An Update on Carotid Ultrasound Measurement of Intima-Media Thickness

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Coronary atherosclerosis is a chronic, multifactorial disease process. Some individuals with atherosclerosis receive treatment in the form of mechanical or pharmacologic interventions after an acute event has occurred. Others receive treatment in the form of risk factor–based systemic intervention, the effectiveness of which is assessed by its ability to prevent an acute event. Surrogate endpoints in the study of atherosclerosis interventions are needed to better define disease course and disease response to interventions during the prolonged asymptomatic period. Several techniques for assessing arterial health are available, including quantitative intima-media thickness (QIMT) measurement by carotid ultrasound. QIMT is a safe, validated, and portable method that may prove highly useful in screening for atherosclerosis and in providing a surrogate measure for response to disease interventions. **©2002 by Excerpta Medica, Inc.**

Am J Cardiol 2002;89(suppl):32B–39B

Complications of atherosclerosis occur suddenly, but they are a very long time and asymptomatic in the making. Most health professionals in the field agree on how atherosclerosis develops. A normal healthy endothelium is exposed to a variety of damaging factors. Eventually, the healthy tissue is injured and endothelial dysfunction results. If the damage persists, raised lesions in the vessel wall and atherosclerotic plaques develop, carrying the risk of plaque vulnerability and rupture.[1,2] Familiarity with the course of disease is vital in determining how to develop and use surrogate markers in clinical trials, because different markers may be more appropriate at different stages of cardiovascular disease (Figure 1).[3] The notion that we do not need such markers and can rely instead on observation of symptomatic disease to trigger treatment or to evaluate effectiveness of treatment is based on a number of incorrect assumptions about the disease process. One assumption is that acute treatment of a disease event constitutes treatment of the disease; this assumption appears to be coupled with the assumption that reversal of disease is still an option after an acute event has occurred. Acute events are almost always treatable, and treatment may prevent damage to the heart or vessels. However, it is well known that in ≥25% of patients with coronary artery disease, their first symptom of disease is sudden cardiac death. The likelihood of reversibility is also thrown into question because about 40% of cardiac patients have normal blood pressure and/or normal blood cholesterol levels.

It also seems to be tacitly assumed that intervention based on a single risk factor has a neutral effect on the many other potential factors involved in disease progression or in protection from disease—some 250 potential factors by recent count.[4] This seems highly unlikely, particularly in the case of systemic therapy that must be administered for prolonged durations. For example, β-blocker therapy may reduce blood pressure but may also adversely affect lipid metabolism. Such potential effects go unrecognized if the effect of treatment is assessed as effect on the risk factor rather than on the disease process itself—that is, if measures of the effects of treatment on the disease process itself are not available or are not used. Similarly, assessing response to treatment (and putative effect on disease course), by assessing response of the risk factor targeted by treatment, fails to take into account the different degrees to which different risk factors may contribute to disease course at different stages of the disease. Most recognized risk factors do not exhibit a linear relation with disease progression. As shown in Figure 2, the relation of major reversible risk factors to risk of progression varies, indicating that the time point at which the risk factor is assessed is important in determining the impact of the risk factor. Figure 2A shows the linear relation between smoking and progression of disease. Figure 2B shows the relation between serum cholesterol and risk of progression. A threshold value needs to be exceeded before excess levels contribute exponentially to progression, reflecting the physiologic requirement for cholesterol and reminding us that there is some limit to the dictum of "the lower the better." Figure 2C displays the famous "J curve" association of hypertension and risk, and Figure 2D shows the "inverse S curve" association of lack of exercise with disease progression.

Some individuals with normal cholesterol levels have major coronary events. Others with very high cholesterol levels do not have coronary events. With regard to the latter, consider a recent report of Sijbrands et al,[5] who assessed 200 years of a Dutch familial hypercholesterolemia pedigree and found that, although the family members were hypercholesterolemic, 40% of them had a normal life span. Instead of using different risk-factor measurements, a triage using quantitative intima-media thickness (QIMT) as surrogate endpoint would help disease management.

