Arterial Imaging and Atherosclerosis Reversal

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Abstract This review explores evidence for the reversibility of atherosclerosis and augmentation of angiography with noninvasive arterial wall imaging. Meta-analysis from coronary angiographic trials demonstrates that regression and stabilization are 1.5 to 2 times more common in treated than placebo subjects, and progression is reduced by half in treated subjects. Odds ratios for clinical coronary events are significantly reduced with treatment. Lesion improvement occurs more readily in women than men and more so in women receiving concomitant estrogen replacement therapy. Lesions with ≥50% diameter stenosis (%S) at baseline respond more readily to lipid lowering than those <50%S, whereas reduction in coronary events is related to stabilization of lesions <50%S. Lipoproteins have a differential effect on lesion progression according to lesion size, and triglyceride-rich lipoproteins play an important role in the progression of coronary artery lesions <50%S. Improved therapeutic regimens to alter progression of atherosclerosis may require adjunctive therapy, such as with antioxidants or hormone replacement therapy, in concert with low-density lipoprotein cholesterol reduction to prevent new lesion formation or early lesion progression. Sequential coronary angiographic determination of progression evaluated by both quantitative coronary angiography and global change score, a visual assessment of overall lesion change, predicts clinical coronary events. Only inferences about the state of the arterial wall can be made from angiography, because it delineates only the lumen. Therapy testing and study of atherosclerosis progression can be improved with noninvasive B-mode ultrasonographic imaging of the distal common carotid artery far-wall intima-media thickness (IMT), a reliable measure of early preintrusive atherosclerosis. Measurement of common carotid IMT is useful for the study of coronary artery risk factors and can augment studies of coronary artery intrusive lesions, because it is associated with coronary artery disease. B-mode measurement of common carotid IMT has the potential of serving as a noninvasive surrogate end point for clinical coronary events. Screening for peripheral vessel changes indicative of high risk for coronary artery disease is possible and cost-effective with the noninvasive procedures now available. (Arterioscler Thromb. 1994;14:177-192.)

Key Words • atherosclerosis • angiography • ultrasound • regression • clinical trials • intima-media thickness • quantitative computerized angiography • common carotid artery • coronary arteries • meta-analysis

Evidence that progression of atherosclerosis can be retarded and atherosclerotic lesions can regress derives from several sources. These sources include studies of arterial lesions obtained at autopsy from starved human populations, animal experimentation, and clinical trials using serial angiography. In the first half of this article, we review serial angiographic evidence for atherosclerotic lesion improvement induced by diverse modes of intervention in 13 clinical trials. The weight of this evidence indicates that atherosclerotic lesions as well as clinical coronary events are reduced by intervention. Conclusions from completed coronary angiographic trials aid in selecting hypotheses to be tested in future clinical trials.

Information learned about atherosclerosis from angiography is limited, because this form of imaging demonstrates only lesions intruding into the lumen. Noninvasive imaging can augment information derived from angiography, because these methods can image the arterial wall. In the second half of this review, we describe noninvasive methods for imaging the coronary arteries and peripheral vessels, the latter of which yields useful information concerning early preintrusive atherosclerotic lesions.

Historical Overview

Studies of atherosclerosis with arterial imaging began in Scandinavia in 1967. Öst and Sténson treated 31 patients with niacin and reported that 3 showed improved femoral angiograms and reduced claudication. The next studies were in Southern California in 1977 at the University of Southern California (USC). Computer image processing developed at the California Institute of Technology Jet Propulsion Laboratory (JPL) for space photography was used to remove noise encountered during transmission from planetary spacecraft. USC and JPL collaborated to adapt image processing to angiography. The project started with an autopsy calibration study and continued with a clinical pilot study of femoral angiography in hyperlipoproteinemic patients treated at the Los Angeles County–USC Medical Center. Nine of 25 patients showed evidence of regression by visual inspection and computer image processing.

In 1977, human atherosclerosis was generally considered to be irreversible, with surgery the only accepted clinical management. It was believed to be unaffected by any treatment less drastic than wartime starvation. Öst and Sténson's 1967 study was virtually unknown. The reports from USC received attention but also encountered skepticism. In 1977, there was a convincing body of evidence that reversal of atherosclerosis could occur in animal models, but it was discounted because animal lesions were of relatively short duration.
In 1984, the Lipid Research Clinics Coronary Primary Prevention Trial reported that cholestyramine treatment reduced the incidence of coronary heart disease, and the NHLBI Type II angiographic study indicated that progression could be reduced in coronary artery lesions with ≥50% diameter stenosis (%S). In 1987, the USC Cholesterol-Lowering Atherosclerosis Study (CLAS) reported that combined colesterol-niacin therapy produced angiographic evidence of coronary artery lesion regression. Since 1987, a second generation of imaging trials has changed the consensus, and it is now generally believed that stabilization and reversal of atherosclerosis are possible.

Background Information on Arterial Imaging Trials

Coronary Lesion Staging

Lesion staging is necessary for studies of progression and regression. We have detailed scenarios for lesion progression based on the gross, microscopic, and ultramicroscopic anatomy of the disease. Plaques begin as fatty streaks and progress through raised fibrotic lesions to later complications, such as fissuring, thrombosis, hemorrhage, ulceration, and calcification. Gross examination leads to several stages of lesion grading. Microscopic or ultramicroscopic examination greatly expands this grading and is more specific. In contrast, scales used to grade atherosclerosis from images are rudimentary.

Angiography measures the internal vessel lumen, and we infer lesion severity from the extent of lumen lost. Clinicians typically stage coronary artery lesions on a scale of 3: complete occlusion, ≥50% %S, and <50% %S. For the most extended scale used in a clinical trial to date, lesions were divided into 100% %S, 75% %S, 50% %S, and 25% %S.13 As discussed later, B-mode ultrasoundography can expand these scales by adding measurements of arterial wall thickness.

Selection of End-Point Measures

Imaging trials that study a general hypothesis about atherosclerosis (such as the lipid hypothesis) can be targeted on any atherosclerosis-prone vessel. They have greatest validity if end points in the target vessel have been calibrated with specimens of known degrees of atherosclerosis. Angiograms of femoral and carotid arteries as well as ultrasound images of the carotid artery have been calibrated with autopsy and operative specimens. Individual lesions or vessel segments can be used as the experimental unit to reduce the number of subjects and cut study costs.

Imaging trials that evaluate specific treatments must use the subject as the experimental unit. For coronary arteriography, this involves averaging results from multiple vessel segments or lesions. A preferred statistical strategy for this assumes that lesions and vessel segments act as independent units. Results from three clinical trials support the Rosner approach of a per-subject analysis, taking into account the between-segment (lesion) correlation. Observations in trial subjects requiring angioplasty also indicate that large changes induced in a single lesion by angioplasty can influence change in untouched vessel segments.

