Meeting Summary

Progression and Regression of Carotid Atherosclerosis in Clinical Trials

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A 2-day international workshop on the progression and regression of carotid atherosclerosis in clinical trials, sponsored by the Bowman Gray School of Medicine, was convened in August, 1989, in Winston-Salem, N.C. The objectives of the conference were to review 1) arterial anatomy as it relates to the etiology and progression of atherosclerosis, 2) the current state of knowledge of methodology of B-mode ultrasonography and end-point definition, 3) the epidemiology of carotid atherosclerosis, and 4) related clinical trials issues. Meeting participants came from such diverse areas as the National Heart, Lung, and Blood Institute, the Food and Drug Administration, academia, and industry.

Methodology and End-Point Definition of Carotid Atherosclerosis

The first speaker, Dr. Seymour Glagov of the University of Chicago, discussed the evolution of nonatherosclerotic and atherosclerotic lesions and the organization and complications of carotid plaque. Nonatherosclerotic intimal thickening may be diffuse and circumferential in straight arterial segments, but it is usually localized and eccentric at bifurcations and branches. Evidence from human artery studies and experimental models strongly suggests that lowered mean wall shear stress induces such focal thickening to restore wall shear to normal baseline levels of 15–20 dynes/cm². In addition, total wall thickness in normal arteries tends to maintain a fairly constant relation to lumen diameter for homologous segments, and intimal thickening appears to participate in this process. Such intimal thickenings differ from atherosclerotic lesions by the absence of circumscribed lipid accumulations and by the absence of necrosis or the characteristic plaque topography. The thickenings instead tend to be well organized into fibrocellular layers, lending further support to their role in an adaptive process to altered wall shear and tensile stresses.

Animal studies have demonstrated that arteries compensate for sustained increases or decreases in volume flow by adjusting vessel radius. Since wall shear stress is inversely related to the third power of the radius, a small change in radius will markedly affect wall shear stress. The radial increase, in response to increased flow, raises wall tension. Changes then occur both in wall composition and thickness, including intimal widening, to maintain stability and an appropriate level of tensile stress. In the case of sustained reduced flow, intimal thickening may narrow the lumen to increase flow, thereby restoring normal wall shear stress.

Unlike nonatherosclerotic thickening, atherosclerotic plaques contain lipid in the form of fatty streaks, which comprise foam cells. More advanced plaques are characteristically structured with a fibrous cap that often forms a discrete layer below the endothelial surface of the plaque. Within the plaque are regions of lipid accumulation and/or necrosis (necrotic center), fibrosis, and calcification. Although this topography is often seen, there is a wide range of plaque composition.

Contrary to usual representations, atherosclerotic lesions that are not ulcerated or surmounted by thrombi maintain circular or regular, nearly ovoid configurations on cross section. The plaque enlarges, it bulges outwardly away from the lumen. This process distorts the vessel shape but tends to keep the lumen round, thus effectively sequestering the plaque from the lumen and maintaining patency and lumen symmetry. The resulting adaptive enlargement is a generalized phenomenon, occurring in all atherosclerotic-prone locations studied. One cannot therefore simply equate extent or volume of plaque with severity of lumen stenosis: an artery with a large plaque may maintain an adequate lumen.

mechanisms underlying this compensatory enlargement remain unclear.

Despite this compensatory process, occlusive disease with its clinical consequences does occur. There is a point beyond which the artery seems no longer able to adapt, and the lesion begins to encroach on the lumen. On average, this situation is approached when the plaque occupies 40% of the cross-sectional area encompassed by the internal elastic lamina (i.e., the potential lumen area). Although the plaque may stabilize, it can induce clinical symptoms when stenosis finally impedes flow or when the plaque becomes disrupted, with rupture into the lumen (ulceration), plaque hemorrhage, and thrombosis. Factors predisposing to such an event include thinning (or absence) of the fibrous cap and physical forces related to flow, pressure, and wall stresses. Regions of continued plaque formation, liquification necrosis, inflammation, sclerosis, and calcification result in changes of stress distribution and alter vulnerability of plaques to disruption.67

Dr. Paolo Pignoli of the University of Milan began his presentation on the anatomic basis of ultrasound interpretation by reviewing the drawbacks of such indirect methods of atherosclerotic blood vessel measurements as contrast angiography and Doppler ultrasound.8 These procedures can yield significant measurement errors, resulting in erroneous percent stenosis calculations, since dilatation may interfere with the accurate assessment of lesion status by angiography or Doppler ultrasound. Another major problem of angiography concerns the potential misinterpretation of an artery as "normal" (i.e., no detectable stenosis) when diffuse arterial wall thickening prevails.

