Carotid Plaque Compared With Intima-Media Thickness as a Predictor of Coronary and Cerebrovascular Disease

Stein Harald Johnsen, MD, PhD, and Ellisiv B. Mathiesen, MD, PhD

Corresponding author
Stein Harald Johnsen, MD, PhD
Department of Neurology, University Hospital North Norway,
N-9038 Breivika, Tromsø, Norway.
E-mail: stein.harald.johnsen@unn.no

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Atherosclerosis is the underlying cause of most myocardial infarction (MI) and ischemic strokes. B-mode ultrasound of carotid arteries provides measures of intima-media thickness (IMT) and plaques, both widely used as surrogate measures of cardiovascular disease. Although IMT and plaques are highly intercorrelated, IMT's role as a marker of atherosclerosis has been questioned, especially when measurements include the common carotid artery (CCA) only. Plaque and intima-media thickening may reflect different biological aspects of atherogenesis with distinctive relations to clinical vascular disease. Plaque measured in the carotid bulb or internal carotid artery is stronger related to hyperlipidemia and smoking and is a stronger predictor for MI, whereas CCA-IMT is stronger related to hypertension and ischemic stroke. Echolucent plaque morphology (ie, lipid-rich plaques) seems to increase the risk for MI and stroke. New evidence suggests that total plaque area is the most strongly predictive of cardiovascular risk of the ultrasound phenotypes.

Introduction

Atherosclerosis is the underlying cause of most of myocardial infarction (MI) and ischemic strokes. The ability to identify persons with atherosclerosis and quantify the extent of atherosclerosis is of great value in stratifying the future risk for cardiovascular diseases and also for monitoring ongoing treatment. Noninvasive detection of atherosclerosis should involve methods that are safe, inexpensive, reliable, and reproducible. Additionally, their results should correlate with the extent of atherosclerotic disease and have high negative and positive predictive value for clinical events.

B-mode ultrasound of carotid arteries provides measures of intima-media thickness (IMT) and plaques, both widely used as surrogate measures of cardiovascular disease. IMT is made up of about 80% media and 20% intima, whereas atherosclerosis is largely an intimal process. Although IMT and plaques are highly intercorrelated [1,2], IMT's role as a marker of atherosclerosis has been questioned, especially when measurements include the common carotid artery (CCA) only [3,4]. IMT usually has been measured in the CCA because high measurement precision is easily obtained from this artery. However, plaques in this arterial segment are rare. Plaques usually occur at sites of nonlaminar turbulent flow, such as in the carotid bulb and the proximal internal carotid artery (ICA) [5].

IMT and plaque each represent end-organ disease in the arterial wall but reflect different disease attributes or stages. IMT, especially in its early development, reflects a hypertensive hypertrophic response of the medial cells, and is likely to reflect the influence of genes related to hypertension, such as angiotensin II, and angiotensin-converting enzyme [6,7]. Evidence indicates that CCA-IMT is related to changes in local shear stress and tensile stress and may be a direct function of lumen diameter, as a part of the arterial remodeling at early stages of atherosclerosis. In contrast, formed arterial plaques probably represent a later stage of atherogenesis related to inflammation, oxidation, endothelial dysfunction, and/or smooth muscle cell proliferation [8]. The pathologic processes leading to intima-media thickening and to plaque formation therefore may not be similar, and plaque and intima-media thickening may reflect different biological aspects of atherogenesis with distinctive relations to clinical vascular disease. Measurements of plaque may also reflect a different genetic influence than would IMT [9•].

Whereas IMT is solely a quantitative measure that is measured continuously, carotid plaques can be assessed qualitatively (plaque echogenicity, plaque heterogeneity) and quantitatively (plaque numbers, plaque area, plaque volume). As a continuous ultrasound trait, IMT is a relatively insensitive measure of plaque evolution because plaque grows longitudinally along the carotid axis of flow more than two times faster than it thickens [10]. Plaque area may therefore be a more sensitive and representative measure of the atherosclerotic burden than plaque thickness or IMT. Total carotid plaque area is also a stronger predictor of events than IMT [11,12•]. IMT is an established end point for efficacy studies and relatively uniform definitions of IMT exist, compared with a much greater variety in plaque definitions across studies. IMT measurements provide information on risk even when no plaque is present. This is an advantage in population-based studies in which a major proportion of the participants have no plaques. The extent to which these phenotypes predict cardiovascular risk depends in part on the population being studied.