Computerized image analysis of coronary angiograms has not been adequately calibrated against specimens with known degrees of atherosclerosis. The most widely used measure, %S, compares the narrowest point in the vessel with a “normal” segment. This measure has the advantage of an extensive background of clinical observation relating symptoms to disease distribution and severity. It provides a common scale to compare lesion severity in different-size vessels. Minimum and average lumen diameter are proposed as alternatives for %S because there may be no normal segments in a badly diseased vessel. These measures must be calibrated with an object of known dimensions in the same x-ray field. They require rigorous correction for the geometry of the x-ray equipment system and distortion in the imaging train. Sophisticated x-ray ganttries and computer image processing procedures have been developed to meet these requirements, but less elaborate systems have been used in most trials.

Coronary Atherosclerosis Severity Versus Symptoms and Risk of Clinical Events

The most straightforward relation between coronary atherosclerosis severity, cardiac symptoms, and risk of clinical coronary events occurs with isolated stenosis of the left main coronary artery. In this case, increased flow past a single proximal narrowing relieves symptoms and improves survival. When there are multiple lesions, the relation between change in any single lesion and symptoms or risk is more complex. There are several reasons for this. First, when multiple coronary lesions are present, the extent of concurrent myocardial damage influences symptoms and risk. Second, equations predicting blood flow from lesion measurements in an unbranched vessel oversimplify real coronary blood flow, which pulsates through highly branched vessels. Last, certain plaques are likely sites for the local catastrophe of plaque fissuring with hematoma or thrombosis causing a rapid increase in size. Fissure and acute thrombotic occlusion from a small plaque are dangerous because of a sudden loss of coronary blood flow. Accumulating evidence indicates that acute clinical events result from instability of small, lipid-rich plaques rather than large, fibrotic, calcified, stenosing plaques. Although large plaques tend to progress to total occlusion more frequently than small plaques, occlusion by large plaques infrequently results in acute clinical events because of the formation of collateral vessels. Some, but not all, high-risk plaques can be identified by their angiographic appearance.

Endothelium-Derived Relaxing Factor and Vascular Remodeling

The arterial wall undergoes compensatory remodeling as lesions form in response to changing shear stress on the endothelium. As a result, extensive atherosclerosis can be present before lesions intrude into the vessel lumen. Adjustment of arterial size by endothelium-derived relaxing factor (EDRF) accompanies lesion formation. Cholesterol feeding in monkeys produces a generalized loss of arterial compliance that precedes formation of focal atherosclerotic lesions. When cholesterol feeding is stopped, arterial compliance returns toward normal before there is improvement in lesions. Loss of compliance is the result of the loss of EDRF activity induced by elevation of low-density lipoprotein cholesterol (LDL-C). Acute ef-
ffects of EDRF have been documented with coronary angiography in humans. Experiments compare vessel diameters before and after acetylcholine infusion in diseased and normal coronary segments. Elevated LDL-C reduces dilation that normally occurs, and visible lesions reduce or even reverse dilation. Vascular remodeling and chronic EDRF effects, which appear closely related to lesion progression and regression, have been observed in several lipid-lowering trials. Early indication of lesion remodeling came from the Lifestyle Heart Trial, in which favorable changes in the entrance and exit shape of lesions were reported in the intensively treated group. In the Stanford Coronary Risk Intervention Project (SCRIP), adjustment of coronary size in response to increased flow after angioplasty was influenced by LDL-C reduction. Changes occurred in coronary segments untouched by angioplasty. Dilation occurred distal to a lesion that had been reduced; constriction occurred in adjacent segments with reduced flow. Both of these effects were accentuated by reduction in LDL-C levels. Remodeling was also observed in the Monitored Atherosclerosis Regression Study (MARS), in which vessels opposite arterial segments with progressing lesions dilated, whereas vessels opposite arterial segments with regressing lesions constricted. Reduction in LDL-C levels correlated with these compensatory changes.

**Early Trials**

The NHLBI Type II Coronary Intervention Study was a pioneering trial that established the feasibility of randomized, double-blind, coronary angiographic trials. Men and women with LDL-C levels exceeding the age-corrected 95th percentile were included. There were baseline and 5-year angiograms on 57 placebo-treated and 59 cholestyramine-treated subjects. Film pairs were evaluated by three separate panels of three expert angiographers each, with film order and treatment assignment masked. Overall results did not establish a significant therapeutic effect. In a subgroup analysis, lesions ≥50%S at baseline were less likely to progress in the cholestyramine group than in the placebo group. Progression of these lesions occurred in 12% of the cholestyramine subjects versus 33% of the placebo subjects (P<.05). Increases in total cholesterol/high-density lipo- protein cholesterol (TC/HDL-C) and LDL-C/HDL-C ratios were the best predictors of progression.

The Leiden Intervention Trial, although not a randomized controlled trial, provided the first evidence that diet could influence coronary atherosclerosis without major weight loss. A vegetarian diet with a polyunsaturated/saturated fat ratio >2.0 and cholesterol intake <100 mg/d was prescribed for 39 angina subjects. Baseline and 2-year coronary angiograms were analyzed by visual assessment and computerized image processing. Both visual and computer-assisted assessment showed progression in 21 of 39 subjects and no lesion growth in 18 subjects. Lesion growth determined by both visual and computer assessment of angiograms was related to the TC/HDL-C ratio, confirming internal consistency of the study. Lesion growth occurred in subjects with TC/HDL-C ratios >6.9. Subjects with TC/HDL-C ratios <6.9 at baseline or who had ratios >6.9 and then reduced them to <6.9 had no lesion growth. Mean regression of +3.47% (mean percent increase in vessel diameter) occurred in lesions ≥50%S at baseline, whereas mean progression of −4.29% (mean percent decrease in vessel diameter) occurred in lesions <50%S at baseline.

CLAS tested combined colestipol-niacin therapy and reported clear evidence of coronary artery benefit. CLAS randomized 188 nonsmoking men with coronary artery bypass grafts (CABGs) and obtained angiograms in 162 subjects (80 in the drug group, 82 in the placebo group) at 2 years and 103 subjects (56 in the drug group, 47 in the placebo group) at 4 years. Films were evaluated first by panels of expert angiographers and later by fully computerized image processing. Longitudinal measurements of distal common carotid artery (CCA) far-wall intima-media thickness (IMT) were obtained with B-mode ultrasonography and a fully automated computerized edge-detection method, as discussed later.

Global change score (GCS) assigned by blinded panels of angiographers showed treatment benefits at 2 years (P<.001) and 4 years (P<.0001). Regression occurred in 16.2% of subjects at 2 years and 17.9% at 4 years in the drug group compared with 3.6% of subjects at 2 years and 6.4% at 4 years in the placebo group. Treatment benefit in GCS was observed over the entire range of pretreatment TC level, 4.78 to 9.05 mmol/L (185 to 350 mg/dL) at both 2 and 4 years. In native coronary arteries, the average number of lesions that progressed was less at 2 years (P<.03) and 4 years (P=.0002), as was the number of subjects with new lesions at 2 years (P<.03) and 4 years (P=.001). Treatment did not reduce the number of new bypass graft closures at 2 or 4 years but did reduce the formation of new lesions both at 2 years (P<.04) and 4 years (P=.006). This discrepancy indicates a different response to therapy than in native arteries and emphasizes the need for early treatment of lipids after CABG surgery. Analysis of 156 evaluable coronary angiographic film pairs by fully automated computerized quantitative coronary angiography (QCA) indicates a preferential large-lesion response to therapy. Lesions ≥50%S at baseline showed a −4.31%S change after 2 years of intervention, whereas lesions <50%S showed a +1.56%S change.

