CIMT (see above) [42]. During recent years it has emerged that the assessment of carotid plaque was a better predictor of cardiovascular risk, compared with CIMT. In fact, although the Rotterdam Study did not show differences between CIMT and a carotid plaque score as predictors of myocardial infarction [47], several subsequent studies stressed the importance of carotid plaque evaluation as compared with CIMT in predicting coronary artery disease. In the initial presentation of the results of the Tromsø Study, CPA, evaluated in more than 6,000 subjects of a general population, was a stronger predictor of myocardial infarction than was CIMT [48]; after 10 years of follow-up CPA was highly predictive for stroke also, whereas CIMT was still not predictive [49]. Subsequently, the Strong Heart Study demonstrated that the presence of carotid plaque was an important predictor of coronary artery disease, whereas CIMT was not an independent risk factor for CVD [50]. More recently, Polak et al., in a cohort of the Framingham Offspring Study, and Plichart et al., in the French Three-City Study, demonstrated that carotid plaque, but not CIMT, improved cardiovascular risk prediction [51, 52]. A large meta-analysis, which evaluated most of these studies, confirmed these conclusions and stressed again the differences between the measurements of the vascular wall in the CCA (deliberately not containing plaque) and in the carotid bulb (possibly comprising a plaque) [53]. Furthermore, in the large cohort of the REACH registry (more than 10,000 subjects), Sirimarco et al. showed that carotid atherosclerosis was an independent predictor of coronary events in the recruited subjects, with different types of symptomatic vascular disease and presence of risk factors at baseline [54]. In comparison with other markers of atherosclerotic damage, such as serum CRP and CCS, Brook et al. demonstrated that, although each test may improve CVR stratification, a negative CPA determination is superior to CIMT, CCS, and CRP in its ability to reduce the likelihood of concomitant significant coronary atherosclerosis [55]. The main results of the cited trials are presented in table 1.

# Three-dimensional ultrasound and contrast enhanced ultrasound

# An improvement in carotid assessment and cardiovascular risk prediction?

Only a few studies analysed the role of carotid three-dimensional ultrasound (3dUS) in the assess-

ment of CVR, in which the plaque is evaluated in both a longitudinal and a perpendicular cross-sectional axis [56, 57]. This technique seemed to improve the carotid burden evaluation through the estimation of the total plaque volume (TPV). A recent trial showed that progression of TPV better predicted CVEs compared with total plaque area and CIMT [58]. Subsequently, Kuk et al. showed that also the volume of carotid ulceration, evaluated with the same technique, significantly correlated with CVEs [59]. The strong correlation between 3dUS and coronary artery disease was confirmed by Johri et al. in subjects undergoing carotid ultrasound evaluation and concomitant coronary angiography [60].

Another important emerging test for the early detection of plaque instability and prediction of CVEs is contrast-enhanced ultrasound (CEUS) of the carotid artery. This technique is able to identify intraplaque neovascularisation and adventitia vasa vasorum neoproliferation through the injection of microspheres via a peripheral vein [61]. Staub et al., evaluating 147 subjects retrospectively, demonstrated the association of these features with CVD and previous CVEs [62]. For further confirmation, Deyama et al. showed that, in subjects with known carotid plaque undergoing coronary angiography, CEUS evaluation of the carotid plaque neovascularisation is strongly correlated with the severity of coronary artery disease [63]. In addition, van den Oord et al. demonstrated that CEUS significantly improved the accuracy of plaque assessment by ultrasound [64]. See table 1 for a summary of the cited articles.

Further studies are needed to confirm the role of 3dUS and CEUS as new tools for early identification of individuals at risk of new CVEs [65].

#### Conclusions

Carotid ultrasound is a useful, extremely safe technique for the evaluation of vascular anatomy and may allow a net reclassification improvement of the CVR. Several reports indicate that CIMT is clinically useful at least in subjects at intermediate risk [33, 34]. The carotid plaque has a greater predictive value: the evaluation of the CPA seems to give the best information for the initial assessment of the atherosclerotic damage and the response to appropriate therapies. In recent years, new sophisticated ultrasound-based techniques have emerged, such as carotid 3dUS and carotid CEUS. Large ongoing observational studies already underway include 2d and 3d carotid ultrasound for the screening of subclinical atherosclerosis and the evaluation of its progression [66]. Another im-