Unlike angiography, B-mode ultrasonography allows for direct measurement of arterial wall thickness in vivo.9-11 Comparing gross pathology with B-mode imaging, Dr. Pignoli and his coworkers demonstrated good validity for the latter, concluding that ultrasound can measure the intimal plus medial wall thicknesses at the level of the far wall of the common carotid artery, but that valid near-wall measurements are probably unattainable even if reliable measurements could be demonstrated.

B-mode ultrasonography does remain vulnerable to numerous factors that can compromise the integrity of the images obtained. The range of ultrasound velocity can contribute to a 4% error in wall thickness interpretation. Also, calcium and cholesterol deposits in the arterial wall influence acoustic properties, making this technique more accurate and reliable for early atherosclerotic lesion evaluation.

Dr. Daniel O'Leary of Brigham and Women's Hospital presented a discussion on ultrasound validity and reproducibility. Few studies demonstrate the validity and reproducibility of carotid ultrasound relative to a "gold standard" such as angiography. Investigators examining repeatability and accuracy of assessing arterial atherosclerosis using B-mode ultrasound with respect to angiography and pathology have shown little correlation between angiography and the other two techniques.12 Better correlation, however, does appear between pathology and ultrasound imaging than between pathology and angiography.13 Carotid artery studies have substantiated the usefulness of ultrasonography for visualizing the carotid arterial wall, demonstrating increased intimal-medial thickness in the carotid artery in hypercholesterolemic patients.10

Reproducibility data have been closely scrutinized in the ongoing Cardiovascular Health Study (CHS), permitting assessment of between-sonographer variability as well as between-reader variability. Prompt reading (by the same reader) of paired scans performed by two different sonographers on the same participant has enabled early identification and resolution of problems. Close attention to reproducibility and variability can result in smaller sample sizes for studies using a sonographic end point.

Dr. O'Leary emphasized the importance of using Doppler instrumentation in conjunction with ultrasonography, especially in the presence of advanced atherosclerotic disease. Ultrasonography yields many errors when visualizing vessels with extensive disease. Doppler ultrasound is particularly useful if B-mode ultrasonography incorrectly visualizes what appears to be a large lesion when the Doppler image indicates normality.14 In this situation, the Doppler data should take precedence, alerting the sonographer to rescan more carefully. According to Dr. O'Leary, ultrasound is also limited in terms of accurate assessment of plaque surface (e.g., smooth or ulcerated) or plaque composition and density.15

Dr. Ward Riley of AUTREC, Inc., Winston-Salem, N.C., discussed ultrasound quality control and assurance, noting that numerous issues are involved. The study protocol must provide detailed documentation of the training program, the scanning and reading procedures, and instrumentation operation. Sampling methods (anatomic references, number of near- and far-wall sites visualized per image frame, angle of interrogation) and personnel/scheduling constraints (e.g., time allotted per study, availability of sonographers and readers for reliability studies, amount of supervision of personnel) must be well defined before implementing the study protocol.

Selection of instrumentation is a key step toward attaining maximal quality control. Key selection criteria include axial and lateral resolution, minimal image distortion, suitable transducer design, and ease of use by sonographers. Additionally, serious consideration must be given to the quality of the image/Doppler recording equipment, to instrument performance and reliability, and to service contracts and cost. Even with selection of the most sophisticated equipment, investigators must be vigilant in monitoring its performance. This would entail using a tissue-equivalent phantom, critically examining the image recording equipment, employing recognized standards when evaluating equipment, and using regular preventive maintenance.
The best ultrasound equipment cannot guarantee high-quality data without the expertise of the sonographers who operate the equipment and the readers who interpret the images. Standardized training of ultrasonography personnel is critical to the quality control of a study. Personnel must be properly instructed in ultrasound physics, pertinent anatomy, physiology and pathology, instrument operation, general scanning techniques, and performance of the scanning protocol. The certification program must be comprehensive enough to ensure that once completed, personnel will perform the scanning protocol as consistently and as accurately as possible. Finally, sonographer and reader variability must be assessed continuously by monitoring inter- and intra-reader/sonographer variability.