IMT and plaque have been widely used as surrogate end points in interventional trials. However, because the annual rate of IMT progression is below the resolution of carotid ultrasound (~ 0.3 mm), large sample sizes are required to evaluate therapy's effects. Each dimension added (from one-dimensional IMT to two-dimensional plaque area, to three-dimensional [3-D] plaque volume) substantially lowers the sample size and duration of studies required to evaluate new therapies [13••]. Thus far, no studies have been published on the relationship between progression of IMT and clinical end points.

IMT and Plaque as Predictors of Coronary and Cerebrovascular Disease

Population-based studies

Studies on the relationship between IMT and coronary heart disease (CHD) have been conflicting [14]. The association of IMT with coronary atherosclerosis is weaker than its association with left ventricular mass [15,16] and weaker than the association between carotid plaque and coronary atherosclerosis [3,4,17,18]. IMT has also been found to be a better predictor of stroke than of ischemic heart disease and MI [4,19]. Because IMT largely represents medial hypertrophy related to hypertension and a substantial proportion of strokes are due to hypertensive small-vessel disease, it is not surprising that IMT predicts stroke more strongly than it does MI. This probably reflects the differences in the pathologic processes leading to intima-media thickening of the distal part of CCA and plaque formation in the coronary arteries, whereas plaque formation in the carotid and coronary arteries are more closely related [20] and are thought to have similar atherogenesis [21].

Carotid plaque burden as an MI predictor has been evaluated in several large population-based studies. In the Kuopio Ischemic Heart Disease study, CCA-IMT and carotid plaque were studied as risk factors of acute coronary events in 1288 eastern Finnish men [22]. No significant association was found for IMT, whereas the risk (95% CI) for MI in men with nonstenotic and stenotic plaque was 4.2 (1.5–11.5) and 6.7 (1.3–33.9), respectively, compared with men free of any structural changes in the carotid wall at baseline [22]. The CHS observed 4476 persons ≥ 65 years of age for a median of 6.2 years. The adjusted hazards ratio for 1-SD increase in the combined maximal CCA-IMT and ICA-IMT was 1.36 (95% CI, 1.23–1.52) for MI and 1.33 (95% CI, 1.20–1.47) for stroke. The risk associated with the CCA-IMT was lower than that associated with the ICA-IMT (Table 1) [23].

In the ARIC study, carotid IMT was related to CHD incidence over 4 to 7 years of follow-up of nearly 13,000 men and women 45 to 64 years of age who were free of clinical CHD at baseline. Adjusted for age, race, and center, the hazard rate ratio (95% CI) comparing IMT ≥ 1 mm with IMT less than 1 mm was 5.1 (3.1–8.4) for women and 1.9 (1.3–2.7) for men. The association was reduced by including major CHD risk factors, but remained significant [24]. In the ARIC study, CHD risk prediction was assessed by increase in area under receiver operating characteristic curves resulting from adding nontraditional risk factors and IMT to a basic model containing only traditional risk factors. These factors substantially improved prediction of future CHD for men (less for women) and increased attributable risks [25].

Lorenz et al. [26] observed 5056 patients for 4.2 years and found that IMTs at all carotid segments were highly predictive of MI and stroke. The relative risks (95% CI) per 1-SD CCA-IMT increase were 1.43 (1.35–1.51) for MI, 1.47 (1.35–1.60) for stroke, and 1.45 (1.38–1.52) for MI, stroke, or death. Even after adjusting for age, sex, and vascular risk factors, the predictive value of CCA-IMT and bifurcation IMT remained significant for MI and the combined end point [26]. The same authors recently performed a systematic review and meta-analysis to examine IMT's ability to predict future clinical cardiovascular end points. Carotid IMT was found to be a strong predictor of future vascular events, with relative risk per IMT difference slightly higher for stroke than for MI [27••].

