Surrogate Markers for Cardiovascular Disease

Structural Markers

Carotid Intima-Media Thickness

Pignoli et al.1 validated the concept that intima-media thickness (IMT), as measured by B-mode ultrasound and applied either in vitro or in situ at the time of autopsy, reflected direct measurements of aortic and/or carotid specimens. Values obtained by ultrasound at autopsy and by direct measurement were similar to those obtained from living subjects. The characteristic double-line pattern was most consistently found in the far wall of postmortem specimens judged to be relatively normal or affected only by fatty streaks. Histologically, these segments showed homogenous intima with varying amounts of intimal thickening, intimal fibrosis, internal elastic lamina fragmentation, and duplication. In specimens with more advanced atherosclerosis, the double-line pattern was sometimes perturbed and more complex; these samples showed evidence of a fibrous/muscular cap with a lipid and/or necrotic core and, histologically, the intima showed focal areas of fibrotic smooth muscle cell proliferation, microcalcification, and necrosis. Based on this important article, it is clear that carotid IMT is a direct measure of the status of the vascular wall, and abnormalities are not a surrogate but a direct measure of atherosclerotic and arteriosclerotic processes. The issue of surrogacy pertains to whether a measurement in the carotid bed is associated with atherosclerosis in other beds, particularly the coronary bed and, even more important, whether this measurement is predictive of vascular events that result from atherothrombotic disease.

Methodology

Carotid ultrasound is routinely applied for evaluation of ischemic cerebrovascular signs (eg, bruits) and symptoms. In the context of risk stratification, however, the goal is to identify preclinical disease. The degree of carotid disease that appears to be of prognostic value is much subtler, requiring meticulous and detailed measurements of IMT through B-mode ultrasound. These measurements can be made in a reproducible and reliable fashion if sonographers and those making the measurements are trained comprehensively and rigorously at the outset and if steps are taken to ensure consistency and reproducibility over time.2 This standard can and must be achieved for clinical trials.

If meticulous quantitation is considered mandatory for routine clinical application, then the next challenge pertains to the diversity of measurement protocols.3–5 Methods measuring many predefined anatomical areas to create a "mean maximum IMT" measurement have the inability to measure all predefined segments in all subjects (ie, missing data). There are differences in the ease with which anatomical areas can be measured (eg, the far wall is easier to measure than the near wall, the common carotid is easier to measure than the internal carotid). Ambiguity exists regarding whether reported measurements represent diffuse thickening or focal plaque formation or both. Measuring only the far wall of the common carotid artery within a prespecified distance of the carotid bifurcation and flow divider allows the risk of missing important information in other parts of the carotid tree. In this approach, the IMT may reflect either diffuse thickening or the effects of a focal plaque that, by chance, happen to be in this prespecified area. Plaque, not uniform and diffuse thickening, may be the more important feature.6–8 and some evidence suggests that determinants of diffuse thickening differ from those of plaque formation.9 The location and characteristics of plaques may even be determined to some extent by ethnicity.9

A compromise method has been proposed in which the goal is to measure diffuse IMT separate from focal plaques while accepting that in most patients, it is easiest to identify and measure a suitable region of the far wall of the common carotid artery.10 But, when applied in patients with established coronary disease, the overall plaque size had the greatest prognostic value among all ultrasound features that were measured.11,12

Evidence for Carotid Atherosclerosis and IMT as Surrogate Risk Markers

Carotid atherosclerosis has been correlated with risk factors associated with the development of atherosclerosis in...
any vascular bed (Table 1).6,9,13–30 Progression of carotid atherosclerosis also is influenced by concomitant risk factors (Table 2).31–37

Carotid atherosclerosis is commonly found in association with coronary and peripheral atherosclerosis. Craven et al38 demonstrated that a measure of carotid IMT was strongly and independently associated with coronary artery disease (CAD) in patients older than 50 years and was at least as useful as well-known risk factors for distinguishing patients with CAD (>50% diameter stenosis in any vessel) from those without CAD. This group also explored the association of multiple different measures of carotid atheroma and determined that the mean carotid IMT obtained from multiple segments was most strongly correlated with coronary status. However, other measures were of near equal utility, such as the mean common plus bifurcation thickness and even the common carotid IMT measurement alone.39 Men with carotid IMT in the lowest quartile were >6-times more likely to have normal coronary arteries than men with 3- to 4-vessel CAD, whereas men with measurements in the highest B-mode quartile were at least 10-times more likely to have 3- to 4-vessel CAD than normal coronary arteries.40 Findings were similar in women but not as dramatic.