With aggressive lowering of LDL-C below 2.59 mmol/L (100 mg/dL), apolipoprotein C-III in HDL, an indicator of triglyceride-rich lipoprotein metabolism, was the most significant risk factor for lesion progression in the drug group. This was the first clear indication of the importance of triglyceride-rich lipoproteins in lesion progression, an effect manifested after LDL-C was removed as a risk factor.

Although drug-treated subjects formed fewer new coronary lesions than placebo subjects, there was evidence within the placebo group that reducing dietary fat also reduced new lesions. In the placebo group, 64 subjects who substituted low-fat meat and dairy products for high-fat meat and dairy products did not develop new lesions. LDL-C levels, which averaged 4.40 mmol/L (170 mg/dL) at baseline, were reduced to 4.09 mmol/L (158 mg/dL) on trial. Eighteen placebo subjects who made no significant dietary changes except to increase polyunsaturated fat developed new lesions. LDL-C levels of 4.27 mmol/L (165 mg/dL) at baseline did not change on trial. On trial, lipid levels were not
statistically different between the two groups. Recent evidence indicates that LDL-C levels may not correlate with new lesion formation. Therefore, reduction of fat may have direct arterial wall benefit. Although clinical events were not significantly different between drug and placebo groups during 2 years of intervention, 10-year follow-up indicates that 29 subjects had one or more cardiac events after 2 years of randomized treatment; there were 8 cardiac deaths and 26 myocardial infarctions. These events occurred in 8 drug-treated subjects versus 21 placebo subjects ($P=0.01$). Both GCS and QCA assessment of progression at 2 years were predictive of these subsequent cardiac events. These results indicate an internal consistency of the CLAS as well as an internal validity of two distinctly different methods of assessment of lesion change, subjective panel reading and fully automated computerized QCA.

**Later Trials**

The Program on the Surgical Control of the Hyperlipidemias (POCSH) was designed for simultaneous observation of overall and coronary mortality or morbidity and coronary angiographic changes. Men and women with previous myocardial infarction were randomized: 417 to a control group and 421 to ileal bypass surgery for reduction of blood cholesterol level. The primary end point was death due to any cause. Secondary end points were coronary death, recurrent myocardial infarction, and coronary angiographic change 3, 5, 7, and 10 years after randomization. Overall mortality and mortality due to coronary heart disease were not significantly reduced. Deaths due to coronary heart disease and nonfatal myocardial infarction combined were 35% lower in the surgery group (125 versus 82 events; $P<0.001$). Overall mortality in the surgery subgroup with an ejection fraction $\geq 50\%$ was 36% lower (39 control subjects versus 24 surgery subjects, $P=0.021$). GCS in POSCH, as in CLAS, was predictive of clinical events. Comparison of baseline coronary angiograms with those obtained at 3, 5, 7, and 10 years consistently showed less disease progression in the surgery group ($P<0.001$).

The Lifestyle Heart Trial recruited men and women between 35 and 75 years of age and randomized 53 subjects to risk reduction and 43 to a usual-care control group; 28 and 20 subjects, respectively, took part in the trial. Risk reduction included a low-fat vegetarian diet, smoking cessation, stress management, and aerobic exercise. Lipid-lowering drugs were not used. The treatment group target cholesterol intake was limited to $<5$ mg/d, contained 10% of calories as fat, and allowed no animal products except egg white and 1 cup per day of nonfat milk or yogurt. Stress management included stretching exercises, breathing techniques, meditation, relaxation, and imagery. Dietary fat and cholesterol, which averaged 32% of calories and 213 mg/d on entry, respectively, were reduced to 7% of calories and 12 mg/d. Average weight on entry was reduced from 200 to 178 lb, and average blood pressure decreased from 134/83 to 127/79 mm Hg. At the end of the 1-year interventional period, there were 22 treated and 19 control subjects with analyzable film pairs in which 105 coronary artery lesions in the treated group were compared with 90 lesions in the control group by fully computerized image processing. Average %S was reduced from 40.0% to 37.8% in the treated group and increased from 42.7% to 46.1% in the control group ($P=0.001$). Degree of adherence to lifestyle changes was directly correlated with extent of change in %S. The five women (all postmenopausal and not taking hormone replacement therapy) in this study, one in the intervention group and four in the control group, demonstrated regression with only moderate lifestyle changes. Lesions $>50\%$ demonstrated the greatest overall improvement in this trial.

The University of California, San Francisco, Specialized Center of Research (UCSF-SCOR) Intervention Trial was the first to report statistically significant coronary angiographic evidence of lesion regression in women. It was conducted in 72 subjects (41 women), 19 to 72 years of age, with heterozygous familial hypercholesterolemia, of whom only 3 subjects had objective evidence of coronary artery disease before the baseline angiogram. The treatment group received a combination of lipid-lowering agents, up to 30 g colestipol and 7.5 g niacin daily. When lovastatin became available, 16 subjects were given 40 to 60 mg daily in binary or ternary drug combinations. At first, the control group was treated with diet alone. Later, 7 control men and 7 control women took 15 g colestipol per day. The control group comprised those treated with diet alone and those with diet plus colestipol. After 2 years of treatment, angiograms were evaluated with per-subject averages in percent area stenosis determined by the computer-assisted method of Brown et al. Mean change in percent area stenosis among control subjects was +0.8%, indicating progression, whereas mean change for the treatment group was $-1.53$, indicating regression ($P=0.039$). When analyzed separately, lesion change among women was significant ($P=0.05$), whereas for men it was not ($P=0.42$). Treated women demonstrated a response of $-2.06$ in percent area stenosis, whereas men demonstrated a $-0.88$ change. Change in percent area stenosis was correlated with on-trial LDL-C levels.

The Familial Atherosclerosis Treatment Study (FATS) was the first angiographic trial to report reduced cardiac morbidity with medical treatment. One hundred forty-six men $\pm 62$ years of age with elevated apolipoprotein B levels ($\geq 125$ mg/dL) and a family history of coronary artery disease were randomized to colestipol- lovastatin, colestipol-niacin, or conventional care. Angiograms were separated in time by an average of 2.5 years and analyzed by a computer-assisted method. In the control group, 46% of subjects had lesion progression in at least one of nine proximal coronary segments. Progression was less frequent in subjects treated with colestipol- lovastatin (21%) and colestipol-niacin (25%). Regression was more frequent in subjects treated with colestipol- lovastatin (32%) and colestipol-niacin (39%) than in control subjects (11%). Multivariate analysis indicated that reduction in apolipoprotein B (or LDL-C) and systolic blood pressure and increase in HDL-C correlated with regression. Lesions $\geq 50\%$ at baseline showed a preferential response to therapy in both the proximal and all-lesion analyses. In the colestipol- lovastatin and colestipol-niacin groups, proximal lesions $\geq 50\%$ at baseline regressed an average of $-3.9\%$ and $-6.5\%$, respectively. In contrast, lesions...
<50%S progressed +0.2%S in both groups. Results were similar in the all-lesion analysis. In the colesterol-
lovastatin and colesterol-niacin groups, lesions ≥50%S at baseline regressed —2.6%S and —6.4%S, respectively, whereas lesions <50%S progressed +0.4%S and +0.1%, respectively. Clinical events (death, myocardial infarction, or revascularization) occurred in 10 of 52 control subjects compared with 3 of 46 colesterol-
lovastatin and 2 of 48 colesterol-niacin subjects. Relative risk of a clinical coronary event during lipid-
lowering therapy compared with conventional care was 0.27 (95% confidence interval, 0.10 to 0.77).