Study	Year	Population	Methods	Main results
Kitamura et al. [11]	2004	1,289 pts.	Carotid IMT and plaque evaluation in pts. without a previous stroke or CAD. The sub- sequent incidence of stroke was investigated with a mean follow-up of 4.5 yrs.	34 strokes occurred. Multivariate-adjusted RR (95% CI) for the highest vs lowest quartiles of maximum IMT of the CCA ( $\geq$ 1.07 vs $\leq$ 0.77 mm) was 3.0 (1.1–8.3) for stroke. Combination of CCA and ICA wall thickness was better predictor of the risk of stroke than CCA wall thickness alone. Men with plaque in the ICA had a 3–fold higher risk of stroke than those without plaque. Plaque surface irregularity further increased the stroke risk. Significant excess risk of stroke demonstrated in men with an uncalcified plaque.
Prabhakaran et al. [12]	2006	1,939 stroke-free pts.	Evaluation of the irregularity of the plaque with 2d carotid US with a a mean follow-up of 6.2 yrs.	69 ischaemic strokes occurred. After adjusting for demographics, traditional vascular risk factors, degree of stenosis and plaque thick- ness, irregular plaque (vs no plaque) associated with ischemic stroke (HR 3.1).
Honda et al. [14]	2004	286 CAD pts.	Assessment of the echogenicity of carotid plaques with US and of the coronary plaque complexity by use of angiography with a follow-up of 30 months.	Echolucent carotid plaques predicted the existence of complex coro- nary plaques (83% predictive power). Higher probability of coronary events in pts. with echolucent carotid plaques than in pts. •• <i>is there</i> <i>something missing here?</i> •• Presence of echolucent carotid plaques in stable CAD pts. predicted future coronary events independent of other risk factors (OR 7.0).
Singh et al. [15]	2013	154 pts. with ischaemic stroke	Carotid US with gray-scale technique in ischaemic stroke pts. Follow-up of pts. for 6 months for the recurrence of stroke and its association with plaque echogenicity.	Significant association between the presence of plaque and traditional cerebrovascular risk factors. Also significant association between recurrence of stroke and echolucent character of carotid plaque. Recurrence of stroke related to advanced stage of ATS, specified by carotid plaque and its characteristics.
Polak et al. [35]	2011	5,028 pts. of the MESA trial free of CVD	IMT rate of change with a mean follow-up of 3.22 yrs.	42 first-time strokes occurred. In multivariable models age (HR 1.05 per year), SBP (HR 1.02 per mm Hg), lower HDL-chol. (HR 0.96 per mg/ dl), IMT rate of change (HR 1.23 per 0.05 mm/year) associated with incident stroke. The upper quartile of IMT rate of change had HR of 2.18 compared with the lower 3 quartiles combined.
Morito et al. [41]	2008	116 pts.	Pts. undergoing carotid US and coronary angiography. Pts. divided into 2 groups based on the presence or absence of CAD.	CAD correlated with plaque score and with number of plaques.
Xie et al. [42]	2011	1,734 pts.	Pts. undergoing carotid US and examination of traditional risk factors. Mean follow-up of 5 yrs.	IMT at baseline associated with the risk of CVD among participants without carotid plaque (multivariable adjusted HR 1.59) but not among those with plaque (H 1.04). CPA (HR 1.29), the number of plaques (HR 1.14) and the number of segments with plaque (HR 1.45) associated with CVD. Combined carotid IMT and number of segments with plaque to establish a summary index with improved prediction of the 5-year risk of CVD compared with IMT or the number of segments with plaque alone. Improved risk prediction by the index compared with the conventional risk score.
lkeda et al. [43]	2012	501 pts.	Pts. undergoing carotid US and coronary angiography	Excellent negative predictive values of plaque score and IMT with regards to the complexity of CAD.
Spence et al. [44]	2002	1,686 pts.	Carotid US at baseline and annual follow-up visits for up to 5 years (mean, $2.5 \pm 1.3$ yrs). Plaque area progression (or regression) defined as an increase (or decrease) of $\geq 0.05$ cm <sup>2</sup> from baseline.	CPAs categorised in 4 quartile ranges: 0.00–0.11 cm2, 0.12–0.45 cm <sup>2</sup> , 0.46–1.18 cm <sup>2</sup> , 1.19–6.73 cm <sup>2</sup> . Combined 5–yr risk of stroke, MI, and vascular death increased by quartile of CPA: 5.6%, 10.7%, 13.9%, and 19.5%, respectively, after adjustment for all baseline pt. characteristics. 63.1% of pts. with carotid plaque progression, 28.2% plaque regression, and 16.2% no change during follow-up. The 5-year adjusted risk of combined outcome was 9.4%, 7.6%, and 15.7% for patients with CPA regression, no change, and progression, respectively.
van der Meer et al. [45]	2004	6,389 pts. of the Rotter- dam Study	Carotid plaques and IMT measured by use of US, abdominal aortic ATS with x-ray, and lower-extremity ATS with ABI.	All measures of ATS good predictors of MI independently of traditio- nal cardiovascular risk factors. HRs were 1.83 for carotid plaques, 1.95 for carotid IMT, 1.94 for aortic ATS, 1.59 for lower extremity ATS. HR for MI for pts. with severe ATS according to a composite ATS score was 2.77 compared with subjects with no ATS. Predictive value of MI for a given measure of ATS was independent of the other ATS measu- res.
Johnsen et al. [46]	2007	6,226 pts. of the Tromsø Study	US measurement of IMT, TPA, and plaque echogenicity. Follow-up for 6 yrs.	MI occurred in 6.6% of men and 3.0% of women. Adjusted RR between the highest TPA tertile versus no plaque was 1.56 in men and 3.95 in women. In women significant trend toward a higher MI risk with more echolucent plaque. Adjusted RR in the highest versus lowest IMT quartile was 1.73 in men and 2.86 in women. With exclusion of the bulb IMT from analyses, IMT did not predict MI in either sex.