Dr. Jeffrey Raines of the University of Miami next presented a perspective on future directions in carotid atherosclerosis ultrasonography. Although extensive pathological data describing the atherosclerotic plaque exist, there are limited pathological/ultrasonography correlation studies of plaque. Collaboration between these specialties, however, is increasing. In terms of ultrasound interpretation, visualization of the plaque margins in arterial walls, although currently available, falls far short of characterizing the nature of a lesion, that is, whether it is ulcerated, hemorrhagic, possesses a fibrous cap, and so forth. More in vitro studies are needed to achieve this goal as well as improved instrumentation that will increase penetration and resolution.

The role of sonography in clinical applications and in clinical trials holds great promise. Dr. Raines foresees the quality of sonography attaining such excellence that clinicians will routinely perform carotid artery surgery based on ultrasound data alone. Following peripheral vascular disease as well as carotid artery plaque by this method may serve as an indicator of coronary atherosclerosis as well as general cardiovascular morbidity/mortality. Only by performing well-designed clinical trials involving vessels such as the iliac, femoral, and popliteal arteries will such potential be realized. When these objectives are attained, ultrasonography of the carotid and other peripheral vessels will no doubt qualify as hard endpoints in clinical trials.

**Epidemiology of Carotid Atherosclerosis**

Dr. A. Richey Sharrett of the National Heart, Lung, and Blood Institute presented an overview of the relation between risk factors and carotid atherosclerosis. Because of a dearth of information directly relating risk factors to carotid atherosclerosis, Dr. Sharrett began by referring to indirect evidence that links risk factors to stroke.

Dr. Sharrett noted that high blood pressure represents the most important risk factor for stroke, followed by fibrinogen levels, smoking, and diabetes. (The gender difference for stroke is less than that for coronary heart disease.) The status of elevated blood cholesterol as a risk factor is much less clear, showing both positive and negative correlations in the Framingham Study and in the Multiple Risk Factor Intervention Trial (MRFIT), depending on the type of stroke (nonhemorrhagic versus hemorrhagic) and the age groups analyzed. These studies, along with autopsy studies of Japanese men living in Japan and Hawaii and a series of pathology studies, lead to the following conclusions. Risk factors for thrombotic stroke are similar to risk factors for coronary heart disease, except that blood pressure is relatively more important in stroke, and cholesterol, less important. In the United States, elevated serum cholesterol levels are positively correlated with atherothrombotic stroke in those under 65 years but are correlated negatively with hemorrhagic stroke in this same age group. In subjects 65 years or older, the relation between elevated cholesterol levels and both atherothrombotic and hemorrhagic strokes appears to be inverse. Additionally, the very high incidence of stroke in Japan is associated with nonatherosclerotic sclerosis of the very small intraparenchymal arteries (i.e., no intimal proliferation or increased lipid accumulation) and is not associated with atherosclerotic lesions in larger vessels such as the circle of Willis.

Dr. Sharrett then summarized numerous studies, which evaluated the relation between extracranial carotid atherosclerosis and coronary and intracranial vessels. Data from these studies indicate that clinical carotid disease is strongly associated with both coronary heart disease and coronary atherosclerosis. The presence of asymptomatic carotid bruit is associated with an increased risk of coronary heart disease proportionally as much as for stroke. Extracranial carotid atherosclerosis is correlated strongly with major intracranial vessel atherosclerosis and only moderately with coronary atherosclerosis. Finally, severe coronary artery disease is associated with a large relative risk for atherosclerosis in the major intracranial arteries.

In terms of direct evidence for risk factors in carotid atherosclerosis, Dr. Sharrett related the results of a meta-analysis, which reported a stronger association between lipids and coronary artery disease than between lipids and cerebral atherosclerosis, mostly intracranial disease. Others, more recently employing ultrasonography to evaluate extracranial carotid atherosclerosis, have shown a strong association with lipids.

In summary, elevated blood cholesterol and hypertension continue to be regarded as important indicators of extracranial carotid disease, with cholesterol serving as a strong risk factor for atherosclerosis in the larger vessels and high blood pressure showing a much stronger association with nonatherosclerotic sclerosis of smaller vessels.