The St Thomas’ Atherosclerosis Regression Study (STARS) randomized 90 men with coronary heart dis-
ease; 74 subjects completed the study with paired angiograms, 24 in the usual-care group, 26 in the dietary intervention group, and 24 in the diet-cholestyramine group.14 Angiograms were performed at baseline and after 39 months. Mean absolute arterial width, the primary end point, was measured by a fully automated computerized method. The proportion of subjects who showed overall progression of coronary narrowing was reduced by both interventions, 15% of subjects in the diet group and 12% in the diet-cholestyramine group compared with 46% in the control group (P < .02 for trend). Regression occurred in 38%, 33%, and 4% of subjects, respectively (P < .02 for trend). Per-patient average width of coronary segments decreased 0.201 mm in control subjects and increased 0.003 mm with diet and 0.103 mm with diet-cholestyramine (P < .012 for trend). Per-patient change in %S did not show a significant trend effect (P = .077). With segments rather than subjects as the experimental unit, treatment effects were significant for trend (P .07). Regression occurred in 38%, 33%, and 4% of subjects as the experimental unit, treatment effects were significant for trend (P = .07). Regression occurred in 38%, 33%, and 4% of subjects with baseline and 2-year angiograms available for inter-
pretation. Although mean change in %S by QCA for all lesions was not significant, +1.6%S versus +2.2%S in the lovastatin and placebo groups, respectively, there was a significant response to therapy according to baseline lesion size. There was no statistical difference between treatment groups for change in lesions <50%S at baseline: +2.6%S in the lovastatin group and +3.0%S in the placebo group. However, for lesions ≥50%S at baseline, there was a mean decrease of —4.1%S with lovastatin therapy compared with +0.9%S with placebo (P = .005). Minimum lumen diameter (MLD), an absolute measure of lumen width, paralleled %S, providing this latter measure with an internal consistency, since MLD is independent of the assump-
tion that adjacent segments are normal. Mean change in MLD for all lesions was not significant, —0.03 versus —0.06 mm in the lovastatin and placebo groups, respectively. For lesions <50%S at baseline, there was no statistical difference between treatment groups in change in MLD, —0.05 mm for lovastatin versus —0.07 mm for placebo. However, for lesions ≥50%S at baseline, lovastatin increased mean MLD +0.13 mm compared with —0.04 mm with placebo (P = .002).

Assessed by QCA, progression occurred in fewer lovastatin subjects (29%) than placebo subjects (41%), P = .07. Regression was twice as frequent in lovastatin subjects (23%) as placebo subjects (12%), P = .04. By panel evaluation, mean GCS in lovastatin subjects was By subjects (23%) as placebo subjects (12%), P = .04. Panel evaluation, mean GCS in lovastatin subjects was

SCRIP included 300 men and women (13%) ≤75 years of age and randomized 155 subjects to usual care and 145 subjects to multifactorial risk reduction with drug treatment (principally colesterol-niacin), diet, smoking cessation, weight reduction, and exercise.50 Fully computerized arterial diameter measurements were made in nonbypassed coronary segments at base-
line and 4 years later. Annual rate of change in mini-

mum coronary artery diameter was —0.046 mm in the

control group and —0.022 mm in the risk reduction group (P < .01). Regression occurred in 21% of risk reduction subjects and 10% of control subjects (P = .025). New lesion formation was reduced, occurring in 20% of risk reduction subjects versus 36% of control subjects (P = .01).51 In the first study year, there were 7 deaths or nonfatal myocardial infarctions in the risk reduction group and 14 in the control group (P = .18). Over the next 3 years of the study, there were 2 clinical cardiac events in the risk reduction group and 13 in the control group (P = .006).

MARS is the first angiographic trial to test the effects of single-drug therapy with a 3-hydroxy-3-methylglu-
taryl coenzyme A reductase inhibitor.52 In this 2-year coronary angiographic/carotid ultrasonographic trial, 270 smoking and nonsmoking men and women 37 to 67 years of age were randomized to lovastatin 40 mg twice daily or placebo. Both treatment groups had daily cholesterol intake targets of ≤250 mg and daily fat intake ≤27% of calories, with saturated fat constituting ≤7% of total calories and monounsaturated and poly-
unsaturated fats ≤10% of calories each. This is the only trial to prospectively evaluate coronary angiographic films by computerized QCA with automated edge-
detection algorithms (primary end-point methodology), which is independent of human interpretation, and by panel-based readings with GCS (secondary end-point methodology). Longitudinal B-mode ultrasonographic measurement of distal CCA far-wall IMT with a fully automated computerized edge-detection method was an additional end point, as discussed later. Because of the minimal side effects of lovastatin, this was the first truly double-blind clinical imaging trial.

There were 247 subjects (123 lovastatin, 124 placebo) with baseline and 2-year angiograms available for inter-
pretation. Although mean change in %S by QCA for all lesions was not significant, +1.6%S versus +2.2%S in the lovastatin and placebo groups, respectively, there was a significant response to therapy according to baseline lesion size. There was no statistical difference between treatment groups for change in lesions <50%S at baseline: +2.6%S in the lovastatin group and +3.0%S in the placebo group. However, for lesions ≥50%S at baseline, there was a mean decrease of —4.1%S with lovastatin therapy compared with +0.9%S with placebo (P = .005). Minimum lumen diameter (MLD), an absolute measure of lumen width, paralleled %S, providing this latter measure with an internal consistency, since MLD is independent of the assump-
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placebo subjects regressed or stabilized (53% versus 35%, P<.01). By panel evaluation, progression was also deemed to occur in fewer lovastatin subjects (47%) than placebo subjects (65%), P<.01. Regression was also considered by the panel to be twice as frequent in lovastatin subjects (23%) as in placebo subjects (11%), P<.02.

Multivariate analysis indicates absolute change in TC/HDL-C to be the best predictor of lesion change in the placebo group for lesions <50%S and ≥50%S. With LDL-C reduction below 2.20 mmol/L (85 mg/dL) in the lovastatin group, on-trial LDL-C/HDL-C was the best predictor of lesion change for lesions ≥50%S. For lesions <50%S, on-trial apolipoprotein C-III levels in LDL+very-low-density lipoprotein, a marker of triglyceride-rich lipoprotein metabolism, were the best predictor of lesion change. These analyses confirm CLAS findings, indicating that triglyceride-rich lipoproteins play an important role in coronary artery lesion progression, their importance unmasked once LDL-C is aggressively lowered. These results are the first to indicate that lipoproteins have an important differential effect on lesion progression according to lesion size.