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Mathiesen et al. [47]	2011	6,584 pts. of the Tromsø Study	US measurement of IMT and TPA, and plaque echogenicity. Follow-up for 10 yrs.	Incident ischaemic strokes occurred in 7.3% of men and 4.8% of women. The HR for 1 SD increase in square-root-transformed plaque area was 1.23 in men and 1.19 in women when adjusted for other CV risk factors. The multivariable-adjusted HR in the highest quartile of plaque area versus no plaque was 1.73 in men and 1.62 in women. The multivariable-adjusted HR for 1 SD increase in IMT was 1.08 in men and 1.24 in women. No differences in stroke risk across quartiles of IMT.			
Roman et al. [48]	2012	2,441 pts. of the Strong Heart Study	US measurement of IMT of the CCA. Arterial mass calculated from IMT and end-diastolic diameter. ATS defined as focal plaque and the number of carotid segments containing plaque (plaque score). Follow-up for a mean of 7.7 yrs.	495 CVEs occurred. Atherosclerotic plaque was a strong independent predictor of CHD (HR 1.88) and plaque score was an independent pre- dictor of stroke (HR 1.19).			
Polak et al. [49]	2011	2,965 pts. of the Framing- ham Off- spring Study	US measurement of the mean IMT of the CCA and the maximum IMT of the ICA. CVD outcomes evaluated for an average follow- up of 7.2 yrs Evaluation of the reclassifica- tion of CVD on the basis of the 8-year FRS category (low, intermediate, or high) after adding IMT values.	296 CVEs occurred. The risk factors of the FRS predicted the events, with a C statistic of 0.748. The adjusted HR for CVD with a 1-SD incre- ase in the mean IMT of the CCA was 1.13, with a non significant change in the C statistic of 0.003; the HR for the maximum IMT of the ICA was 1.21, with an increase in the C statistic of 0.009. NRI increased significantly after addition of IMT of the ICA (7.6%) but not IMT of the CCA (0.0%). With the presence of plaque the NRI was 7.3%, with an increase in the C statistic of 0.014.			
Plichart et al. [50]	2011	5,895 pts. of the Three-City Study	US examination of carotid arteries: measure- ment of mean IMT of both CCAs at plaque- free sites and assessment of focal plaques in the near and far walls of the CCAs, the bi- furcations and the origin of the ICAs. Median follow-up of 5.4 yrs.	223 CVEs occurred. In multivariate analysis, carotid plaques were independent predictors of CAD: HR (plaques at 1 site) 1.5; HR (plaques at ≥2 sites) 2.2; contrary to mean CCA-IMT. Adding carotid plaques to conventional risk factors significantly improved CHD risk prediction.			
Sirimarco et al. [52]	2013	23,364 pts. of the REACH re- gistry	Carotid US evaluation; follow-up of 4 yrs.	Carotid ATS in 46% of pts. and associated with increasing conventio- nal CV risk factors and extent of symptomatic vascular disease. 4,304 pts. experienced ≥1 coronary event. After adjustment for CV risk fac- tors and geographic region, risk of coronary events increased by 22% in pts. with vs without carotid ATS. Relative increase was 18% in pts. with multiple risk factors only, 25% in pts. with CAD, 46% in pts. with cerebrovascular disease, and 37% in pts. with peripheral artery disease. Carotid ATS was associated with increased risk, even among pts. with previous MI but no known stroke or among pts. with previ- ous stroke but no known MI.			
Brook et al. [53]	2006	42 pts. un- dergoing 16-slice co- ronary CT angiography	Measurement of CPA, IMT, and CRP	CT angiographyidentified clinically significant CAD in 43% of pts. CPA >0 was more sensitive (72%) and specific (58%) than a CCS >0 (58% and 55%) for identifying CAD. "Clean" carotid artery (CPA = 0) provi- ded superior negative predictive value (74%) and likelihood ratio of a negative test (0.48) than all other studies, in particular vs a CCS = 0 (65% and 0.72). The areas under the ROCs for CPA and CCS in relation to any CAD were similar (0.640 vs 0.675). CIMT and CRP performed poorly compared with CPA and CCS. For detecting CAD in only the left main or left anterior descending artery, the negative predictive value and likelihood ratio of a negative test remained superior for CPA (87% and 0.33) compared with CCS (80% and 0.56). In a population with a prevalence of coronary lesions of 30%, the post-test probability in any patient with a negative CPA result reduced to 10%			
Wannarong et al. [56]	2013	349 pts.	3d US measurement of IMT, TPA, and TPV. Follow-up of ≤5 years (median 3.17 yrs) for detection of vascular death, MI, stroke, and TIAs.	Progression of TPV predicted stroke, death or TIA, stroke/death/MI and stroke/Death/TIA/MI (any CVE). Progression of TPA weakly predic- ted stroke/death/TIA but not stroke/death/MI or any CVE. Change in IMT did not predict stroke/death/MI or any CVE. In Cox regression, TPV progression remained significant predictor of events after adjust- ment for coronary risk factors but change in TPA did not. IMT change predicted events in an inverse manner.			
Kuk et al. [57]	2014	349 pts.	Measurement of carotid 3d US and evaluation for ulceration with a $\leq$ 5-year follow-up.	Pts. with total ulcer volume ≥5 mm <sup>3</sup> showing significantly higher risk of developing stroke, TIA, or death and of developing stroke/TIA/ death/MI/revascularisation. Lower ulcer volumes and ulcer depth did not predict CVEs.			
Johri et al. [58]	2013	70 pts. un- dergoing coronary angiography	Carotid evaluation with 2d and 3d US.	Total 3d plaque volumes less than 0.09 ml predicted the absence of significant CAD in 93.3% of patients (98% sensitivity), whereas maxi- mal 2d plaque thickness less than 1.35 mm provided significantly lower negative predictability at 75% (93.9% sensitivity).			

