B-Mode Ultrasound in Clinical Trials
Answers and Questions

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B-mode ultrasound imaging of the extracranial carotid arteries has been used to identify the outcome variable in case-control studies relating risk factors to disease progression, and in this issue of Circulation, Blankenhorn et al provide evidence regarding its use in clinical trials.

Several factors promote the potential use of B-mode imaging in clinical trials that explore the association of risk factor reduction to athero-sclerosis change. First, the method images the artery wall rather than its lumen. Because atherosclerosis affects arterial walls and because the association of wall and lumen is complex, methods that image the wall are preferable to those that image the lumen for relating risk factors or interventions on risk factors to athero-sclerosis or change in atherosclerosis. Conversely, clinical events are related predominantly to compromise of the lumen, and research that seeks to relate arterial disease to symptom status or development of symptoms may focus profitably on lumen stenosis. The noninvasive nature of the B-mode examination is a further impetus for its use in clinical trials. Quantification of disease on a yearly or half-yearly basis and performance of duplicate scans increase reliability and provide new opportunities for outcome analysis that take advantage of the pattern of disease change. The noninvasive nature of the method makes it suitable for studies in large numbers of asymptomatic individuals as well. Finally, the B-mode investigation can be accomplished at relatively low cost in a research setting ($150.00 to $250.00 per patient per examination).

On the other hand, some of the features that contribute to the strength of the B-mode method pose new questions related to the definition of atherosclerosis, the quantification of the outcome variable, the differences in associations based on various levels of the artery, the potential for differences in various clinical samples, the precise relation between wall thickness and lumen diameter, and the use of the carotid artery wall as a "surrogate" for coronary disease.

Angiography defines disease as reduction of lumen diameter in reference to a "normal" proximal or distal diameter. A reduction of 20% may be considered as beyond the measurement error of the technology and thus defines plaque. In angiography studies, the effect on atherosclerosis so defined generally is of greatest interest. B-mode ultrasound visualizes normal as well as diseased walls, and to date there are no generally agreed-on definitions of the level at which normal ends and disease begins. For the case-control analyses in the Atherosclerosis Risk in Communities Study (ARIC; a population-based cohort study of the relation of risk factors to cardiovascular disease), wall thicknesses that exceeded the 90th percentile for the population were considered as diseased. Carotid wall thicknesses in "healthy" men and women in ARIC were about 0.75 mm for women and 0.90 mm for men, and "disease" was identified as a condition manifest by "at least two measurements of carotid artery far wall thickness of >2.5 mm or bilateral thickening corresponding to a mean intima media thickness of at least 1.7 mm in the internal carotid and/or at least 1.8 mm in the carotid bifurcation and/or at least 1.6 mm in the common carotid arteries." Alternatively, in other population-based studies, Doppler ultrasound has been used to identify stenosis in conjunction with use of B-mode to identify minimal wall thickening. Other approaches to defining plaque include identification of shadowing or bright reflectors as markers for calcification or the divergence and convergence of lumen-intima and media-adventitia boundaries. Identification of "plaque" compared with "wall thickening" may be important because minimal increases in wall thickness may be manifestations of "nonatherosclerotic" or "fibromuscular intimal thickening" rather than atherosclerosis. Larger arteries have thicker walls that merely reflect differences in shear stress and tensile stress, and the thicker walls of carotid arteries in men compared with women probably relate in part to differences in the diameters of their arteries. In the article by Blankenhorn et al, mean wall thickness is 0.65 mm and probably represents very early atherosclerosis or "nonatherosclerotic thickening."

Evolution also is apparent in the approach to imaging in clinical trials. Ongoing clinical trials designed primarily with carotid ultrasound as outcome have taken advantage of the opportunity to obtain duplicate scans at baseline and at the end of the trial and sequential scans every 6 months and to model sequential change as a function of time. In the present pilot study, individual scans were available at baseline, year 2, and year 4;

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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the data show essentially all of the change occurring between baseline and year 2 in the drug treatment group but stepwise progression in the control group.