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0002-9149/02/$ – see front matter
PII S0002-9149(01)02329-3

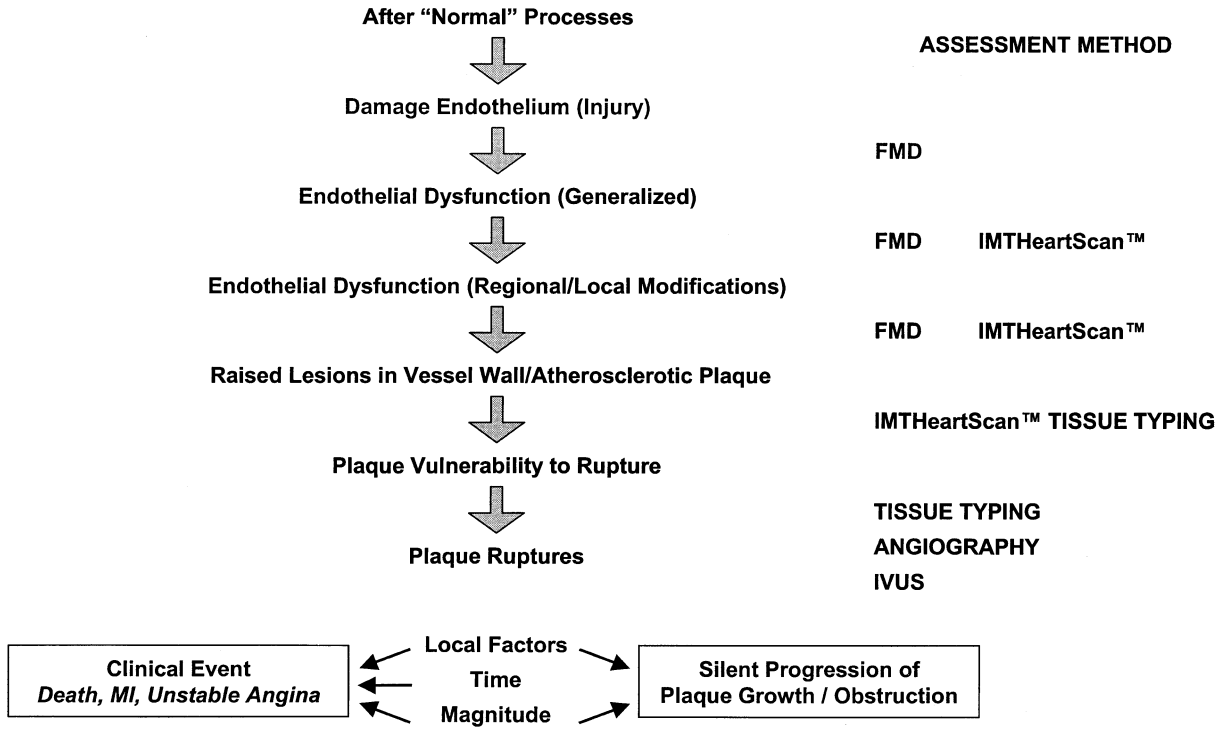

FIGURE 1. Sequence of events leading to adverse outcomes in coronary artery disease if cardiovascular risk factors persist, and proposed technique for assessing disease or response at disease stage. FMD = flow-mediated dilation (via IMTHeartScan; Ultrascan Health Technologies, Salt Lake City, UT); IMT = intima-media thickness; IVUS = intravascular ultrasonography; MI = myocardial infarction. (Reprinted with permission from *Am J Cardiol.*[3])

After all, the disease itself should be treated and not a risk factor for the disease. It would appear that the precise mechanism of disease course in such individuals is better determined by a surrogate marker of the disease itself than by evaluation of a risk factor, and that management of disease, as assessed by such a marker, may be preferable to management of the risk factor for disease.

A surrogate endpoint is a biomarker intended to substitute for a clinical endpoint in a clinical trial. Surrogate markers have some inherent limitations. For example, response, as determined using the surrogate marker, may not translate into clinical benefit or survival benefit and may not be intervention dependent. Nevertheless, the wait for clinical endpoints, such as revascularizations, angina, and acute myocardial infarction in the prolonged asymptomatic phase of disease, can be as long as a decade.[6] Development of surrogate markers allows us to establish prevention measures during this time frame, and it is hoped that these measurements will provide us a safe, noninvasive, and reproducible method for assessing the progression and change of the disease.

Several noninvasive vascular imaging procedures have been developed as potential surrogate measures of disease. It is important to determine whether such techniques can provide a useful surrogate endpoint to identify high-risk subjects. The focus of this report is on carotid ultrasound measurement of intima-media thickness (IMT).