Subgroup analyses of women in MARS indicate two trends: Women may have a better lesion response to lipid lowering than men, and estrogen replacement may enhance lesion response to aggressive lipid lowering. The %S change after 2 years was +2.0%S for men on lovastatin, +0.8%S for women on lovastatin, and -2.1%S for women on lovastatin and estrogen. The observation in MARS that women may have a better lesion response to therapy than men has also been reported in the UCSF-SCOR and Lifestyle Heart Trial. It is also consistent with evidence indicating that lesions in women appear pathologically younger than those in men. Compared with those in men, coronary artery lesions in women consist of more cellular fibrous tissue, found at earlier stages of plaque development, and less dense fibrous tissue, found at later stages of plaque development. This difference in plaque composition suggests a pathological basis for expecting a greater potential for response to therapy in women.

The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) randomized 331 subjects ≥70 years old to dietary therapy and either placebo or lovastatin. Lovastatin or placebo was titrated to 40 mg or 80 mg per day to attain an LDL-C ≤3.40 mmol/L (131 mg/dL). This occurred in 69% of lovastatin and 10% of placebo subjects. Coronary angiograms were obtained at baseline and at 2 years in 299 subjects. Mean reduction in MLD, indicating progression, was -0.05 mm for lovastatin and -0.09 mm for placebo subjects (P<.02). There was no significant difference in the number of lovastatin and placebo subjects with regression. Progression and new lesion formation occurred in fewer lovastatin subjects (P<.05).

Meta-analysis of Lipid-Lowering Trials

Data from the NHLBI Type II, CLAS, POSCH, UCSF-SCOR, FATS, STARS, and Lifestyle Heart Trial have been combined for a meta-analysis of lipid lowering in secondary prevention (personal communication from Dr Jacques E. Rossouw). Analysis demonstrates that regression and stabilization are 2 and 1.4 times more common in treated than placebo subjects and that progression is reduced by half in treated subjects. Odds ratios for regression, stabilization, and progression comparing the 688 treated subjects with the 593 control subjects demonstrate that lesions in women consist of more cellular fibrous tissue, found at earlier stages of plaque development, and less dense fibrous tissue, found at later stages of plaque development. This difference in plaque composition suggests a pathological basis for expecting a greater potential for response to therapy in women.

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Non-Lipid-Altering Agents and Arterial Wall Protection

Two trials of calcium channel-blocking agents indicate that new and early lesion formation can be reduced by agents that protect the vessel without greatly modifying the risk factor level. The feature of both trials was concentration of therapy benefits on clinical coronary events and all-cause mortality, comparing all 793 treated with 708 control subjects from the seven coronary angiographic trials (see text for details).
TABLE 1. Summary of Angiographic Trial Treatment Groups: Mean Lesion Changes According to Baseline Lesion Size

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>n</th>
<th>&lt;50%S</th>
<th>&gt;50%S</th>
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</thead>
<tbody>
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<td>MARS</td>
<td>Lovastatin</td>
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<td>+2.6*</td>
<td>-4.1</td>
</tr>
<tr>
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<td>Cholestyramine</td>
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*All values except those for Leiden Intervention Trial represent mean change in percent diameter stenosis (%S): (+) change represents increased %S or lesion progression, (-) represents decreased %S or lesion regression.

Leiden values represent mean percent change in vessel diameter: (+) change represents mean percent increase in vessel diameter, or lesion regression; (-) change represents mean percent decrease in vessel diameter, or progression.

†Proximal lesions only; all other values are irrespective of location.
‡Mean %S change for lesions 15%S to 50%S at baseline.
§Mean %S change for lesions <15%S at baseline.

the earliest lesions visible on an angiogram. Recent data from the International Nifedipine Trial on Anti-atherosclerotic Therapy indicate that although progression of existing lesions was correlated with LDL-C levels and the LDL-C/HDL-C ratio, new lesion formation was not. It is important to remember that these are the earliest intrusions into the vessel lumen, not the earliest stage of lesion formation. These findings have important implications, since NHLBI Type II, CLAS, FATS, STARS, MARS, Leiden Intervention Trial, and Lifestyle Heart Trial indicate that LDL-C reduction may preferentially alter progression of lesions ≥50%S (Table 1) and typically retards coronary artery lesion progression in only 50% to 80% of subjects. Improved therapeutic regimens to alter progression of coronary atherosclerosis may require adjunctive therapy in concert with LDL-C reduction to prevent new lesion formation or early lesion progression, such as for lesions <50%S. This adjunctive therapy could be envisioned as being non-lipid-altering drugs, such as calcium channel blockers; antioxidants; or hormonal agents, such as estrogen replacement therapy in postmenopausal women, as MARS has suggested. Recent data from CLAS also reconfirm this proposition. Subjects with >30 IU/d of supplemental intake of vitamin E demonstrated less coronary artery lesion progression (P < .03) than those whose intake was ≤30 IU/d, an effect apparent in lesions <50%S (P < .04). Likewise, adjunctive therapy may include agents that concomitantly affect other lipoprotein particles, such as lipoprotein(a) or triglyceride-rich lipoproteins, which CLAS and MARS indicate are prominent risk factors for progression of lesions <50%S.

Sequential Coronary Angiographic Determination of Progression as a Surrogate End Point for Future Clinical Coronary Events

POSCH demonstrated that the GCS between 695 baseline and 3-year angiographic film pairs, assessed by human panel readers according to CLAS methods, predicted clinical coronary events between years 3 and 10 (mean follow-up after 3-year angiogram was 6.7 years). Progression by GCS predicted overall (P = .01) and atherosclerotic coronary heart disease (P = .003) mortality and combined atherosclerotic heart disease mortality and confirmed nonfatal myocardial infarction in the surgery group (P = .04) and control group (P < .0001). A recent report from a controlled angiographic trial of nicardipine indicated that progression of coronary artery disease, defined as an increase of ≥15%S in one or more coronary segments as assessed by QCA between baseline and 2-year angiograms, predicted subsequent cardiac events determined over a mean follow-up period of 44±10 months from the second angiogram. The relative risk (95% confidence interval) of subjects with progression compared with those without was 7.3 (2.2 to 24.7, P < .001) for cardiac death, 2.3 (1.3 to 4.2, P = .009) for cardiac death or nonfatal myocardial infarction, 1.4 (1.0 to 2.0, P = .057) for revascularization, and 1.7 (1.3 to 2.3, P < .001) for any cardiac event. Ten-year follow-up (median, 85.2 months after 2-year angiogram) in CLAS indicates that per-patient assessment of coronary artery lesion progression by both GCS and QCA predicts subsequent cardiac events. Relative risk (95% confidence interval) predicted by GCS for nonfatal myocardial infarction was 1.6 (1.0 to 2.5,
and for nonfatal myocardial infarction and cardiac death combined, 1.6 (1.1 to 2.5, P=.04). For every 10% decrease in the mean per-patient %S assessed by QCA, the relative risk for nonfatal myocardial infarction was 2.1 (1.2 to 3.9, P=.01) and for nonfatal myocardial infarction and cardiac death combined, 2.2 (1.3 to 3.9, P=.006). When lesions were dichotomized by size, QCA-assessed change in lesions <50%S at baseline predicted subsequent clinical coronary events, whereas lesions ≥50%S did not.43