In the Rotterdam study, CCA-IMT was related to future stroke and MI in a nested case-control study. The mean duration of follow-up was 2.7 years. Adjusting for age and sex, the odds ratio (95% CI) for stroke per SD IMT increase (0.163 mm) was 1.41 (1.25–1.82). For MI, an odds ratio of 1.43 (1.16–1.78) was found. After additional adjusting for other cardiovascular risk factors, the risk was attenuated but still significant for stroke (odds ratio, 1.34 [1.08–1.67]), but no longer reached significance for MI (odds ratio, 1.25 [0.98–1.58]) [19]. In the

Table 1. Relative risk of stroke and MI as a function of the CCA and ICA IMT expressed as quintiles and as a continuous variable

	Multivariable adjusted relative risk (95% CI)	
Maximal IMT	**MI**	**Stroke**
Maximal CCA IMT		
< 0.87 mm	1.00	1.00
0.87–0.96 mm	1.79 (1.08–2.98)	1.33 (0.83–2.12)
0.97–1.05 mm	1.40 (0.83–2.38)	1.21 (0.76–1.93)
1.06–1.17 mm	2.07 (1.27–3.39)	1.39 (0.88–2.18)
≥ 1.18 mm	2.46 (1.51–4.01)	2.13 (1.38–3.28)
Per 1-SD (0.20-mm) increase	1.24 (1.12–1.38)	1.28 (1.16–1.42)
Maximal ICA IMT		
< 0.90 mm	1.00	1.00
0.91–1.10 mm	1.55 (0.89–2.73)	1.34 (0.84–2.14)
1.11–1.39 mm	2.30 (1.36–3.88)	1.69 (1.09–2.62)
1.40–1.80 mm	2.68 (1.60–4.48)	1.22 (0.77–1.93)
≥ 1.81 mm	3.00 (1.80–5.01)	2.35 (1.55–3.57)
Per 1-SD (0.55-mm) increase	1.34 (1.20–1.50)	1.25 (1.12–1.39)

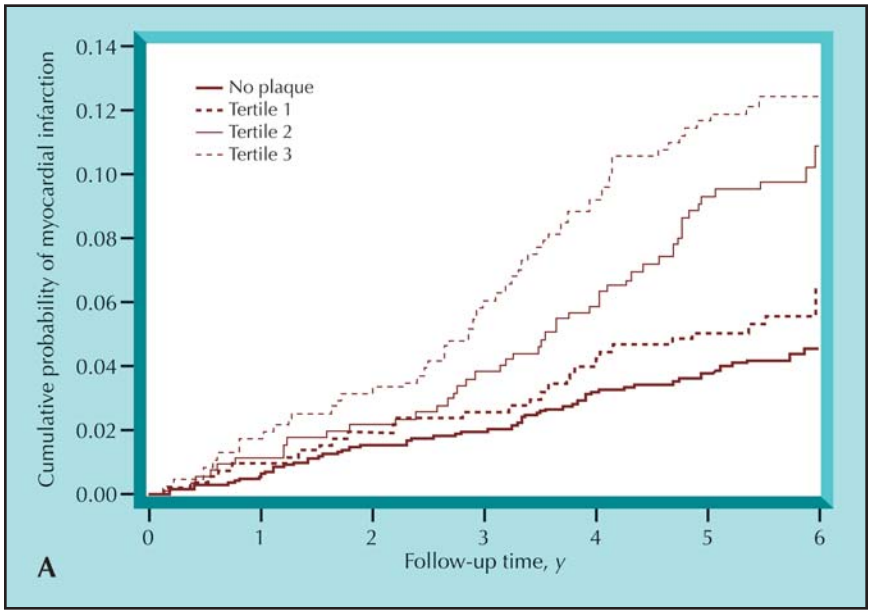
CCA—common carotid artery; ICA—internal carotid artery; IMT—intima-media thickness; MI—myocardial infarction.
(*Data from* O'Leary et al. [23].)

same population, adding IMT to a risk function for CHD and cerebrovascular disease did not result in a substantial increase in the predictive value when used as a screening tool [14]. In the British Regional Heart Study, CCA-IMT, bulb-IMT, and plaque were correlated with each other but showed differing patterns of association with risk factors and prevalent disease. CCA-IMT was strongly associated with risk factors for stroke and with prevalent stroke, whereas bulb-IMT and plaque were more directly associated with ischemic heart disease risk factors and prevalent ischemic heart disease. The analyses suggested that presence of plaque, rather than the thickness of bulb-IMT, was the major criterion of high risk for disease [4].