Table 1: Continuation.						
Staub et al. [60]	2010	147 pts.	CEUS analysis for the presence of intralumi- nal plaque, plaque neovascularisation (Grade 1 = absent; Grade 2 = present), and degree of adventitial vasa vasorum (Grade 1 = absent, Grade 2 = present).	Presence of intraluminal carotid plaque directly correlated to CV risk factors, CVD, and CVEs. Adventitial vasa vasorum Grade 2 associated with significant more subjects with CVD than Grade 1 (73 versus 54%). Pts. with intraplaque neovascularisation Grade 2 showing significantly more often a history of CVEs than subjects with Grade 1 (38 vs 20%). With multivariate logistic regression analysis presence of plaque sig- nificantly associated with CVD (OR 4.7) and intraplaque neovasculari- sation grade 2 with CVE (OR 4.0).		
Deyama et al. [61]	2013	304 pts.	Carotid CEUS evaluation for intraplaque neo- vascularization with microbubbles within the plaque, graded as: G0, not visible; G1, mode- rate; or G2, extensive microbubbles. Assess- ment of coronary lesions by angiography.	Higher grade of carotid CEUS-assessed plaque neovascularisation associated with greater complexity and extent of coronary lesions. Grade 2 plaque neovascularisation was a risk for acute coronary syn- drome, independent of traditional risk factors (OR 1.91). Regression of carotid CEUS-assessed neovascularisation in 46% of plaques in pts. during 6 months of statin treatment, in 14% of plaques in pts. not taking a statin.		
van den Oord et al. [62]	2013	100 pts.	Evaluation of standard carotid US and CEUS for the presence of atherosclerotic plaques.	The addition of CEUS to the standard US protocol demonstrated atherosclerotic plaques in 88% of pts. The incorporation of CEUS into the standard carotid US protocol resulted in a significantly improved detection of patients with subclinical ATS.		
Nambi [64]	2012	13,145 pts. of the ARIC study	Carotid IMT and plaque evaluation in pts. without a previous stroke or CAD.	Adding to TRF, C-IMT+plaque information was reclassified ~23% of subjects with a NRI of ~9.9%. The addition of C-IMT and plaque sepa- rately or together to the TRF model improved the AUC, which increa- sed from 0.742 to 0.750, 0.751 and 0.755 for the TRF-only, TRF+C-IMT, TRF+plaque and TRF+C-IMT+plaque model respectively.		
Rundek [65]	2008	2,189 pts. of the NOMAS study	Evaluation of maximum carotid plaque thickness. Mean follow-up of 6.9 years.	Carotid plaque in 58% of subjects. CVEs occurred among 319 subjects. Pts. with maximum carotid plaque thickness greater than 1.9 mm had a 2.8-fold increased risk of combined CVEs in comparison with the subjects without carotid plaque (HR 2.80). Approximately 44% of the low-risk individuals by FRS had a 10-year CV risk of 18.3% if having carotid plaque.		

