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Letters to the Editor

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Ultrasound Measurement of Atherosclerosis

To the Editor:

The recent review of intima-media thickness (IMT) measurements by Bots et al., while presenting cogent arguments for use of maximum versus mean carotid IMT for studies of interventions, failed to discuss important limitations of IMT. They claim as an important advantage of IMT, as opposed to morbidity and mortality as end-points, the considerable reduction in sample size and duration of study needed to show efficacy of new interventions; however they neglect to mention methodology that has significant advantages compared with IMT, namely the measurement of carotid plaque.

IMT is very insensitive to change in plaque, because plaque grows along the carotid in the axis of flow 2.4 times faster than it thickens. Thus, measurement of plaque, as opposed to measurement of IMT, detects change with treatment much more readily.

It is also very important to understand that ultrasound measurements of various aspects of atherosclerosis such as stenosis, plaque, or IMT assay biologically distinct phenomena. The main determinants of IMT are age and blood pressure; multiple regression with traditional risk factors gives an $R^2$ of only 0.15 to 0.17 for IMT, compared with an $R^2$ of 0.52 for carotid plaque area. This leads to important distinctions that must be made both for genetic studies of atherosclerosis and for studies of interventions aimed at atherosclerosis. These issues were discussed in a recent paper in Stroke.

Total carotid plaque area is a stronger predictor of outcomes than IMT: patients in the top quartile of plaque area have 3.5 times the risk of stroke, death, or myocardial infarction when compared with patients in the lowest quartile, after adjustment for age, sex, blood pressure, cholesterol, smoking, diabetes, homocysteine, and treatment for lipids and blood pressure; in contrast, patients in the top quintile of IMT had a relative risk of 3.15 versus the lowest quintile, after adjustment for a smaller panel of risk factors.

While IMT represents end-organ disease in the artery wall, it consists mainly of media and correlates poorly with coronary disease; it represents mainly hypertensive medial hypertrophy and correlates better with left ventricular mass than with coronary stenosis. Carotid plaque correlates better with coronary artery disease than does IMT.

For the most successful study of carotid IMT, Bots et al provide sample size estimates ranging from 408 per group for a parallel clinical trial with an effect size of 30% over 2 years, to 30 per group for a 100% effect size over 3 years. This is far inferior to measurement of plaque: study of 2-D plaque area requires sample sizes of 150 per group for a 30% effect size over 2 years, and the study of 3-D plaque volume can show significant changes in 3 months in 20 patients per group with an effect size of 100% (presented at the AHA stroke meeting in February 2004).

Instead of fussing over what is the best way to use IMT, a 1980s technology, it would be better to move to 3-D ultrasound measurement of plaque volume for evaluating effects of interventions aimed at atherosclerosis. For genetic studies, it is important to distinguish among noninvasive phenotypes, as they will be influenced differently by genetic factors affecting blood pressure, oxidative stress, lipids, and other factors affecting atherosclerosis.

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Response: Carotid Intima-Media Thickness Measurements in Intervention Studies

First, on behalf of Drs Evans, Riley, Grobbee, and myself, I would like to thank Dr David Spence for his supportive but critical remarks on our paper. He indicates that in our paper we failed to address the measurement of carotid plaque in randomized controlled clinical trials. Indeed, our paper was on carotid intima-media thickness (CIMT) measurements rather than focusing on plaques. However, in our discussion of the paper we provided a paragraph discussing some aspects of why our review was based on CIMT measurements and not plaque measurements. The main issues were that, when compared with plaque changes, CIMT is an established endpoint for efficacy studies; that relatively uniform definitions of CIMT exist, compared with much greater variety in plaque definitions across studies; that maximum CIMT measurements do capture plaque information, especially in recently developed elaborate protocols.

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tantly, the paper discussed the pros and cons given that a trial is
designed with CIMT progression as primary outcome.

We did not intend to address which minimally invasive or
noninvasive measurement of the vasculature is the best measure-
ment for use in randomized trials on the efficacy of interventions.
Such a paper does indeed need a balanced discussion of the pros
and cons of various techniques and approaches, such as CIMT,
plaque measurement, coronary calcifications, and MRI for mea-
surement of central aortic atherosclerosis. Apart from the tech-
niques, issues around the ability to measure change over time
comes into play.

In his letter, Spence provides strong arguments for using 2-D
and 3-D plaque measurements in trials rather than CIMT. Based
on our experience, we tend to disagree with some of the
arguments, given that they are based on a limited set of
references. In contrast to what Spence writes, we showed that
smoking and elevated lipids, apart from age and blood pressure,
were already related to increased CIMT at the age of 30 years.2
Also, the magnitude of the increased cardiovascular risks related
to upper quintile CIMT measurements compared with the lowest
quintile has been described as at least 4.8 in fully adjusted
models.4 Furthermore, plaque measurements in the Rotterdam
study were not better in predicting risk of stroke than CIMT; in
fact, the reverse was true.4 Finally, when viewing the entire
literature, there have been studies showing no association of
CIMT with coronary heart disease, but also studies showing
modest or even strong relations with coronary heart disease.

The noninvasive measurement of plaque is promising and
important in research on determinants of atherosclerosis and its
associated risks. We fully see the benefit of using 2-D and 3-D
techniques in single and multiple center trials performed in a
variety of populations. And indeed the data from Spence’s group
on that issue is important and challenging, and certainly merits
further application in other trials by his and other groups. In light
of the discussion, a direct comparison with the CIMT technique
would be ideal. In fact, this is currently being done in a
randomized controlled trial performed by Dr P. Verhoef at the
Wageningen University in the Netherlands with a main objective
to study the effect of folic acid supplementation on CIMT
progression (the FACTT study).

Yet, one should remember that the CIMT approach does
provide information on risk even when no plaque is present.