In the Tromsø study (Fig. 1A and Fig. 1B), carotid IMT and total plaque area (TPA) were studied prospectively as predictors for first-ever MI. Follow-up time was 5.5 years. In multivariable adjusted gender-specific analyses, carotid plaque area was a stronger predictor of first-ever MI than was IMT. When bulb-IMT, and therewith most of the plaques, were excluded from analyses, IMT no longer predicted MI [12•]. In the Tromsø study, stenotic carotid plaque was found to be a strong and independent risk factor for death. The adjusted relative risk of death in persons with stenosis versus controls was 3.47 (95% CI, 1.47–8.19). Carotid stenosis was a stronger predictor of death than self-reported cardiovascular disease or diabetes. The major cause of death was CHD [28]. Similar findings were reported in the Italian CAFES-CAVE study, a 10-year follow-up of more than 13,000 healthy, asymptomatic individuals [29].

Clinical studies

In a study of patients presenting with one or several cardiovascular risk factors, the presence and number of plaques was a stronger predictor of cardiovascular risk compared with IMT [30]. Adams et al. [3] found that IMT was not strongly associated with coronary artery disease (CAD). TPA was more specific and sensitive for detecting coronary stenosis on CT angiography than IMT, C-reactive protein, or coronary calcium score [31•]. Carotid stenosis measured by Doppler velocity was a weaker predictor of risk than TPA for stroke, MI, and death combined [32]. A follow-up study of atherosclerotic patients found a relative risk of 3.4 in the top quartile compared with the lowest quartile of carotid TPA after multivariable adjustment [11]. In a study of asymptomatic hypercholesterolemic patients, carotid plaque demonstrated by B-mode ultrasound significantly improved the diagnostic specificity of exercise electrocardiography in predicting atherosclerotic lesions by coronary angiography [33]. In the Swedish APSIS study, 809 patients with stable angina pectoris were studied prospectively during double-blind treatment with verapamil or metoprolol. Ultrasonographic assessments of IMT, lumen diameter, and plaques in the carotid and femoral arteries were evaluated in a subgroup of 558 patients, and related to the risk of cardiovascular death or nonfatal MI, or revascularization. After adjusting for age, sex, smoking, previous cardiovascular disease, and lipid status, carotid IMT failed to predict any cardiovascular event, whereas carotid plaques tended to predict the risk of cardiovascular death or MI [34].