Dr. Jukka Salonen of the University of Kuopio continued the discussion of risk factors in carotid atherosclerosis by presenting data from a population-based study that uses B-mode exams, the Kuopio Ischemic Heart Disease Risk Factor Study (KIHDS).
Dr. Salonen described two primary manifestations of atherosclerosis, intimal–medial thickening and plaque/stenosis, both of which increase linearly with increasing age in the KIHD study population (men aged 42–60 years).\textsuperscript{23} He noted further that elevated serum low density lipoprotein (LDL) cholesterol was strongly correlated with increased carotid artery intimal–medial wall thickening and with carotid artery plaques.\textsuperscript{24} He and his associate Dr. Riitta Salonen also observed that cigarette smoking represents a weak risk factor for increased intimal–medial thickening but is strongly associated with plaque. Although they were unable to find a link between a history of hypertension or current diastolic hypertension and carotid atherosclerosis in general,\textsuperscript{22,23} they did note an association between systolic hypertension and carotid intimal–medial thickness.\textsuperscript{24–26}

An interesting finding in the KIHD study related to the apparent synergistic effect of high LDL cholesterol and smoking on intimal–medial wall thickening.\textsuperscript{27} Dr. Salonen cautioned that further studies need to confirm this result, which appeared in a small sample size. Preliminary data on progression were presented. After adjustment for age and LDL cholesterol, progression of carotid atherosclerosis is greater in subjects with detectable lesions at baseline than in subjects free of detectable lesions at baseline (0.17 mm/2 yr vs. 0.08 mm/2 yr, respectively). Variables with predictive value for 2-year intimal–medial progression included age, serum LDL cholesterol, pack-years of smoking, blood leukocytes, and thrombocyte aggregability.\textsuperscript{27}

Dr. Gerardo Heiss of the University of North Carolina also commented on population-based observational studies in atherosclerosis, reviewing cross-sectional components of the ongoing longitudinal study entitled Atherosclerosis Risk in Communities (ARIC). One of the primary goals of the ARIC Study is to examine the associations between risk factors for atherosclerotic cardiovascular disease and ultrasonographically measured carotid artery intimal–medial thickness.\textsuperscript{28} Data were presented on the distribution of established cardiovascular risk factors in individuals with carotid artery intimal–medial thickening greater than 2.5 mm (cases) and their controls, who were free of any evidence of carotid artery wall thickening. Cases were matched to controls based on gender, race, study center, age, and date of examination. Cases and controls were selected from the population-based cohort of the ARIC Study. All individuals included in these analyses were free of manifest cerebrovascular and cardiovascular disease.

Cases and controls were similar in age (by virtue of matching) and in body mass as well as diastolic blood pressure. Clear differences, however, emerged between cases and controls in systolic blood pressure, percentage of cigarette smokers, fibrinogen levels, and plasma levels of the atherogenic lipids and lipoproteins (all of which were higher in cases). Conversely, high density lipoprotein (HDL) cholesterol was found to be higher in controls compared with cases.

Careful monitoring of sonographer ability to successfully visualize images in various segments of the carotid artery (common carotid, bifurcation, and internal carotid) was implemented. As expected, a greater degree of success existed in obtaining good images from the common carotid and the bifurcation than from the internal carotid, which often presents difficult-to-visualize anatomic variations.

The segment of the conference devoted to the epidemiology of carotid atherosclerosis next turned to longitudinal studies of progression and regression, with Dr. Thomas Pearson of Columbia University presenting an overview of arteriography related to coronary atherosclerosis. Serial coronary arteriography provides a useful vehicle for studying the natural history of coronary atherosclerosis,\textsuperscript{29,30} enabling correlation of risk factors such as blood pressure and smoking with development of coronary lesions.\textsuperscript{31} Use of this procedure in longitudinal coronary atherosclerosis studies has facilitated selection of smaller sample sizes over shorter durations of time and has provided an alternative to clinical end points, two assets of great appeal in clinical trials.\textsuperscript{32,33}

There are disadvantages to arteriography that have made consideration of ultrasonography an attractive alternative. Despite a low incidence of complications, the invasive nature of arteriography precludes its use in the general population. A high dropout rate between examinations also compromises its usefulness in following subjects for changes in the amount and extent of disease. The optimal duration to study arteriographically characterized lesions is not known, perhaps ranging from 2 to 5 years.\textsuperscript{32,33} The ability to study early atherosclerotic lesions remains out of reach with this procedure. Measurement of lesions is indirect and is hampered by comparison with potentially diseased adjacent arterial segments.