CLAS follow-up data indicate that reduced progression of lesions <50%S at baseline reduces future cardiac events. Accumulating evidence indicates that coronary artery lesions <50%S to 70%S are responsible for the majority of acute cardiac events.28-30,61 Data from FATS, the only controlled clinical trial to date to examine the relation of acute cardiac events to culprit coronary lesions, are consistent with these findings since progression of lesions <70%S at baseline to coronary events was dramatically reduced by both the colestepliol-lovastatin and colestepliol-niacin regimens. There were 13 on-trial coronary events associated with a culprit lesion in FATS. Of the nine coronary events occurring in the control group, eight arose out of the 414 lesions <70%S at baseline. Only 1 of 683 lesions <70%S at baseline progressed to an event in the two treated groups (per subject or per lesion, P<.004). Lesions ≥70%S at baseline did not appear to benefit from therapy, since three events in the 36 lesions ≥70%S in the treated groups and one event in the 16 lesions ≥70%S in the control group progressed to a coronary event (P=NS).49-62

Taken together, these findings strongly indicate that end points from sequential coronary angiographic films can serve as surrogates for future clinical coronary events, justifying the design of shorter trials for the treatment of atherosclerosis. These findings also offer the opportunity to advance the state of the art of computerized coronary angiography. Among a variety of computer end-point measures, only %S has been consistently reported from trials. CLAS films offer an opportunity to determine whether other measures, such as minimum or average vessel diameters and lesion length and shape, should be added for improved prediction of future clinical coronary events. Until coronary angiograms are more adequately calibrated against specimens with known atherosclerosis, the interpretation of trial results can be improved by additional knowledge of which measures are most predictive of future clinical events.

**Future Directions**

**Improved Computerized Image Processing**

Coronary angiographic trials could be improved by additional calibration of computer measures. It is important to validate at least one coronary measure to compare therapy effects among different trials. Except for adult pigs, animal models for atherosclerosis do not realistically simulate radiographic conditions in humans; rabbits and monkeys are too small. Postmortem human coronary angiograms do not recreate in vivo motion. As a result, the repeatability of coronary image processing has been extensively reported43 in lieu of tests for accuracy in truly representing the coronary status. There is general agreement that coronary angiography in humans underestimates coronary artery disease compared with postmortem specimens.64 The most credible evaluation of coronary angiography reported to date was a study by Weiner et al65 in 200-lb pigs in which it was reported that lesion size was underestimated.

It would be useful to learn which coronary arterial measurements best predict coronary events. Predictability can be determined from long-term follow-up of completed coronary angiographic trials, in particular CLAS, in which both GCS derived from human panel reading and %S from QCA predict future coronary events.66 The finding that GCS and QCA, two independent methods of interpreting lesion change, predict coronary events from the same set of angiographic films adds internal consistency to both human and automated computerized methods of lesion analysis and adds a whole new dimension to determining angiographic predictability of clinical events. In CLAS films, 36% of the variance of GCS can be explained by computer-derived %S,67 suggesting that films from CLAS, evaluated by both human and fully automated methods of automated imaging, can be examined with a variety of computer measures to find which arterial measurements alone or in combination have optimal predictive ability. Since angiograms cannot visualize the constituents of atherosclerosis, this approach would accept all the limitations of angiography and image processing and not attempt to determine the "true" status of lesions, but rather which events are predicted by the angiographic appearance of lesions.

A comparative analysis of CLAS films could also help with the problem of incomplete lesion counts. In two comparisons of clinical trial films from CLAS68 and MARS,32 human readers read a different but overlapping set of lesions compared with fully automated QCA. Trials that have used only QCA14,38,48-50,56-58,60 so far have reported measurements on a selected set of proximal lesions or have reported fewer lesions than trials that use human readers.12,52 For example, in the Life-style Heart Trial, when all QCA-processable lesions were measured, there were 4.8 lesions per subject. In CLAS and MARS, human readers reported 11.1 and 12.4 lesions per subject, respectively. With CLAS, it should be possible to determine whether future clinical coronary events can be predicted from a subset of lesions. This information may be helpful in establishing the clinical significance of angiographic trial results in secondary prevention of ischemic heart disease.

As the traditional measure used by angiographers, %S has been most widely used in clinical trials, but other measures that better reflect hemodynamics and diffuse coronary artery disease have potential clinical applicability. One such measure links physiological and anatomic descriptors of coronary artery stenosis using coronary blood flow reserve as a single integrated functional measure to account for the combination of all geometric dimensions of a lesion.57,68 This physiologically oriented method reflects a physiological measure of the severity of coronary artery stenosis. Other measures that relate coronary artery cross-sectional lumen area, sum of coronary artery branch lengths, and regional myocardial mass can be used to assess diffuse coronary artery disease with or without segmental narrowing, since they are independent of a "normal" lumen.
Hypothesis Testing and Trial Design

Conclusions from completed imaging trials will help select hypotheses for testing in future imaging trials. To date, imaging trials have tested only hypotheses based on epidemiological, tissue culture, or animal studies. The results of imaging studies can provide entirely new hypotheses. For example, as observed in CLAS and MARS when LDL-C is aggressively reduced, triglyceride-rich lipoproteins assume control of atherogenesis. It is important to expand the scope of in vivo lesion staging to take full advantage of the new intervention targets that now seem possible.

Need for Low-Cost Noninvasive Imaging

Noninvasive Population Screening

Therapy testing as well as study of atherosclerosis progression and risk factor associations could be greatly improved with noninvasive imaging procedures. Furthermore, if noninvasive images could serve as an early warning procedure and be applied to populations at risk, it would be advantageous to detect lesions growing at a hazardous rate, particularly in individuals who may not be recognizable by the presence of high risk-factor levels.

Each of the two broad categories of noninvasive imaging of atherosclerosis addresses different issues. Those that image the arterial lumen are useful for studying obstructive disease and relations to clinical events. Noninvasive coronary angiographic measurements of arterial lumen changes can be performed frequently and, combined with perfusion imaging, yield a comprehensive cardiac evaluation combining both anatomic and functional information. Noninvasive imaging that focuses on the arterial wall, and more specifically on IMT, quantifies risk factor relations to early atherosclerosis. Arterial wall imaging has an advantage over imaging procedures that focus on lumen changes because it directly assesses response of early atherosclerosis to risk factor modification. However, noninvasive imaging of the coronary arterial wall has severe limitations, and surrogate peripheral vessels, such as the CCA, must be used. Clearly, the type of imaging procedure used in study design depends on the question being addressed. Trials now in progress or being planned are designed primarily to compare the relative effectiveness of therapies for retarding and reversing atherosclerosis rather than proving that regression can occur. In practical terms, this means comparing new therapy with conventional therapy rather than a placebo.

Images used in current clinical trials are those attained with available clinical imagers or clinical imagers with minor modification. Typically, reducing the invasiveness of procedures and/or improving image quality has increased the cost of imaging. For example, intravenous digital angiography reduces invasiveness and increases image quality of angiography; computerized tomographic (CT) scanning reduces invasiveness of intravenous digital angiography; and magnetic resonance imaging (MRI) improves image quality of CT scanning. This progression in instrument sophistication has resulted in a 20- to 30-fold increase in instrument cost. Similar cost increases have occurred in cardiac ultrasound imagers.