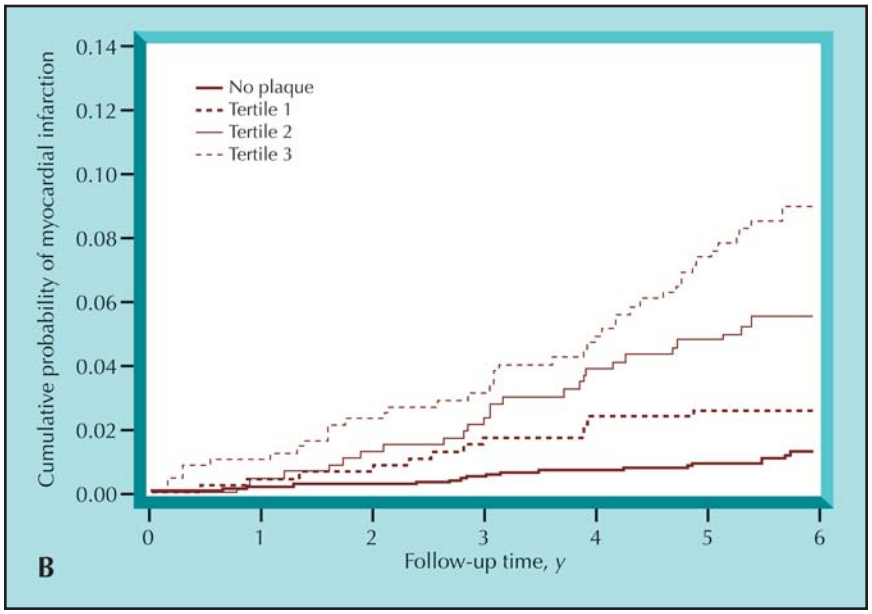


Figure 1. The Tromsø study. **A,** Proportion of myocardial infarction in men according to total plaque area. **B,** Proportion of myocardial infarction in women according to total plaque area. (*Adapted from* Johnsen et al. [12•].)

In a study of 146 men who had previously had coronary artery bypass graft surgery, atherosclerosis in the CCA was evaluated every 6 months with B-mode ultrasonography, and intrusive atherosclerosis in the coronary arteries was evaluated at baseline and at 2 years with quantitative coronary angiography. After the trial, the incidences of coronary events (nonfatal acute MI, coronary death, and coronary artery revascularization) were documented. For each 0.03-mm increase per year in carotid arterial IMT, the relative risk for nonfatal MI or coronary death was 2.2 (95% CI, 1.4–3.6) and the relative risk for any coronary event was 3.1 (CI, 2.1–4.5). Absolute IMT was also related to risk for clinical coronary events [35]. Sakaguchi et al. [36] found that plaque score and bulb-ICA IMT were equally effective and could be better than CCA-IMT for predicting coronary lesions in a population with cardiovascular risk.

A case-control study by Raso et al. [37] evaluated the association between IMT and the presence and extent of CAD and the presence of left ventricular hypertrophy. The patients with CAD had significantly increased IMT compared to patients without CAD. After adjusting for classic risk factors, IMT was found to increase with the number of coronary vessels affected. IMT of the common carotid arteries was significantly increased in patients with left ventricular hypertrophy [37].

Plaque echogenicity and risk of stroke

Plaque characteristics associated with vulnerable plaques can be assessed by ultrasound. An echolucent (low-echogenicity) plaque typically contains a lipid-rich core, macrophages, and a relatively low content of collagen, and may contain hemorrhage. Echogenic (echorich) plaques

have a higher content of collagen and dense fibrous tissue and may have various amounts of calcification.

The first study showing an association between plaque echogenicity and stroke was reported by Johnson et al. [38] in 1985. After 3 years of follow-up of 297 asymptomatic patients, 51% with echolucent plaques had experienced transient ischemic attack or stroke, compared with 4.4% of patients with echogenic plaques. Similar results have been shown later in several prospective studies, both population-based and clinical studies. In the CHS, the relative risk of ipsilateral stroke for echolucent plaques was 2.78 (95% CI, 1.36–5.69). In the Tromsø study, the adjusted relative risk for cerebrovascular events in individuals with echolucent stenotic plaques was 4.6 (95% CI, 1.1–18.9), compared to individuals without stenosis, and a significant linear trend existed for higher risk with increasing plaque echolucency [39]. In a study on symptomatic patients with carotid stenosis, the relative risk of ischemic stroke for echolucent versus echorich plaques was 3.1 (95% CI, 1.3–7.3) [40]. Liapis et al. [41] demonstrated that echolucency of plaques removed by endarterectomy was associated with restenosis and with the combined end point of MI and stroke. A higher frequency of cerebrovascular microembolic signals and symptoms has also been reported in patients with echolucent plaques [42,43].