The B-mode measurement described in the present article was obtained from the common carotid artery. Several reports (eg, Reference 12) have identified this as a site that is far easier to image reliably than the bifurcation or internal carotid artery. On the other hand, the common carotid artery is less susceptible to disease. B-mode data are available from several sources that suggest that plaque is more commonly found in the internal carotid artery and at the bifurcation than in the common carotid artery. These data support previous clinical observations that identified the bifurcation and the internal carotid as the sites most commonly affected by plaque.10 It is not clear which of these three sites or combination of these three sites best correlates with coronary artery disease. Tell et al13 identified differences in relations of risk factors to common carotid disease compared with internal carotid disease. Recent research also has identified differences in the relation of arterial wall thickening to lumen diameter in the common carotid and internal carotid arteries.14 Histologic differences between the arteries (the internal carotid artery is a muscular artery, whereas the common carotid artery is an elastic artery) may provide rationale for these differences15; furthermore, the mechanism of disease development at various carotid artery sites may differ. Turbulence and potential for endothelial damage with resultant influence of growth factors and coagulation factors probably are exaggerated in the bifurcation and internal carotid arteries compared with the common carotid. These observations suggest a need for assessment of the influence of risk factor reduction on disease at several sites in future clinical trials.

Early communications identified differences in the association of risk factors to arterial disease in patients with and without coronary artery disease (CAD); there was a greater variety of risk factors related to carotid artery wall thickness in patients with CAD than in CAD-free control subjects, and relations of risk factors to extracranial carotid artery disease were stronger in patients with CAD.16 In these cross-sectional studies, the slope of the line relating age to wall thickness of the extracranial carotid arteries was steeper in patients with CAD than in CAD-free control subjects, suggesting faster progression rates of extracranial carotid artery disease in (untreated) CAD patients than in CAD-free controls.16 All the patients in the study of Blankenhorn et al14 had prevalent coronary disease; extracranial carotid artery disease in this control group with CAD probably progresses at a more rapid rate than in a CAD-free control group, and risk factors probably are more closely linked to progression of extracranial carotid wall thickening in them. These are good reasons for recruiting such patients for clinical trials to evaluate the association of risk factor reduction to change in extracranial carotid wall thickness; on the other hand, extrapolation of carotid artery progression rates such as those found in the control group in Blankenhorn et al to populations free of CAD might be hazardous.

The association between wall thickness and lumen stenosis, as described above, is complex and depends on the artery studied. Considerable thickening of the wall of the common carotid artery occurs in the absence of compromise of the lumen, whereas wall thickening and arterial compromise proceed hand-in-hand in the internal carotid arteries of predominantly asymptomatic populations.14 It is of interest that reduction of wall thickness in the active treatment group of the present report was associated with no enlargement of the lumen, and, in fact, the sign of the change favored larger lumens developing with age in patients in the placebo group compared with the intervention group. It will be important with further experience to evaluate effects of interventions on both wall thickness and lumen diameter.

Finally, is it reasonable to consider extracranial carotid artery wall thickness as a "surrogate" for coronary disease? As mentioned above, B-mode and angiography measure different characteristics—wall thickness versus lumen stenosis. Furthermore, an imperfect correlation of disease of the two arterial beds has been noted in autopsy specimens17 and in case-control studies.16 However, thickening of the extracranial carotid arteries (predominantly a reflection of internal carotid and bifurcation disease) is one of the best predictors of coronary status in vivo,18 and the two arterial beds share many of the same risk factors.16 Carotid stenosis relates to incidence of coronary heart disease events.9 It is not clear to what extent these associations are a reflection of disease of the bifurcation and/or the internal carotid artery compared with the common carotid artery. Data presumably are available from the present study that would enable Blankenhorn et al to correlate change in coronary arteries to change in the common carotid arteries, and we look forward to this analysis.

In summary, data from this clinical trial with change in carotid artery wall thickness as outcome emphasize both the importance of the methodological approach and the magnitude of the challenge remaining. Numerous questions about methodology, atherosclerosis definition, and data interpretation lie ahead and present a multitude of challenges for the future.

References


KEY WORDS *Editorials *ultrasound *atherosclerosis *clinical trials
B-mode ultrasound in clinical trials. Answers and questions.
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Circulation. 1993;88:319-321
doi: 10.1161/01.CIR.88.1.319

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
http://circ.ahajournals.org/content/88/1/319.citation

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