Prevalence of CAD, cerebrovascular disease, and peripheral vascular disease increased in parallel with increasing IMT.41 Significant but weak mathematical correlations have been reported between several measures of coronary disease (number of vessels with ≥70% diameter stenosis, extent score, and a modified Gensini score) and the measure of common carotid IMT.42,43 Holaj et al44 identified a significant association between the severity of coronary disease and the IM. Although studied less intensively, increased carotid IMT also correlates with calcific coronary disease as detected by computed tomography (CT).45 Finally, increased levels of carotid artery IMT have been associated with positive exercise test results.46,47

Accordingly, the finding of a significant association between a quantitative abnormality of the carotid IMT and evidence of established CAD is reassuring and is concordant with the principle that atherosclerosis is a diffuse disease. Detection in one bed implies a high likelihood of association with atherosclerosis in a different bed.

Even more compelling is evidence showing that carotid atheroma is a predictor of vascular events and that it is useful for risk stratification. The risk of acute coronary events was 3.29-fold in patients with any structural abnormality of the carotid artery, and relative risk increased progressively from 2.17 times with IMT, up to 6.71 times if plaques of ≥70% diameter stenosis, extent score, and a modified Gensini score) and the measure of common carotid IMT.42,43 Holaj et al44 identified a significant association between the severity of coronary disease and the IM. Although studied less intensively, increased carotid IMT also correlates with calcific coronary disease as detected by computed tomography (CT).45 Finally, increased levels of carotid artery IMT have been associated with positive exercise test results.46,47

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Evidence That Carotid IMT Tracks Regression/Is a Guide to Therapeutic Efficacy

Carotid ultrasound has proved to be a valuable marker for therapeutic benefit in clinical trials. It is noninvasive, can be repeated frequently without incurring risk, is relatively inexpensive, provides continuous and quantitative indices, and provides a direct measure of the mural atherosclerotic process before development of lumen encroachment. As a result, sequential carotid ultrasound has been performed in many studies. Carotid IMT has been used as an end point in clinical trials of several drug classes, including lipid-lowering drugs, antihypertensive agents, and hormone replacement therapy (HRT).

However, use of change in surrogate end points to predict clinical outcome is statistically and mechanistically complex. Many studies show that statins reduce events and reduce carotid atherosclerosis. But these results cannot be extrapolated to other lipid-lowering drugs, even drugs of the same class, without careful assessment of the overall clinical benefit and risk of untoward effects. Similarly, absence of an effect of a drug on carotid IMT might not be relevant in predicting benefit. Consider the stark contrast between the positive effect of ramipril on carotid atherosclerosis and the negative report using the same drug. The clinical benefit of angiotensin-converting enzyme inhibitor therapy in many disease states is unquestioned, but it remains uncertain whether changes in atherosclerosis adequately explain or closely relate to their overall benefit. Consider also the report of the neutral effect of HRT on the progression of carotid atherosclerosis. This result is consonant with the fact that women using active HRT had a poorer clinical outcome, perhaps related to other actions of HRT not affecting atherosclerosis. Thus, despite examples of concordance between outcome trials and carotid atherosclerosis regression trials, the net benefit of any given therapy is determined by a variety of factors that may not be reflected in changes or lack of changes in carotid IMT.

Unresolved Issues/Controversies

Serial IMT measures are considered to have the potential to monitor changes in response to therapy and, presumably, might affect ongoing treatment decisions. There are major concerns regarding expense, lack of availability, and difficulties with either single or serial measurements based on lack of standardization of measurement protocols. There is debate as to whether generalized IMT or focal plaque formation (and measurement) is of overriding importance (see previous) and whether there is sufficient incremental value of such measures in the patient with diabetes.