Plaque echogenicity and risk of MI

Can ultrasound-assessed plaque morphology (echogenicity) of one arterial territory reflect the individual's plaque morphology in other arterial territories due to a common underlying systemic factor? This possibility has been suggested [44–47]. Several clinical studies have demonstrated that echolucent or unstable carotid plaques predicted coronary plaque complexity and the development of future coronary complications in patients with stable CAD [45,47]. Association between carotid plaque echolucency and CHD has been reported in cross-sectional studies [48,49] and prospective studies [12•,45]. Honda et al. [45] investigated the echogenicity of carotid plaques by integrated backscatter analysis in 286 consecutive CAD patients (71 with acute coronary syndrome and 215 with stable CAD). The presence of echolucent carotid plaques predicted future coronary events independent of other risk factors (hazard ratio, 7.0; 95% CI, 2.3–21.4) [45]. In the Tromsø study, we found a significant trend toward a higher MI risk with more echolucent plaque in women, but not in men [12•]. The unadjusted relative risk for MI was more than five times higher in women in the lowest gray-scale median tertile than in women without plaque, and when adjusted for other cardiovascular risk factors, the risk was 2.79 (95% CI, 1.45–5.37). Statin treatment has been shown to stabilize and increase carotid plaque echogenicity in patients with CHD [50,51].

Conclusions

Carotid IMT is a strong predictor of future vascular events. The relative risk per IMT difference is slightly higher for the end point of stroke than for MI.

New evidence suggests that TPA is the most strongly predictive of cardiovascular risk of the ultrasound phenotypes. Echolucent carotid plaques are associated with increased risk of stroke and MI. At present, studies are evaluating plaque volume and vessel wall volume measured by 3-D ultrasound, as well as ulceration of carotid plaques assessed by 3-D ultrasound, as predictors of cardiovascular events.

Clinical Trial Acronyms

APSIS—Angina Prognosis Study in Stockholm; ARIC—Atherosclerosis Risk in Communities; CAFES-CAVE—Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects; CHS—Cardiovascular Health Study.

Disclosures

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Bonithon-Kopp C, Touboul PJ, Berr C, et al.: **Relation of intima-media thickness to atherosclerotic plaques in carotid arteries. The Vascular Aging (EVA) study.** *Arterioscler Thromb Vasc Biol* 1996, **16:**310–316.
2. Bots ML, Hofman A, De Jong PT, Grobbee DE: **Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam study.** *Ann Epidemiol* 1996, **6:**147–153.
3. Adams MR, Nakagomi A, Keech A, et al.: **Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease.** *Circulation* 1995, **92:**2127–2134.
4. Ebrahim S, Papacosta O, Whincup P, et al.: **Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study.** *Stroke* 1999, **30:**841–850.
5. Glagov S, Zarins C, Giddens DP, Ku DN: **Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries.** *Arch Pathol Lab Med* 1988, **112:**1018–1031.
6. Tabara Y, Kohara K, Nakura J, Miki T: **Risk factor-gene interaction in carotid atherosclerosis: effect of gene polymorphisms of renin-angiotensin system.** *J Hum Genet* 2001, **46:**278–284.
7. Chapman CM, Palmer LJ, McQuillan BM, et al.: **Polymorphisms in the angiotensinogen gene are associated with carotid intimal-medial thickening in females from a community-based population.** *Atherosclerosis* 2001, **159:**209–217.