QIMT is a safe, standardized, and validated method that uses ultrasound images and permits quantitative measurements. As with intravascular ultrasonography, QIMT provides a direct assessment of disease. It is suitable for use in all stages of atherosclerotic disease, permitting both diagnosis and follow-up evaluation of disease. Specific advantages of QIMT are: (1) portability, (2) the existence of a large reference database, and (3) relatively low cost. The large database (>26,000 individuals) of Prevention Concepts, Inc. (PCI, West Los Angeles, CA), with a long-term follow-up period (≤10 years) of different populations and ethnic groups, makes a reliable outcome prediction for cardiovascular and cerebrovascular complications a reality. QIMT findings correlate with (1) cardiac and cerebrovascular outcome; (2) absolute and relative risk, as assessed by cardiovascular risk factors; and (3) change in risk during disease management.[7–11] The technique has now been used as the sole surrogate endpoint in the additional approval process of a number of lipid-modifying compounds.

Data from the 10-year follow-up study of the Atherosclerosis Risk in Communities (ARIC) study indicate that the findings, made by imaging the far wall of the common carotid artery, correlate well with all major risk factors.[12] This confirms our earlier finding during the Cholesterol Lowering Atherosclerosis Study (CLAS) that carotid IMT 1 cm below the bulb was reproducible and showed a remarkable correlation with cardiovascular events during 10 years of follow-up study.[8,9] A striking finding of that early research was that there was no discrepancy over time

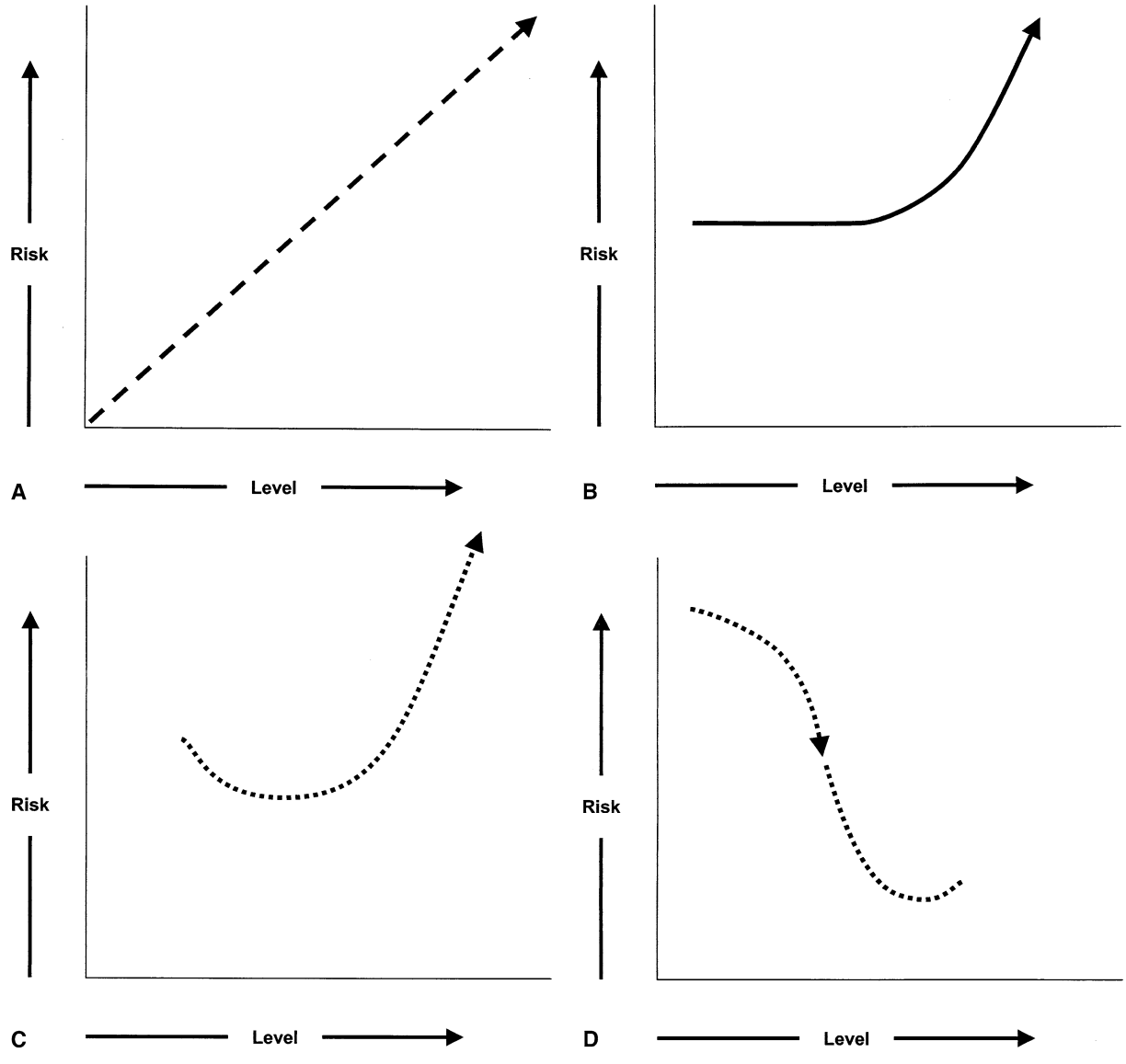

FIGURE 2. Relation between level of risk factor and risk of progression of disease events for smoking (*A*), serum cholesterol (*B*), systolic blood pressure (*C*), and lack of exercise (*D*).