The usefulness of these measures in large groups of patients must be translated into a decision-making algorithm that is applicable to individual patients. Thus, the strength of a continuous measurement in a longitudinal clinical trial must be translated for clinical decision-making into a threshold defining normal and abnormal and perhaps also as mild, moderate, and severe degrees of abnormality. It is clear that IMT is gender- and age-related. Accordingly, designation of what is abnormal must consider at least these basic issues, as well as the presence of focal plaque, which would not be considered normal at any age or in either gender.

Future Directions

The establishment of standards for performance and interpretation of carotid IMT is critical for further utilization of this technique. A normal age-dependent range for quantitative assessment must be established for gender, geographic, and ethnic groups. Distinction between normal and abnormal preferably should be based on outcome data that will require very large screened populations. As the methodology continues to improve and as a cadre of trained ultrasonographers is developed, the technique should become one of an established series of tests to identify and track the progression of atherosclerotic disease.

Conclusions

B-mode ultrasound is a safe, noninvasive, and relatively inexpensive means of assessing subclinical atherosclerosis. Evidence substantiates that carotid IMT correlates with the presence of coronary atherosclerosis and represents an independent risk factor for coronary heart disease events, stroke, and transient cerebral ischemia. Careful carotid ultrasound examination and IMT measurement performed by an experienced laboratory can provide a useful surrogate marker for atherosclerotic disease likely to eventuate in cardiovascular morbidity events.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) as measured by ECG or echocardiogram is an established surrogate end point for cardiovascular prognosis, because evidence for independent continuous risk prediction as well as documented graded benefits from reversal of LVH are now available. It also is possible to detect individual changes of clinical relevance with current techniques, making LVH a valuable clinical tool. For many years, LVH as a fully validated surrogate end point was an elusive target. Although an attractive concept, because LVH represents the product of cardiac burden and may reflect differential reversal among antihypertensive agents, the ultimate randomized study was lacking. The risk and high prevalence in established hypertension has long been recognized. However, evidence that LVH regression influences the rate of cardiovascular events in hypertension independent of blood pressure and treatment has only been gathered from more recent studies.
Pathophysiology
Left ventricular hypertrophy is a cardinal manifestation of preclinical CV disease and a strong independent risk factor for all cardiovascular complications in hypertension. Increased left ventricular mass (LVM)/LVH is a common manifestation of hypertension that integrates the cumulative burden of blood pressure and other pathogenetic stimuli over time. Activation of the renin-angiotensin system is an important inducer of tissue hypertrophy and interstitial fibrosis, with angiotensin II acting as a potent growth factor in the myocardium. Although development of LVH is an adaptive response that reduces LV wall stress in the face of elevated arterial pressure, it is also an ominous prognostic sign that predicts a high rate of cardiovascular events. The difference between physiological LVH secondary to physical training and pathological LVH from hypertension is the difference between intermittent load and continuous overload on the heart. This is a matter of quantitative differences, and qualitative differences have been documented and linked to excess production of cardiac fibrosis secondary to activation of local renin-angiotensin system and other trophic stimuli. The perivascular and interstitial fibrosis is associated not only with cardiac dysfunction but also with arrhythmias and suboptimal oxygenation. Increased LVM or LVH is not uncommon, ranging from a prevalence of 20% in mild hypertension to almost 100% in severe or complicated hypertension. It has consequently become attractive to speculate that LVH regression is a suitable surrogate end point for hypertension trials. To establish such a concept, we need to validate a strong and suitable surrogate end point for hypertension trials. Evidence for LVH as a Surrogate Risk Marker
Numerous studies have established a close link between ECG-LVH or LVH detected by echocardiography and the risk of cardiovascular morbidity and mortality in diverse populations also independent of high blood pressure. Thus, increased echocardiographic LVM has been shown to predict complications in members of the general population and in patients with proven CAD more strongly than any other risk factor except advancing age. However, the bulk of documentation exists for patients with hypertension. In this large population, echocardiographic LVM and ECG-LVH are especially strong predictors of complications and death. A number of studies have used ECG criteria to document a relationship at baseline and an adverse subsequent prognosis. In the latest comprehensive review of the association between LVH (via ECG or echocardiography) at baseline and subsequent adverse events from 20 studies with 48,545 participants, the adjusted risk of future cardiovascular events and all-cause mortality ranged from 1.3 to 3.5, with a weighted mean risk ratio of 2.3, and from 1.5 to 8.0, with a weighted mean risk ratio of 2.5, respectively, for all studies combined. There was a tendency for a worse prognosis in women than in men; otherwise, LVH consistently predicted high risk, independent of other examined covariates.
Evidence That LVH Tracks Regression/Is a Guide to Therapeutic Efficacy
Retrospective and observational data with ECG and echocardiography indicate that cardiovascular events occur in higher proportions of individuals in whom LVH progresses than regresses, thus suggesting that reversal of LVH has prognostic benefits beyond blood pressure reduction and treatment. These findings raised the possibility that the level of LVH during treatment may provide independent information about disease progression or its control during hypertension treatment. This hypothesis has been supported by ECG data from the HOPE and the LIFE trials, but not by some previous intervention studies, perhaps because of larger variability of serial ECGs in the latter. Thus, outcome studies with ECG-LVH support the attractive hypothesis that LVM reduction independently predicts an improved prognosis as a desirable outcome of antihypertensive therapy. However, the relation between lower LVM and improved outcome during hypertension treatment has now been further strengthened with the large LIFE echocardiographic substudy involving 960 patients linking LVM regression with improved prognosis together, independent of blood pressure and treatment modality. The LIFE study supports the relevance to prognosis of serial measurements of LVM during treatment in a prospectively studied cohort of patients with moderately severe essential hypertension as documented by blood pressure (BP) level and the presence of LVH on a screening ECG. Patients with lower values of LVM index, assessed on annual echocardiograms during treatment, were less likely to experience the composite end point of cardiovascular morbidity and mortality, cardiovascular mortality, and all-cause mortality during 4.8 years of follow-up. Dichotomization of patients into those with or without LVH at the time of each echocardiogram during the study also revealed a substantially lower rate of events in patients with normal LVM on follow-up echocardiograms. Of
note, the lower rates of mortality and morbidity associated with lower LVM were, in addition to the predictive value of the baseline levels of LVM and BP, treatment changes in BP and the primary study assignment to losartan or atenolol.116 The LIFE echocardiographic substudy thus prospectively shows that development or maintenance of LVH during antihypertensive therapy, compared with regression or prevention of hypertrophy, is an ominous sign associated with an increased rate of major cardiovascular events.64