8. Hegele RA: **The pathogenesis of atherosclerosis.** *Clin Chim Acta* 1996, **246:**21–38.
9. • Pollex RL, Hegele R: **Genetic determinants of carotid ultrasound traits.** *Curr Atheroscler Rep* 2006, **8:**206–215.
Review of the most recent available data (reports published since 2004) on the genetic determinants of atherosclerosis as measured by one-dimensional, two-dimensional, and 3-D ultrasonography of the carotid arteries.
10. Barnett PA, Spence JD, Manuck SB, Jennings JR: **Psychological stress and the progression of carotid artery disease.** *J Hypertens* 1997, **15:**49–55.
11. Spence JD, Eliasziw M, DiCicco M, et al.: **Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy.** *Stroke* 2002, **33:**2916–2922.
12.• Johnsen SH, Mathiesen EB, Joakimsen O, et al.: **Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromsø study.** *Stroke* 2007, **38:**2873–2880.
A large, prospective, population-based study comparing plaque area versus IMT as a predictor of MI.
13.•• Spence JD: **The importance of distinguishing between diffuse carotid intima medial thickening and focal plaque.** *Can J Cardiol* 2008, **24(Suppl C):**61C–64C.
Insightful review of the different ultrasound-assessed atherosclerotic phenotypes, their correlation to risk factors, and prediction of cardiovascular risk.
14. del Sol AI, Moons KG, Hollander M, et al.: **Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam study.** *Stroke* 2001, **32:**1532–1538.
15. Cuspidi C, Lonati L, Sampieri L, et al.: **Left ventricular concentric remodelling and carotid structural changes in essential hypertension.** *J Hypertens* 1996, **14:**1441–1446.
16. Linhart A, Gariepy J, Giral P, et al.: **Carotid artery and left ventricular structural relationship in asymptomatic men at risk for cardiovascular disease.** *Atherosclerosis* 1996, **127:**103–112.
17. Megnien JL, Simon A, Gariepy J, et al.: **Preclinical changes of extracoronary arterial structures as indicators of coronary atherosclerosis in men.** *J Hypertens* 1998, **16:**157–163.
18. Aminbakhsh A, Frohlich J, Mancini GB: **Detection of early atherosclerosis with B mode carotid ultrasonography: assessment of a new quantitative approach.** *Clin Invest Med* 1999, **22:**265–274.
19. Bots ML, Hoes AW, Koudstaal PJ, et al.: **Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam study.** *Circulation* 1997, **96:**1432–1437.
20. Spence JD, Hegele RA: **Noninvasive phenotypes of atherosclerosis: similar windows but different views.** *Stroke* 2004, **35:**649–653.
21. Craven TE, Ryu JE, Espeland MA, et al.: **Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis. A case-control study.** *Circulation* 1990, **82:**1230–1242.
22. Salonen JT, Salonen R: **Ultrasonographically assessed carotid morphology and the risk of coronary heart disease.** *Arterioscler Thromb* 1991, **11:**1245–1249.
23. O'Leary DH, Polak JF, Kronmal RA, et al.: **Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group.** *N Engl J Med* 1999, **340:**14–22.
24. Chambless LE, Heiss G, Folsom AR, et al.: **Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) study, 1987-1993.** *Am J Epidemiol* 1997, **146:**483–494.
25. Chambless LE, Folsom AR, Sharrett AR, et al.: **Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study.** *J Clin Epidemiol* 2003, **56:**880–890.
26. Lorenz MW, von Kegler S, Steinmetz H, et al.: **Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS).** *Stroke* 2006, **37:**87–92.
27.•• Lorenz MW, Markus HS, Bots ML, et al.: **Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis.** *Circulation* 2007, **115:**459–467.
Informative review of the most important prospective population-based studies using IMT as a predictor of cardiovascular events.
28. Joakimsen O, Bønaa KH, Mathiesen EB, et al.: **Prediction of mortality by ultrasound screening of a general population for carotid stenosis: the Tromsø study.** *Stroke* 2000, **31:**1871–1876.
29. Belcaro G, Nicolaides AN, Ramaswami G, et al.: **Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study(1)).** *Atherosclerosis* 2001, **156:**379–387.
30. Tartiere JM, Henry OF, Safar H, et al.: **Carotid intima-media thickness and carotid and/or iliofemoral plaques: comparison of two markers of cardiovascular risk in hypertensive patients.** *J Hypertens* 2003, **21:**739–746.
31.• Brook RD, Bard RL, Patel S, et al.: **A negative carotid plaque area test is superior to other noninvasive atherosclerosis studies for reducing the likelihood of having underlying significant coronary artery disease.** *Arterioscler Thromb Vasc Biol* 2006, **26:**656–662.
A comparison of coronary calcium score, carotid plaque area, IMT, and C-reactive protein's risk-stratifying abilities for coronary stenosis.
32. Iemolo F, Martiniuk A, Steinman DA, Spence JD: **Sex differences in carotid plaque and stenosis.** *Stroke* 2004, **35:**477–481.
33. Giral P, Bruckert E, Dairou F, et al.: **Usefulness in predicting coronary artery disease by ultrasonic evaluation of the carotid arteries in asymptomatic hypercholesterolemic patients with positive exercise stress tests.** *Am J Cardiol* 1999, **84:**14–17.
34. Held C, Hjemdahl P, Eriksson SV, et al.: **Prognostic implications of intima-media thickness and plaques in the carotid and femoral arteries in patients with stable angina pectoris.** *Eur Heart J* 2001, **22:**62–72.
35. Hodis HN, Mack WJ, LaBree L, et al.: **The role of carotid arterial intima-media thickness in predicting clinical coronary events.** *Ann Intern Med* 1998, **128:**262–269.
36. Sakaguchi M, Kitagawa K, Nagai Y, et al.: **Equivalence of plaque score and intima-media thickness of carotid ultrasonography for predicting severe coronary artery lesion.** *Ultrasound Med Biol* 2003, **29:**367–371.
37. Raso FM, van Popele NM, Schalekamp MA, van der Cammen TJ: **Intima-media thickness of the common carotid arteries is related to coronary atherosclerosis and left ventricular hypertrophy in older adults.** *Angiology* 2002, **53:**569–574.
38. Johnson JM, Kennelly MM, Decesare D, et al.: **Natural history of asymptomatic carotid plaque.** *Arch Surg* 1985, **120:**1010–1012.
39. Mathiesen EB, Bønaa KH, Joakimsen O: **Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the Tromsø study.** *Circulation* 2001, **103:**2171–2175.
40. Grønholdt ML, Nordestgaard BG, Schroeder TV, et al.: **Ultrasonic echolucent carotid plaques predict future strokes.** *Circulation* 2001, **104:**68–73.
41. Liapis CD, Kakisis JD, Dimitroulis DA, Kostakis AG: **The impact of the carotid plaque type on restenosis and future cardiovascular events: a 12-year prospective study.** *Eur J Vasc Endovasc Surg* 2002, **24:**239–244.
42. Sztajzel R, Momjian-Mayor I, Comelli M, Momjian S: **Correlation of cerebrovascular symptoms and microembolic signals with the stratified gray-scale median analysis and color mapping of the carotid plaque.** *Stroke* 2006, **37:**824–829.