Other disadvantages of arteriography include a weak correlation between degree of severity of lesions or stenosis as characterized by arteriography and extent of occlusion or coronary blood flow. False-positive interpretations occur secondary to such phenomena as arterial spasm or thrombosis. Conversely, false negatives appear secondary to factors such as arterial dilation. Variability in measurements over time also limits arteriography.

Dr. D.E. Strandness of the University of Washington reviewed the current status of Doppler ultrasound as a tool for linking lesion progression and symptom development. Reporting on his longitudinal study of the natural history of carotid artery disease in asymptomatic patients with cervical bruits,\textsuperscript{34,35} Dr. Strandness noted that the annual event rate (transient ischemic attack [TIA] and stroke) remained fairly low (4%) in this population, whereas the yearly rate of progression to more than 50% stenosis was twice what would be expected for a symptomatic group (8%). Equally dramatic was the finding that by 36 months' follow-up, nearly 60% showed some carotid artery disease progression. The primary risk factors for higher progression rates in this study were
age (<65 years), type II diabetes mellitus, and cigarette smoking. Interestingly, hypertension was not associated with disease progression.

Stratification of patients by degree of stenosis revealed that those with less than 80% stenosis were not at much risk for developing ischemic events such as stroke, TIA, or asymptomatic occlusion, while individuals with carotid artery stenosis exceeding 80% as well as those who progressed during the 36-month follow-up period stood a much greater risk of experiencing an event. In terms of attaining a clinical event relative to rate of lesion progression, lesions generally progressed stepwise through the various degrees of stenoses.

In 1986, those patients with greater than 80% stenosis during the previous 3 years were surveyed. There were 129 asymptomatic high-grade lesions found. From this population, 43% had undergone carotid endarterectomy. The other 57% with tight stenoses were treated medically. Of these, nine subjects had a complete stroke, of which five were associated with a total occlusion. Fourteen of the 57% of participants with tight stenoses experienced TIA, with three progressing to total carotid artery occlusion. Three of the 57% progressed to asymptomatic occlusion.

Dr. Strandness cautioned that clinical trials evaluating atherosclerosis in the carotid arteries must stratify participants according to the degree of narrowing to obtain a clear picture of severity of disease and its relation to clinical outcome.

Cross-sectional and longitudinal components of hospital-based studies were next covered by Dr. Tell and Dr. Crouse. Dr. Grethe Tell of the Bowman Gray School of Medicine described cross-sectional findings from an ultrasound registry study that included patients referred to the hospital for diagnostic ultrasonography primarily for conditions/symptoms related to stroke, TIA, carotid bruits, and other cerebrovascular problems. B-mode images of the common, the external, and the internal carotid arteries and the bifurcation were visualized and then assigned a score that reflected the degree of wall thickness as an indicator of plaque thickness. (External carotid artery measurements were less well represented in this population.) The scores ranged from 1 to 6 and reflected lesion thicknesses, ranging from 0 (no plaque) to greater than 4.0 mm (severe plaque) to total occlusion.

Looking first at race-specific mean plaque thickness, Dr. Tell noted that in the white population studied, lesion thickness across most sites (as reflected by the assigned plaque thickness score) correlated with increasing age, with the largest increase spanning the youngest to 55-year-olds. After age 55 in men, the scores leveled off. This could be attributed to such factors as cohort effect or selective mortality; perhaps it may signal the relative unimportance of age as a risk factor for atherosclerosis once a certain level of disease is attained. The effect of age on mean plaque thickness indicated that whites 60 years of age or younger had significantly lower mean plaque scores over all sites evaluated. For blacks, the only significant age difference between those less than 60 and those 60–70 years was seen at the bifurcation. Those aged 60–70 and greater than 70 years differed significantly only at the midcommon carotid artery and at the bifurcation. The anatomic distribution of lesions in this study agrees with published results from autopsy studies: whites manifest more extracranial disease, while intracranial disease predominates in blacks.