More than 500 studies have tested the effects of various antihypertensive agents on echocardiographic LVM, but only a few have used strict-enough criteria to provide reliable information.120 Meta-analyses, which for obvious reasons cannot provide definitive answers, have indicated more effective reversal of LVM with similar blood pressure control for modern antihypertensive agents like calcium antagonists and blockers of the renin-angiotensin system, particularly angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers.68,121,122 However, there are few studies that have fulfilled the few vital criteria of reasonable power, adequate technique, and unbiased central reading.120 These studies have not shown beyond doubt any benefit for angiotensin-converting enzyme inhibition (lisinopril, enalapril, and fosinopril) over calcium antagonists (amlodipine, nifedipine, and amlodipine, respectively123–125) and less efficacy compared with indapamide.126 Moreover, no difference has been detected in comparisons of enalapril versus candesartan or of lacidipine versus atenolol.127,128 However, angiotensin-receptor blockers (valsartan, irbesartan, losartan) have shown a consistently better reversal of LVM in comparison with atenolol.129–131 The only study with sufficient power for linking reversal of LVM with improved prognosis was the LIFE in Hypertension study, which compared losartan with atenolol in 9194 hypertensive patients with ECG-LVH for almost 5 years. In this study, it was possible to demonstrate a significantly better reversal of both ECG and echocardiographic LVH for losartan- versus atenolol-based therapy,119,132 and also the link improved prognosis, independent of blood pressure and therapy, for both ECG-LVH and echocardiographic LVM.116,117,133