between direction of disease in coronary arteries on angiography and on imaging of the carotid IMT; with hindsight, we appreciate that we had already identified those patients who would benefit from lipid lowering with a combination of colestipol and niacin after an intervention of only 6 months (Figure 3).[13] Data from the Monitored Atherosclerosis Regression Study (MARS) confirmed these findings in patients receiving statin therapy.[14] Subsequently, in the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC II) study, Byington et al[15] confirmed that the part of the carotid tree that most reliably indicated the efficacy of lipid lowering in the coronary tree was the far wall of the common carotid artery. In this study, no other imaging point, not even the aggregate of 12 different points, was significantly correlated with progression or regression of disease. Other studies that we have conducted with different lipid-lowering agents (eg, rosuvastatin) provide further support for the finding that only the assessment of the far wall of the common carotid artery shows significant correlation with coronary artery changes. An explanation can be found by considering the rheology in the carotid tree (Figure 4)[16]; laminar flow indicative of generalized atherosclerosis is present only proximal to the bulb. The coronary arteries also adhere to the laws of physics and therefore have a similar impact on changes in blood flow. These findings are of particular interest, because image acquisition of 12 points is a much more time-consuming process than image acquisition of 1 reliable area, and the analyses of these points cannot always be done by other groups with a computerized system. In addition, we should realize that plaque formation in the bulb is more dependent on different risk factors than those for coronary artery disease. Risk factors for the development of cardiovascular plaque formation seems to be different than thickness of the IMT.[17]

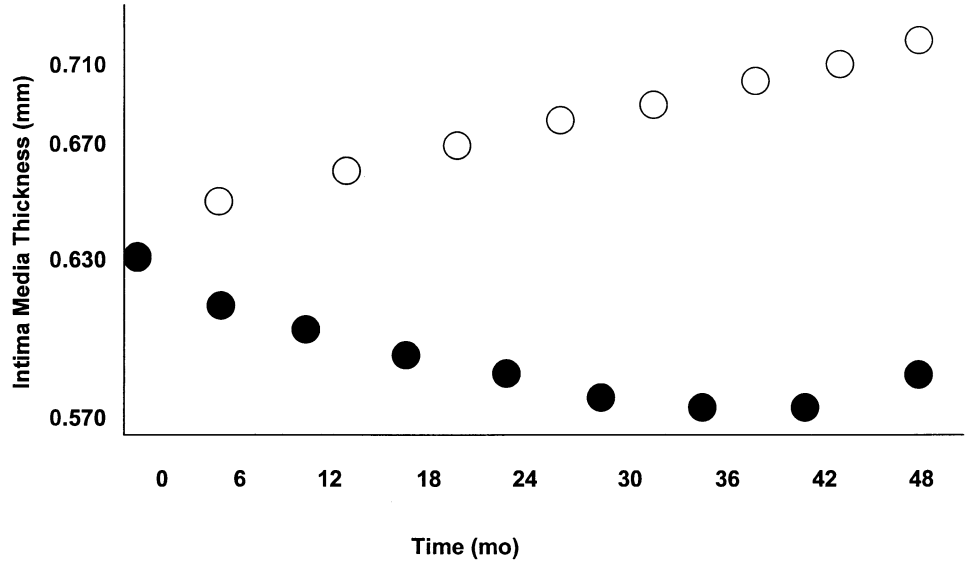

FIGURE 3. Change in carotid intima-media thickness during 48 months of treatment with colestipol/niacin (*solid circles*) or placebo (*open circles*) in the Cholesterol Lowering Atherosclerosis Study (CLAS). (Adapted with permission from *Arterioscler Thromb.*[13])

Figure 5 shows 2 examples of digitized images of the common carotid artery in 2 patients matched for age, sex, and ethnicity. The patient on the right has hypercholesterolemia and hypertension; the patient on the left does not have these major reversible risk factors. It is notable that the near wall of the common carotid artery is difficult to assess, because the focus can be on only 1 part of the picture.