Noninvasive Imaging of the Coronary Arteries

MRI provides excellent contrast of soft tissues and visualizes coronary arteries without contrast agents. However, visualization of coronary arteries with standard spin-echo or gradient-echo MRI is limited because cardiac and respiratory motion results in confounding artifact. More recent techniques, such as MRI fast-subtraction angiography, three-dimensional MRI angiography from two-dimensional planar image scanning, fast spiral MRI, and ultrafast MRI coronary angiography have been developed to assess coronary arteries. Only ultrafast MRI coronary angiography has been applied to the detection of coronary artery occlusion. This technique shows great potential as a noninvasive tool for detecting intrusive coronary artery disease. The other techniques await further study for applicability.

CT requires contrast enhancement to accentuate differences between blood and cardiac tissue to visualize coronary artery occlusion. Only portions of coronary arteries can be imaged, and the artery must be aligned in the plane of the CT section. Therefore, CT techniques have limited value for imaging native coronary artery lesions. However, CABGs can be imaged in cross section because they are of greater caliber than native coronary arteries, they are not tortuous, and their proximal portions course vertically. Even though CT can image CABGs, error rates make this method more reliable for graft patency rather than occlusion.

Two-dimensional echocardiography is another noninvasive technique that images coronary artery occlusion. Although two-dimensional transthoracic echocardiography can visualize left main and proximal right coronary segments, it has limited capability in other coronary artery segments and has questionable reliability in detecting coronary artery stenosis. A slightly more invasive technique, transesophageal two-dimensional echocardiography, can detect occlusion of the left main coronary artery but also has limited visualization capabilities elsewhere.

Because of its greater resolution, ultrafast CT is more sensitive for imaging and quantifying calcification within the coronary arterial wall than other radiographic techniques. Calcium is frequently present in coronary artery atherosclerotic plaques and is associated with increased mortality. However, the natural history of coronary artery calcification and its clinical significance are unknown. Coronary artery calcification as presently imaged is not a reliable indicator of atherosclerosis. Furthermore, this technique has limited capability in measuring extent of coronary artery atherosclerosis. These major issues limit the usefulness of this noninvasive technique for clinical trials.

Despite the availability of noninvasive methods for assessment of coronary arteries, none have sufficiently proven precision, accuracy, or reproducibility to warrant use in large-scale population studies or clinical trials for tracking atherosclerotic lesion changes. The cost of these imaging procedures indicates the need for a surrogate vessel such as the CCA, in which imaging precision and accuracy have been determined and which
can be readily and reproducibly surveyed in a cost-effective fashion.

**Noninvasive Imaging of Peripheral Vessels Cross-Correlation Between Vessel Beds**

Current trials typically target secondary prevention because of the risks from coronary angiography. These trials have taught us that formation of new coronary lesions can be reduced by a variety of treatments. Peripheral vessels are inherently easier to image than are coronary arteries. Therefore, noninvasive peripheral vessel imaging offers a next step toward the study of primary coronary prevention through reduction of new lesion formation.

The CCA is an attractive peripheral surrogate vessel for coronary artery atherosclerosis. Data from the International Atherosclerosis Project (IAP) show parallel age-related trends in raised lesions in the abdominal aorta and coronary and carotid arteries (Fig 3). The sequence of lesion development is aorta, coronary artery, and then carotid artery in both men and women. The degree of carotid atherosclerosis in both men and women is significantly correlated (range, 0.4 to 0.6) with the degree of atherosclerosis found in the coronary arteries. Fig 4, also from the IAP, compares fatty streaks and fibrotic lesions in five divisions of the common and internal carotid arteries. Four hundred twenty-seven men from Oslo, an area with a high risk of atherosclerosis, are compared with 161 men from Guatemala, a low-risk area. The distal CCA contains fatty streaks in 100% of men ≥25 years of age in both Oslo and Guatemala. Fibrotic lesions in the distal CCA
approach 90% prevalence after age 35 in Oslo and 80% prevalence after age 55 in Guatemala. Formation of fatty streaks and early fibrotic lesions in the carotid artery is influenced by position within the vessel but not by sex. Fig 5 and other IAP data indicate that advanced complicated lesions are significantly less frequent in the distal CCA than in the internal carotid artery. Ku et al demonstrated that flow separation at the carotid bifurcation accelerates lesion progression. In the distal CCA, where blood flow is laminar, fatty streaks and early fibrosis are ubiquitous but progress slowly.

The lower abdominal aorta is a clear first choice for imaging as a sentinel vessel for coronary artery atherosclerosis. This was first shown in IAP and confirmed by the World Health Organization (WHO) Study. Both studies were autopsy surveys comparing the distribution of atherosclerosis in diverse populations. Fig 6, from WHO, shows the parallel age-related trends in abdominal aorta and coronary artery atherosclerosis, with the aorta always exhibiting a greater degree of atherosclerosis in both men and women. Like carotid atherosclerosis, the degree of atherosclerosis in the abdominal aorta is significantly correlated (range, 0.4 to 0.6) with the degree of coronary artery atherosclerosis in both men and women. Studies by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group have added three important facts relevant to the aorta as a sentinel vessel: (1) Significant correlation in the severity of atherosclerosis between coronary arteries and the aorta is seen as early as 15 to 34 years of age; (2) smoking influences coronary and aortic lesion prevalence at ages 15 to 34; and (3) the exact location of aortic lesions in young individuals has been mapped. The prime aortic area for lesion formation is on both lateral walls just above the aortic bifurcation.

In sum, data indicate that the degree of intervessel correlation between coronary and aortic and coronary and carotid artery atherosclerosis is sufficient to allow aortic and carotid images to be used to identify individuals with a high probability of coronary artery disease. However, as stated earlier, lesions within the coronary arterial bed behave independently of each other, and mixed lesion responses to lipid lowering have been reported in clinical trials. In the NHLBI Type II study, 5% of subjects had mixed lesion responses, both progression and regression. One explanation for this may be that atherosclerotic lesions of different ages respond differently to lipid lowering because of differing physiochemical and histological characteristics, as reported by Small et al and others. Therefore, there are limitations to drawing conclusions about specific coronary artery lesions from changes in peripheral vessels. When the consideration is to demonstrate specific coronary artery lesion changes within an individual, direct coronary artery imaging will have to be performed.

### Lesion Staging in Peripheral Vessels

Sophisticated assessment of in vivo lesion staging is more likely in peripheral than in coronary vessels, for several reasons. First, images of straight unbranched peripheral vessels are simpler to evaluate. Second, vessels close to the body surface can be imaged with higher resolution than deep vessels with procedures now available (radiography, ultrasound, and MRI).
Last, grading schemes require reference vessels with lesions of known severity. Postmortem specimens are ideal for this purpose, since they can be examined by any required reference: microscopy, ultramicroscopy, histochemistry, or analytical chemistry. Postmortem imaging can accurately mimic in vivo imaging in peripheral vessels, which are relatively motionless, but not coronary vessels, in which in vivo images are in constant motion. It follows that solutions to problems in lesion staging are linked to the cross-correlation of disease severity in peripheral versus coronary vessels. The CCA is a prime site for early preintrusive atherosclerosis lesion tracking by ultrasound, because it lies at a depth in tissue that can be reached by short wavelengths that give high-resolution images.