**Future Directions**

Important aspects to investigate for the future to potentially improve on the prognostic prediction of LVH, both for baseline risk prediction and for therapy success through reversal of LVH/LMH, include systolic and diastolic function, natriuretic peptides, fibrosis of the myocardium through nuclear magnetic resonance imaging, echorefectivity and serum-markers, and improved determination of LVM through nuclear magnetic resonance imaging.68,131

**Conclusions**

LVH detected via ECG or echocardiography is a valuable clinical tool for prediction of risk in hypertension (Table 3). The best-documented ECG-LVH criteria are Sokolow-Lyon and Cornell Voltage Duration Product. As a risk indicator for future cardiovascular events, LVH is strong and independent, and second only to age in predictive power. Finally, we now have the ultimate documentation for both ECG-LVH and echocardiographic LVH that reversal has an independent prognostic value, independent of therapy and blood pressure. That LVH has become a validated surrogate end point for the treatment of hypertension has clinical implications. However, many new diagnostic advances may further refine this valuable tool.

**Other Structural Surrogate Markers**

Additional putative structural surrogates that have been proposed are electron-beam computed tomography, retinal photography, and collagen markers. These have not undergone the extensive evaluation needed to document their usefulness as markers. Therefore, they are discussed only briefly. A summary of the usefulness of all structural surrogates is shown in Table 4.

**Electron-Beam Computed Tomography and Other Calcium-Imaging Techniques**

These methods are being widely used to screen asymptomatic individuals for the presence of clinically silent coronary atherosclerosis. Because calcium frequently infiltrates the artery wall in the neighborhood of plaques, it is not surprising that the presence of calcium in a CT scan is fairly specific for plaque formation. However, calcium accumulation is dependent on age, gender, and genetic variability.134–136 Therefore, some advanced disease may exist in the absence of calcium, and early atherosclerosis and acute events associated with soft plaques may occur in the absence of calcium. The majority of men younger than age 50 and women younger

**TABLE 3. Strength of Left Ventricular Hypertrophy Regression as a Surrogate Endpoint**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>+</td>
</tr>
<tr>
<td>Clinical relevance</td>
<td>+</td>
</tr>
<tr>
<td>Epidemiology (risk)</td>
<td>+</td>
</tr>
<tr>
<td>Benefit from reduction (independent)</td>
<td>+</td>
</tr>
<tr>
<td>Feasibility (individual change)</td>
<td>+</td>
</tr>
</tbody>
</table>

**TABLE 4. Clinical Applicability of Potential Surrogate Structural Markers for Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Methodology Available/Convenient</th>
<th>Methodology Standardized</th>
<th>Sensitivity/Specificity for Disease</th>
<th>Identifies Severity of Disease</th>
<th>Tracks With Treatment of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid intimal medial thickness</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Electron-beam computed tomography (calcium score)</td>
<td>+</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Retinal photography</td>
<td>+</td>
<td>+</td>
<td>++ (7)</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
than age 60 have normal scans, despite the fact that >50% of them will die from cardiovascular disease.\textsuperscript{137} Electron-beam computed tomography may therefore be helpful in detecting advanced CAD, but it is an expensive technique, it does not provide a target for therapy, and it is highly unlikely to serve as a useful guide to a therapeutic response.

**Retinal Photography**

The retina provides access to imaging of the microvasculature. This is a vasculature that has traditionally been visualized ophthalmoscopically to grade the severity of hypertension.\textsuperscript{138} Difficulty in viewing and interpretation has reduced its use. Nonmydriatic cameras facilitate collection of digital images that allow rigorous assessment of the arterial–venous crossings and arterial architecture. This method is sensitive in detecting early vascular disease, but it is currently not widely available enough to be used as a general surrogate for progression.

**Collagen Markers**

Myocardial fibrosis is a contributor to LV dysfunction and possibly to arrhythmias in patients with LV overload or damage. Recent data suggest that a serum marker for collagen synthesis, the C-terminal propeptide of procollagen type I, may be a useful surrogate for fibrosis.\textsuperscript{139} Further data are needed in larger populations before this marker can be accepted as a surrogate for the structural abnormality and for adverse clinical events.

**References**


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