Risk factor assessment by race yielded interesting results. For whites, age, gender, diabetes mellitus, hypertension, and smoking history all related to the mean combined plaque score over all sites, whereas in blacks, only age and smoking significantly influenced the scores. Other risk factor data pointed to advanced age and cigarette smoking as the most potent determinants of carotid artery atherosclerosis as judged by lesion thickness scores. Age influence may relate less to age per se than to protracted exposure to etiologic determinants of disease. Stratifying cigarette smokers into nonsmokers, past smokers, and current smokers suggested that quitters may progress at a slower rate than those who continue to smoke. Longitudinal smoking cessation studies should confirm this preliminary finding. Dr. Tell concluded by comparing the shortcomings of hospital-based versus population-based studies (lack of generalizability, selection bias) and the advantages of such studies (inexpensive, less dependent on outside funding).

Dr. John Crouse of the Bowman Gray School of Medicine presented an overview of his studies in patients with and without coronary disease and summarized his findings correlating coronary heart disease and carotid atherosclerosis. Dr. Crouse discussed the possibility that coronary and carotid artery disease share common risk factors. In his ongoing collaborative case–control study of risk factor associations in cardiac catheterization patients, cases had more than 50% stenosis of one or more coronary arteries while controls were completely free of coronary disease. Risk factors for carotid atherosclerosis in patients with coronary disease included age, blood pressure, cigarette smoking, left ventricular hypertrophy, uric acid, HDL cholesterol, race, and LDL cholesterol. For controls, age, blood pressure, triglyceride concentration, and ideal body weight represented risk factors, whereas cigarette smoking did not. Coronary status was associated with extracranial carotid atherosclerosis independent of the other risk factors. Risk factors served as better predictors of the extent of carotid atherosclerosis in patients with coronary disease than in patients free of coronary disease.

Does the extent of coronary atherosclerosis relate to the extent of extracranial atherosclerosis? Preliminary analyses indicate that subjects afflicted with triple-vessel disease have more extensive carotid atherosclerosis than individuals with single- or double-
Clinical Trials in Carotid Atherosclerosis

Dr. Ross Pierce, representing the Food and Drug Administration, discussed clinical trials from the perspective of the FDA*. Because the drug interventions used in cardiovascular clinical trials could themselves prove dangerous, large clinical studies should specifically test one member of each class of drug targeted for cardiovascular disease control. Such trials should have the potential to determine all-cause mortality and should provide useful information for cause-specific mortality and morbidity.

Clinical trials that test interventions to reduce carotid atherosclerosis must have clearly stated criteria that define the appropriate study population. If a trial enrolls those with a higher risk for developing atherosclerosis, the potential for lesion progression at a faster rate could reduce the sample size as well as the length of follow-up needed for hypothesis testing. It may be difficult, however, to find adequate numbers of people with such qualifying lesions. Conversely, recruiting those with less risk would prove easier in terms of more accessible numbers, but the sample size and follow-up period would have to be much greater.

Other important features of clinical trials include a prerandomization run-in period to test for adherence, averaging of multiple lipid profiles when computing baseline values and dose titrations to allow for variability in individual response, and use of FDA-approved agents as appropriate interventions.

Dr. Curt Furberg of the Bowman Gray School of Medicine reviewed the design of and rationale for cardiovascular prevention trials. Interventions may reduce the risk of clinical manifestation of atherosclerosis by preventing precipitating factors (e.g., prevention of thrombus formation by anticoagulants or aspirin) as well as by slowing the progression of atherosclerosis (with lipid-lowering, antihypertensive, or antithrombotic agents).

No clinical trials using B-mode end points have yet been completed. Follow-up studies using B-mode imaging, however, have quantified carotid lesion progression rates of 0.1–0.3 mm/yr. Treatment effects documented in femoral arteriography, coronary angiography, and carotid B-mode/Doppler studies suggest that there is a potential to reduce atherosclerotic lesion progression by as much as 50%.

It is assumed that the sequence of intervention effects for atherosclerotic disease is as follows: 1) risk factor modification, 2) slowing of the atherosclerotic process, 3) reduced morbidity, and 4) decreased cause-specific mortality. Proceeding through these phases from a clinical trials perspective necessitates more time and more study subjects as the focus changes from the first step in the sequence to the final step.