ABI = ankle/brachial index; ARIC = Atherosclerosis Risk In Communities; ATS: = atherosclerosis; CAD = coronary artery disease; CCA = common carotid artery; CEUS = contrast-enhanced ultrasound; CI = confidence interval; CPA = carotid plaque area; CT = computerised tomography; CV = cardiovascular; CVD: = cardiovascular disease; CVE = cardiovascular event; 2d = two-dimensional; 3d = three-dimensional; FRS = Framingham Risk Score; HDL-chol. = high density lipoprotein-cholesterol; HR = hazard ratio; ICA = internal carotid artery; IMT = intima-media thickness; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; NOMAS = NOrthern MAnhattan Study; NRI = net reclassification improvement; OR: = odds ratio; pts. = patients; REACH = REduction of Atherothrombosis for Continued Health; RR = relative risk; SBP = systolic blood pressure; TPA = total plaque area; TPV = total plaque volume; US = ultrasound; vs = versus; yrs = years.

> portant clinical effort, within the High-Risk Plaque Initiative, is the BioImage Study in which enrolled subjects were subdivided in a survey-only group, a group undergoing traditional risk factor scoring, and a third group with the risk factor scoring and the additional evaluation of subclinical atherosclerosis (in conjunction with the determination of various new biomarkers): follow-up will be terminated by the occurrence of an adequate number of atherothrombotic events [67].

Correspondence: Aldo Pende, MD Department of Internal Medicine, University of Genoa School of Medicine IRCCS AOU San Martino – IST Viale Benedetto XV 6 ITI-16132 Genoa Italy apende[at]unige.it

Although it is without doubt that the development of carotid and coronary plaques is closely related [68], the transition from a population level to an individual patient management in terms of cardiovascular prevention remains not unanimously stated, since in the individual subject the presence of a carotid plaque does not automatically imply the presence of an underlying coronary artery disease and hence the need to perform a coronary angiography [69].

In addition, some studies suggest that carotid evaluation does not seem to motivate patients to follow a healthy lifestyle or to improve treatment adherence [70, 71]. Nevertheless CIMT and/or carotid plaque detection in subjects at low or intermediate risk can certainly represent a useful biomarker to start, or to change with a more aggressive strategy, drug treatment aimed to correct the traditional risk factors.

#### Funding / potential competing interests

This work was supported by a PRA Grant of the University of Genoa (Italy) to Prof. F. Dallegri. No other potential conflict of interest relevant to this article was reported.

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- The full list of references is attached to the online version at www.cardiovascmed.ch.

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