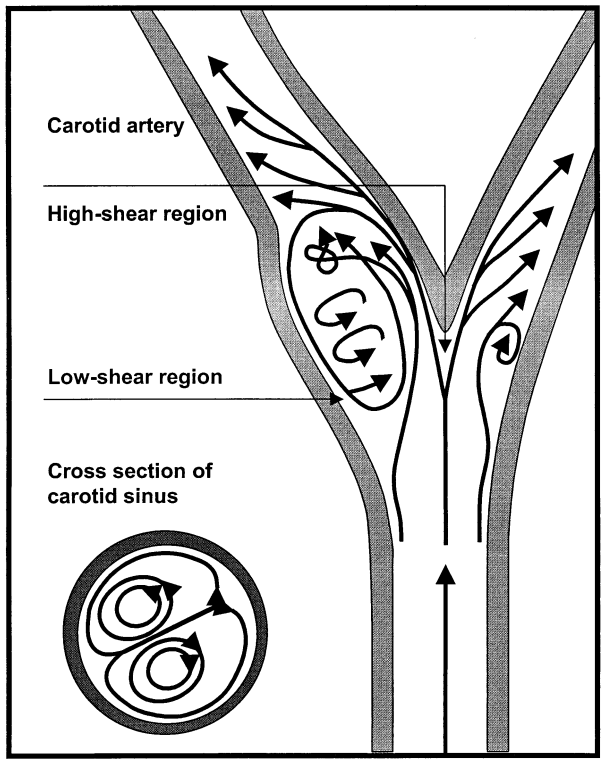

FIGURE 4. Depiction of the carotid artery showing the region of flow separation with formation of secondary vortices. Although flow remains laminar and mainly unidirectional in the high-shear flow-divider area, a very low-shear area is present on the lateral wall of the internal carotid artery. This area is where plaques are most likely to form and where blood flow accelerates with each cardiac cycle. (Adapted with permission from *Stroke.*[16])

The availability of our large QIMT database has enabled us to establish that the measurement of the far wall of the common carotid artery alone is the most reliable and reproducible measurement for predicting coronary disease. In addition, our comparisons of manual and quantitative assessments have made it clear that a computerized contour detection technique is far more reproducible and accurate than caliper or manual assessment (Figure 6). We found that according to standardized measures, the computer program was 4 times more accurate than the caliper IMT, and repeated caliper measurements were within the normal variation of the technique.

The predictive value of QIMT has been established in a number of populations. Smoking, blood pressure, and low socioeconomic status are each correlated with carotid IMT.[18–20] Lakka et al[18] found that blood pressure was significantly correlated with carotid IMT. Postprandial blood sugar correlates with IMT in individuals without diabetes, as does duration of disease in patients with diabetes.[21,22] In addition, Hanefeld et al[21] established that plasma blood sugar level is an independent risk factor for increased carotid IMT in individuals without diabetes. The impact of troglitazone on IMT was found to be dramatic in diabetes patients.[23] Both Diez-Roux et al[24] and Salonen et al[25] found that smoking and secondary smoking had a potent effect on progression of carotid atherosclerosis. Nevertheless, the predictive accuracy of QIMT varies among different cultures,[26] with Woo et al[27] warning that it is sometimes difficult to extrapolate findings among individuals with different ethnic backgrounds. Baldassarre et al[28] investigated the use of IMT to manage risk factors in the clinical setting, supporting