43. Madycki G, Staszkiewicz W, Gabrusiewicz A: **Carotid plaque texture analysis can predict the incidence of silent brain infarcts among patients undergoing carotid endarterectomy.** *Eur J Vasc Endovasc Surg* 2006, **31:**P373–380.
44. Rothwell PM, Villagra R, Gibson R, et al.: **Evidence of a chronic systemic cause of instability of atherosclerotic plaques.** *Lancet* 2000, **355:**19–24.
45. Honda O, Sugiyama S, Kugiyama K, et al.: **Echolucent carotid plaques predict future coronary events in patients with coronary artery disease.** *J Am Coll Cardiol* 2004, **43:**1177–1184.
46. Cohen A, Tzourio C, Bertrand B, et al.: **Aortic plaque morphology and vascular events: a follow-up study in patients with ischemic stroke. FAPS Investigators. French Study of Aortic Plaques in Stroke.** *Circulation* 1997, **96:**3838–3841.
47. Saito D, Shiraki T, Oka T, et al.: **Morphologic correlation between atherosclerotic lesions of the carotid and coronary arteries in patients with angina pectoris.** *Jpn Circ J* 1999, **63:**522–526.
48. Triposkiadis F, Sitafidis G, Kostoulas J, et al.: **Carotid plaque composition in stable and unstable coronary artery disease.** *Am Heart J* 2005, **150:**782–789.
49. Seo Y, Watanabe S, Ishizu T, et al.: **Echolucent carotid plaques as a feature in patients with acute coronary syndrome.** *Circ J* 2006, **70:**1629–1634.
50. Watanabe K, Sugiyama S, Kugiyama K, et al.: **Stabilization of carotid atheroma assessed by quantitative ultrasound analysis in nonhypercholesterolemic patients with coronary artery disease.** *J Am Coll Cardiol* 2005, **46:**2022–2030.
51. Nakamura T, Obata JE, Kitta Y, et al.: **Rapid stabilization of vulnerable carotid plaque within 1 month of pitavastatin treatment in patients with acute coronary syndrome.** *J Cardiovasc Pharmacol* 2008, **51:**365–371.