What are the considerations when designing trials aimed at carotid atherosclerosis intervention using B-mode end points? A primary prevention study should concentrate on high-risk subjects (hyperlipidemias, hypertensives), whereas a secondary prevention trial would target those with coronary or peripheral vascular disease or stroke victims. Ironically, those perhaps most likely to benefit from risk reduction cannot be enrolled in such trials in the United States. These include individuals with high levels of plasma cholesterol who must be given a series of well-defined dietary counseling and/or clinical alternatives according to the National Cholesterol Education Program and those hypertensives who, according to the Joint National Committee IV, must receive standard pharmacological treatment. Such guidelines, intended to meet the immediate medical needs of these people, are likely to limit the magnitude of demonstrable treatment benefits.

End-point measurements and treatment effects represent other issues related to trial design. For carotid artery lesions, end points range from maximal lesion or intimal-medial thickness (presenting only a one-dimensional view of the disease process) to mean lesion thickness and mean intimal-medial area (two-dimensional end points) to mean intimal–medial volume (a true three-dimensional end point, but with no current technical means for determination).

Finally, what is the clinical implication of slowing carotid artery atherosclerosis? This question cannot be answered until we know for certain whether carotid artery lesion progression is correlated with an increased risk of stroke, TIA, or coronary events.

Dr. M. Gene Bond from the Bowman Gray School of Medicine described B-mode ultrasonographic methods that are currently being used in three clinical trials, Pravastatin, Lipids, and Atherosclerosis in the Carotids (PLAC-2), the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS), and the Asymptomatic Carotid Artery Plaque Study (ACAPS). These trials use different interventions (pravastatin, isradipine, and lovastatin/warfarin, respectively) in different populations (151 coronary patients, 883 hypertensives, and 919 high-risk asymptomatic subjects, respectively) and are following ultrasonographically defined carotid artery plaque progression.

Six potential interfaces in the carotid arteries are visualized, three for the near wall and three for the far wall. All major multicenter US trials conducted at the Bowman Gray School of Medicine (both epidemiological and interventional) are examining three areas of the extracranial carotid arteries: the 1.0-cm segments of the distal common carotid and

*The speaker's comments reflect his personal views and not necessarily those of the Food and Drug Administration.
the carotid bifurcation and the proximal 1.0-cm segment of the internal carotid.

Dr. Mark Espeland, also of the Bowman Gray School of Medicine, reviewed the sample size requirements and analysis issues related to the design of a carotid atherosclerosis clinical trial. Determinants of sample size projections for progression models include the variability of measurements, estimated rate of progression, treatment effect, and desired power and mode of analysis. In designing any clinical trial, these factors require careful consideration.

Variability related to trial design includes both variability within individuals and among individuals. The variability within subjects is affected by the appropriateness of the model for progression (e.g., linear progression versus an accelerating model), the measurement error (i.e., the error in B-mode imaging scans), serial correlation, and the number of serial measurements. The higher the serial correlation (the ability to predict subsequent measurements from a prior series of measurements in an individual), the less variability within individuals; that is, increasing the number of serial measurements can often decrease the variability within subjects.

Other important considerations related to variability within subjects include careful selection of end points and technique of measurement as well as account of the reliability of the measurement system and the duration of the study. Variability among individuals also affects the conduct of a clinical trial and depends on such factors as the heterogeneity of the sample population, the appropriateness of the model, and the measurement error. Efforts to attenuate this phenomenon involve careful selection of end points, inclusion/exclusion criteria, techniques of measurement, and a keen attention to reliability and intraobserver consistency.

Sample size determination in carotid ultrasound trials depends largely on the magnitude of the targeted treatment effect and the rate of lesion progression, both factors being inversely proportional to sample size estimate. The noninvasive nature of carotid ultrasonography allows for interim measurements, which decrease the sample size needed by decreasing the standard error of estimated treatment effects.

Ultrasonographic measurements of carotid atherosclerosis represent surrogate end points. Clinical studies employing such end points can use smaller sample sizes over shorter periods and are thus likely to be more cost-effective trials. The disadvantages of such end points compared with clinical events include a greater potential for missed data (e.g., missed clinic visits or missed sites in ultrasound exams), the need for more challenging statistical analyses, and the multifactorial complexity of such trials (no one surrogate end point can adequately describe the disease process).