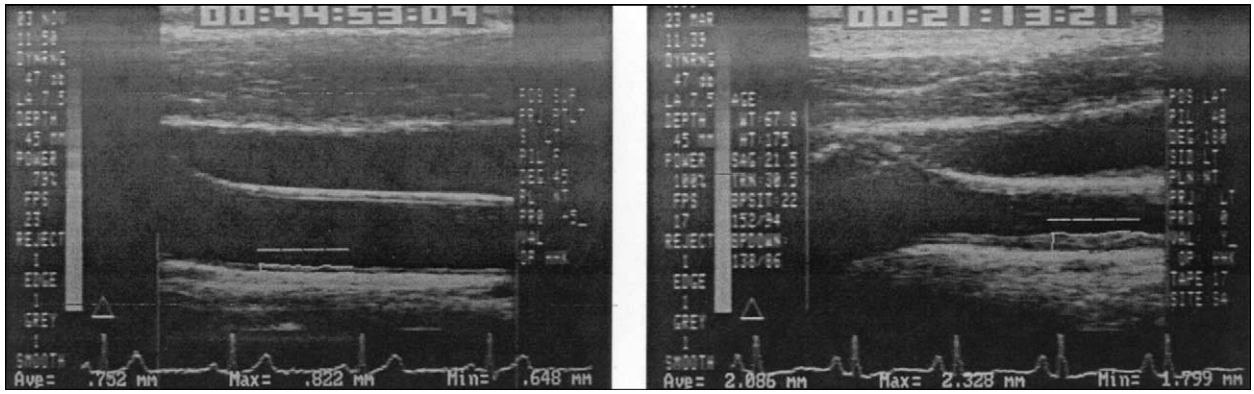

FIGURE 5. Digitized images of the common carotid artery (on the right side of each picture) and the bulb (on the left side of each picture). The far wall of the common carotid is visible in both pictures, as is the jugular vein, which is located above and parallel to the common carotid artery. The 1-cm ruler in the middle of the artery indicates where analyses were done. The picture on the right shows the thickened value in a patient with some hypertension and hypercholesterolemia, whereas the picture on the left shows the value for a patient matched by age, sex, and ethnicity but without hypercholesterolemia and hypertension. Note the fussy boundaries in the near wall above the ruler. (Pictures using the Arterial Imaging Software [ARTIS] postprocessing software system, courtesy of Prevention Concepts, Inc., West Los Angeles, CA).

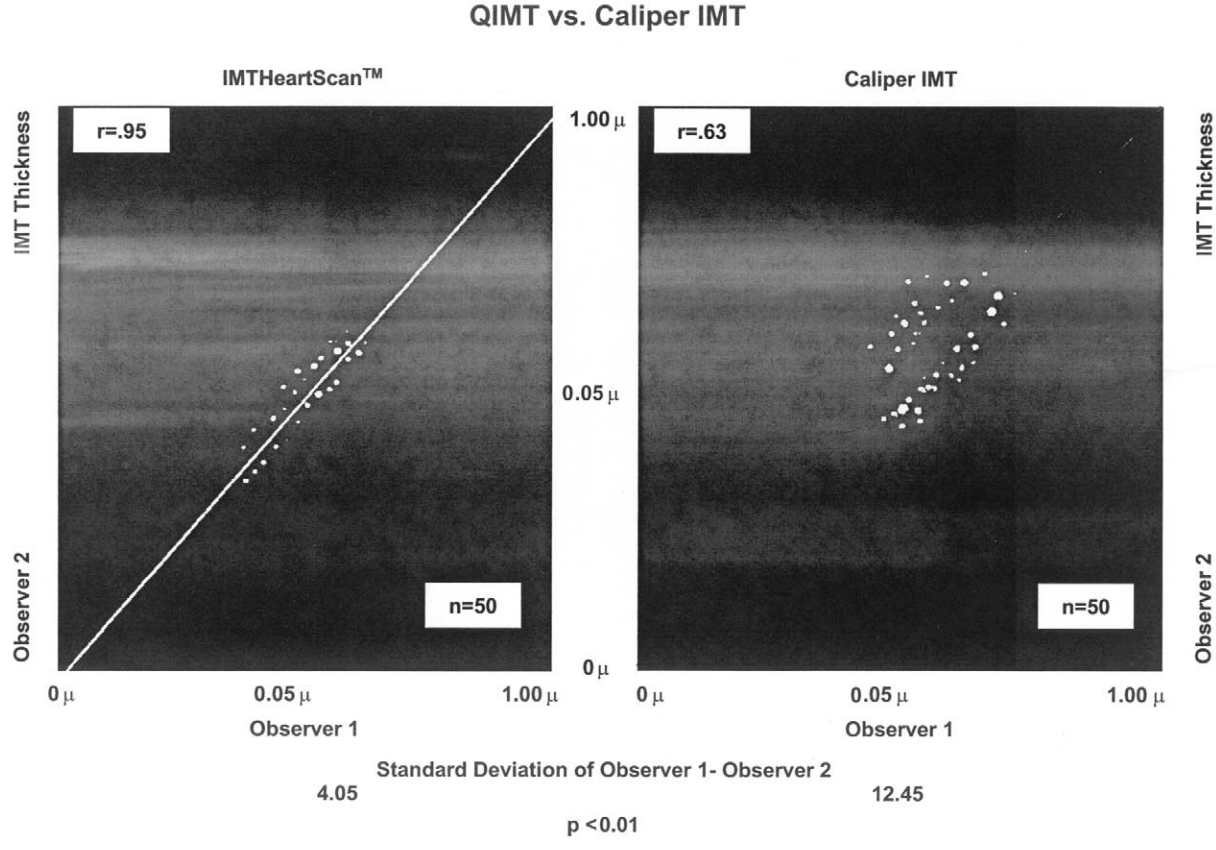

FIGURE 6. Quantitative intima-media thickening (QIMT; IMTHeartScan, Ultrascan Health Technologies, Salt Lake City, UT) versus caliper intima-media thickening. Comparison of absolute laser-measured carotid intima-media thickness (IMT) by user-pointed caliper method with 2 operators (*right*) and the same measurement by the same 2 experienced operators using QIMT with a computerized edge contour measurement technique (*left*). (Reprinted with permission from *Am J Cardiol.*[3])

our experience of using IMT as a triage point for further risk-factor management. IMT also predicts plaque formation in men and women, independently of baseline plaque.[29] Indeed, a study we performed in 13- to 17-year-old high school students showed that 10% were hypertensive, 15% were hypercholesterolemic, and 14% had a carotid atherosclerotic lesion.[30] This rate of atherosclerosis is consistent with the rate of 17% found by Tuzcu et al[31] in intravascular ultrasound transplant studies in a young population. Moreover, providing these young individuals with a customized image of their carotid artery led many to

make lifestyle changes, including weight loss, diet improvement, and cessation of smoking,[30] consistent with other findings we have obtained in a large, patient group.[32] In this latter group, IMT decreased over time in the patients given a customized picture of their artery.

Risk factors for the development of cardiovascular plaque formation seem to be different than risk factors for IMT thickness.[17] In our experience, about 40% of plaques are asymptomatic. In these plaques, which are mostly located in the bulb, tissue type rather than plaque size is the most important factor for determining vulnerability to rupture. It has been shown that calcified plaques are not correlated with stroke, whereas soft plaques have a greater likelihood of rupturing and causing stroke; therefore, an analysis of the constituents of the plaques is critical.[33,34] The Plaque Tissue Typing option provided by Arterial Imaging Software (ARTIS; PCI) can help us to determine whether a plaque has a thin vulnerable cap, which would make it more likely to rupture than a stable plaque with a relatively small cholesterol core. This computerized system enables us to discriminate between "hot" and "cold" plaques, the former implying a plaque with increased likelihood of vulnerability and rupture and the latter implying a stable plaque. These findings have been validated, and they indicate that plaque tissue typing would be of great benefit.

Other noninvasive imaging techniques include (1) measurement of flow-mediated dilation (FMD), (2) electron-beam computed tomography (EBCT) measurement of calcium, and (3) magnetic resonance imaging. FMD assessment of endothelial function is a good surrogate measure of initial risk for atherosclerosis. It indicates very early disease, shows rapid response to change, is an ambulatory method, and may better reflect pathophysiologic response. However, outcome studies with FMD are lacking, and disadvantages exist, including absence of standards, operator sensitivity of the procedure, and inability to track changes because dysfunction either is or is not present on testing. A study by a group comparing angiography and FMD in evaluating coronary artery disease in patients and in asymptomatic control subjects showed that FMD was better than angiography or cholesterol level in identifying the extent of disease.[35]

Another study, evaluating patients with clinical signs of coronary disease and matched control subjects without disease, showed a significant negative correlation between FMD and QIMT, with the investigators concluding that FMD dysfunction may be a precursor to atherosclerosis.[36,37]

EBCT detects calcifications in the coronary arteries, and its interpretation assumes that cardiovascular disease parallels extent of calcification. We already know that soft, not calcified, plaques are the vulnerable plaques, which is why the American Heart Association/American College of Cardiology (AHA/ACC) expert panel statement did not support EBCT.[38] My recent editorial conveys the same blunt message at greater length.[39] Magnetic resonance imaging has high sensitivity and specificity for ex vivo plaque characterization. Use of magnetic resonance imaging may be feasible in the near future in a clinical setting, but the costs of this procedure prohibit its routine clinical use at this time. In addition, magnetic resonance imaging is still too experimental for use as an endpoint.[40]

Atherosclerosis is prevalent in all countries, and clinical trials can be conducted globally in this type of disease. Therefore, availability of various tests must be considered, because many countries do not have facilities similar to those in Western countries, which limits the ability to translate findings consistently from country to country.[26,27]

CONCLUSION

In conclusion, atherosclerosis is a multifactorial disease, resulting from interaction of multiple risk factors with varying effect over a prolonged course. Thus, it is preferable to study the disease and not just the risk factors for the disease. Furthermore, with many patients not having an abnormal cardiovascular risk factor profile, a noninvasive low-cost technique for assessing is disease imperative. QIMT is an appropriate technique for use as a surrogate marker both to screen for disease and to manage disease when risk factors are being modified. QIMT/FMD might be added to several ongoing studies to evaluate the best marker for different stages of cardiovascular disease. FMD might be especially suitable if no obstructive disease is present, because FMD can detect whether a pathophysiologic state is present. When cardiovascular risk is present, QIMT is the best method, if there is endothelial dysfunction and suspected thickening of the far wall of the common carotid artery. Given its standardization, QIMT is especially suited to multicenter studies. If there is plaque formation, tissue characterization should be performed.