Dr. Robert Byington of the Bowman Gray School of Medicine discussed the unique challenges involved in conducting clinical trials that employ carotid ultrasound as an outcome variable. The problem of enrolling high-risk subjects with carotid artery lesions in the acceptable size range (visibly detectable by B-mode imaging, yet not so large as to raise ethical issues), compounded with a host of rigorous exclusion criteria, necessitates having a large sample size for such studies. Hence, many are designed as multicenter trials.

As with all clinical trials, ethical issues always warrant consideration. Imaging of a large lesion during screening calls for informing the subject and advising him/her to seek further medical attention. Those qualifying for and participating in these studies should undergo additional tests in conjunction with regular protocol-defined B-mode imaging. These would include periodic lipid profiles and regular blood pressure monitoring.

General Discussion

A general discussion on carotid atherosclerosis clinical trials followed the presentations. The potential for evaluating antiatherogenic interventions in carotid atherosclerosis trials, that is, being able to use surrogate end points such as ultrasonographic measurements of intimal-medial thickening to predict clinical events, generated varying reactions among the presenters and the attendees. Ideally, validation could be demonstrated by extending intervention trials beyond the detection of a favorable effect on surrogate end points so that a significant number of clinical events could be observed. However, this is unfeasible and perhaps ethically questionable as well, given the low incidence of clinical events and the small sample sizes in ongoing primary intervention trials such as the ACAPS. Still, it would be scientifically desirable to continue a trial until conclusions could be reached concerning correlations between atherosclerotic progression and clinical outcome measures. A number of panelists and presenters expect that the population-based studies such as CHS or ARIC will provide data on the link between progression and events.

The potential for establishing common end-point definitions that would be universally recognized was discussed. No such acceptable end points presently exist. Investigators must instead make concrete decisions based on informed clinical judgments when selecting end points, and they must consistently adhere to the measurement and reporting of these end points for the duration of the study. As with validation, the adoption of universally accepted end points will likely emerge through the combined findings of observational and experimental trials.

The problem of missing data and the analytical strategies for dealing with them were considered. Reasons for missing data include missed clinic visits and the inability to visualize segments in deeper or more tortuous arteries. The analysis of incomplete data is hampered if a relation exists between the presence or absence of a measurement and its underlying value, that is, whether a plaque is measur-
able, depending on its size. If there is no relation, the missing data can be ignored and the analyses can proceed along traditional paths. If a relation does exist but can be controlled for by the selection of an appropriate set of covariates, more complicated approaches based on maximum likelihood and/or imputation are possible. If a relation exists that cannot be controlled for, one must proceed conservatively. Detecting the presence of such a relation can only be done indirectly, for example, by examining correlations between “missingness” and the plaque size at adjacent sites. Some evidence exists for modest relations between plaque size and missingness. For example, internal carotid sites are more difficult to visualize in some populations but tend to have larger plaques. This indicates that missing data cannot be ignored and that the site of the measurement should be included as a term in analyses when data are incomplete.

Future Directions

This conference provided a forum for the exchange of basic research and epidemiological and clinical trial experiences in the field of carotid atherosclerosis. It also served as a springboard for establishing common goals needed to achieve the useful clinical application of carotid ultrasonography. There was discussion and consensus on some of the outstanding issues to be resolved. These included defining when adaptive wall thickening evolves into an atherosclerotic plaque and what risk factors are associated with this transition; elucidating which risk factors trigger destabilization of well-defined plaques; establishing common standard end-point definitions for carotid atherosclerosis trials; and determining the value of ultrasonographic assessment of carotid atherosclerosis in predicting overall cardiovascular morbidity/mortality. Data accumulating from the population-based, intervention, and hospital registry studies discussed during this conference show great potential for addressing and clarifying these complicated issues.

The workshop also highlighted the tremendous benefit that carotid ultrasonography can impart to the field of cardiovascular medicine. To make the quantum leap from research to clinical practice, however, rigorous quality control measures presently used in B-mode ultrasonography trials must be made applicable to the clinical setting.

Acknowledgment

The authors thank Tina S. Boyles for her meticulous preparation of this manuscript.

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doi: 10.1161/01.ATV.11.2.443

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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