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DISCUSSION

Alan Guerci, MD (Roslyn, New York, USA): With respect to the drawbacks of electron-beam computed tomography (EBCT), you noted that soft plaques, not calcified plaques, are most vulnerable to rupturing, and that calcified plaques are not correlated with stroke. However, there are abundant data showing that calcified plaque in the coronary arteries is a marker for vulnerable plaque. In a study by von Birgelen et al,[1] pretty much the "bible" on coronary pathology in patients with stable and unstable coronary syndromes, about 1,300 patients undergoing coronary intervention were examined by intravascular ultrasound (IVUS). The investigators, who had no particular reason to be biased for or against EBCT, made a very strong statement that calcified plaque on IVUS is a marker.

Steven E. Nissen, MD (Cleveland, Ohio, USA): I probably know the IVUS literature as well as anyone—and there is more to this issue. Several studies suggest that there is more soft plaque than calcified plaque at the site of plaque rupture. However, the interesting thing is that often both are present, and 1 of the hypotheses generated is that juxtaposition of soft and calcified plaque is a predisposing factor for rupture. This may be why people are making different findings; it may be that having a soft plaque next to a noncompliant structure is associated with rupture—however, we don't know that yet.

Dr. Guerci: A couple of years ago, 2 studies had autopsy data on >1,200 subjects and showed that people dying suddenly or dying of acute myocardial infarction had 3 to 9 times as much coronary calcium as age-matched controls who died accidentally or of other natural causes. Another point is that in a slide Dr. Barth showed, there was a "±" next to EBCT for association with clinical outcome. I'm sorry, but that is just factually incorrect. Every study looking at the issue that I'm aware of has shown a significant asso-

ciation between high calcium score and risk of myocardial infarction or death, consistent with the autopsy data. The question is not whether EBCT predicts hard events, but whether it predicts them as well or better than standard risk factors. Finally, because I believe what we're supposed to be talking about is coronary disease—not stroke or transient ischemic attack—I don't think the correlation of intima-media thickness (IMT)–defined carotid pathology and coronary atherosclerosis is that strong; the number I carry in my head is about 0.4, but Dr. Crouse may know the literature better than I do.

John Robert Crouse III, MD (Winston-Salem, North Carolina, USA): The extent of disease in the carotids correlates with the extent of disease in the coronary arteries with an *r*-value of about 0.5. However, the extent of disease in the left coronary artery correlates with the extent of disease in the right coronary artery with an *r*-value of about 0.5, too. Therefore, the carotid artery correlates as well with the coronary artery as the coronary arteries correlate with each other.

Christie Ballantyne, MD (Houston, Texas, USA): I think that there are great data on IMT from clinical trials. However, the big problem is the jump from carotid artery IMT to the coronary arteries. Trials that have looked at both show a poor correlation between coronary angiographic progression and carotid IMT progression—a correlation value of about 0.2. Therefore, I think the IMT is a great test for the carotids, but that's not the heart. Carotid thickening is driven far more by hypertension.

Dr. Nissen: I think we have to be careful in talking about correlations, because the data we have to date correlate progression of angiographic stenosis in the coronary lumen versus carotid plaque. We don't know the correlation between progression of the carotid plaque and, for example, progression of coronary plaque on IVUS. Maybe they correlate more closely. I think it would be of interest to study whether the people whose plaques progress by IVUS are the same people whose plaques progress by carotid IMT and whose calcium scores progress on EBCT, and, more importantly, whether drug treatment shows benefits using each of these endpoints separately.

1. von Birgelen C, Klinkhart W, Mintz GS, Papatheodorou A, Herrmann J, Baumgart D, Haude M, Wieneke H, Ge J, Erbel R. Plaque distribution and vascular remodeling of ruptured and nonruptured coronary plaques in the same vessel: an intravascular ultrasound study in vivo. *J Am Coll Cardiol* 2000;37: 1864–1870.