**Noninvasive Imaging of the Common Carotid Arterial Wall**

Low-cost, noninvasive measurement of distal CCA wall thickness, and more specifically IMT, is possible and informative about coronary artery status in groups of individuals. Large epidemiological and case-control studies have demonstrated an association between IMT, as measured by B-mode ultrasound, and cardiovascular risk factors in both men and women. This finding suggests that the association between coronary and carotid atherosclerosis depends, in part, on exposure of both arterial beds to the same risk factors. Several population-based studies have demonstrated a strong relation between carotid arterial wall thickness and angiographic presence (defined as a coronary lesion >50% S) of coronary artery disease or a confirmed history of coronary artery disease in both men and women. In these studies, arterial wall thickness demonstrated a correlation with coronary artery disease as good as or better than traditional lipid and nonlipid risk factors. A strong relation between carotid arterial wall thickness measured by B-mode ultrasonography and the extent of coronary atherosclerosis determined by the number of coronary vessels with lesions has also been demonstrated.

CLAS results support growing evidence for the usefulness of B-mode ultrasound measurement of IMT for the study of coronary artery risk factors. Significant correlations between distal CCA far-wall IMT and carotid and coronary angiographic measurements of atherosclerosis were found in a subgroup of 57 CLAS subjects with matching baseline and 2-year B-mode ultrasonograms of the CCA and matching carotid and coronary angiograms. At baseline, distal CCA far-wall IMT correlated with carotid angiographic edge roughness (r = .31, P < .05) and coronary artery average %S (r = .27, P < .05). Correlations between distal CCA far-wall IMT and carotid angiographic edge roughness (r = .26, P < .05) and coronary artery average %S (r = .29, P < .025) were also demonstrated after 2 years of intervention.

Several observations about these findings should be noted. This is the first evidence that distal CCA far-wall IMT, determined by B-mode ultrasound, correlates with a quantitative computerized angiographic measure of carotid atherosclerosis. We have previously shown that computer measures of angiographic edge roughness correlate significantly with vessel wall cholesterol content (r = .702, P < .001) and the extent of visible atherosclerosis (r = .739, P < .001). Second, this is the first evidence that distal CCA far-wall IMT correlates with coronary artery %S. Unlike previous studies, correlations in CLAS were conducted with computerized measurements of IMT and coronary artery average %S as continuous variables. Furthermore, other studies primarily use averaged arterial wall thickness measurements from both CCA and internal carotid arteries and/or far- and near-wall measurements. CLAS findings indicate that the distal CCA far-wall IMT, as a single measure, is associated with coronary artery disease.

The correlation between carotid and coronary atherosclerosis assessed by imaging is not surprising, since carotid and coronary atherosclerosis are correlated in autopsy series. In addition, IMT assessed by B-mode ultrasound has been validated with tissue specimens. The distal CCA lags behind the carotid bulb and internal carotid artery in formation of intrusive lesions but has a high prevalence of fatty streaks and fibrous plaques in populations both at high and low risk for atherosclerosis. By taking advantage of early preintrusive atherosclerotic lesion formation in the distal CCA, CLAS and MARS findings indicate that B-mode ultrasonography using a fully automated, computerized, edge-detection method for measurement of IMT can augment studies of coronary artery intrusive lesions.

CLAS is the first randomized, placebo-controlled, lipid-lowering study to demonstrate treatment benefit on carotid atherosclerosis using a noninvasive end point derived from ultrasound images of the arterial wall. CLAS findings confirm epidemiological and case-control studies, indicating that B-mode ultrasound measurement of the distal CCA far-wall IMT is a reliable measure of early atherosclerosis. In CLAS, reduction in distal CCA IMT was observed with colestipol-niacin therapy 6 months after randomization, with significant within- and between-treatment effects occurring as early as 1 year after therapy (Table 2). This treatment effect was confirmed 2 and 4 years after randomization (Table 2). Reduction in IMT was not accompanied by an increase in carotid artery lumen diameter. Temporal characteristics of IMT change indicated that with aggressive lipid-lowering therapy, IMT decreased at a rate of 0.026 mm per year over the first 3.2 study years and then plateaued over the remaining year. In the placebo

### Table 2. Longitudinal Change in Distal Common Carotid Far-Wall Intima-Media Thickness Determined by B-Mode Ultrasonography in CLAS Subjects

<table>
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<th>Coleslipol-Niacin</th>
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</tr>
<tr>
<td>P within</td>
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<td>.007</td>
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<td>22</td>
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<tr>
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<td>&lt;.0001</td>
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<td>P within</td>
<td>.001</td>
<td>.002</td>
<td></td>
</tr>
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*Mean(SD). Values are in millimeters.
group, IMT progressively increased over the 4-year study period at a rate of 0.018 mm per year (Fig 7).98 Findings from CLAS suggest that small-scale clinical trials to assess coronary artery risk factors by use of computerized measurements of distal CCA far-wall IMT as a surrogate noninvasive end point are feasible. Fully automated computerized edge-finding algorithms in CLAS detected treatment differences with sample sizes as small as 33 subjects.96 This automated computerized method makes closely spaced measurements of carotid IMT, typically 120 points per centimeter.102 This method is more precise than IMT measurements made by an operator who views a digitized image and places a computer cursor at intervals along lines of interest or manually traces the lines of interest.105,106 Our fully automated, computerized, edge-detection method decreases IMT measurement variability by a factor of two to four relative to manual techniques.102 Another important difference in our method versus others is that our measurement of a relatively uniform area of distal CCA is not pooled with measures from the bulb or internal carotid artery. This technique focuses our results on early stages of atherosclerosis and reduces measurement variability associated with ultrasound visualization of irregularities in intravascular lesions. Pooled standard deviation (0.13 mm) of the 4-year IMT group means obtained with the automated computerized method used in CLAS subjects indicates that a two-arm trial of 50 subjects per group could detect a difference in IMT of 0.07 mm with a power of 80%, and 25 subjects per group could detect a difference of 0.10 mm.97 In the subgroup of 46 CLAS subjects (24 coleste- pol-niacin treated, 22 placebo treated) with matching baseline, 2-year, and 4-year CCA ultrasonography and carotid and coronary artery angiograms, the difference in IMT between drug-treated and control subjects was 0.09 mm at 2 years and 0.12 mm at 4 years (Table 2). Sample size estimates based on the precision of our methodology have been confirmed independently by B-mode IMT measurements in MARS. When men from the MARS cohort who resembled those from the CLAS study (nonsmoking males with CABGs) were analyzed, a significant treatment effect was detected in 30 subjects after 2 years of intervention. In 15 subjects in the lovastatin group, IMT decreased −0.06±0.11 mm, whereas in the placebo group, IMT increased +0.07±0.07 mm (P<.0006).103 The pooled standard deviation from the MARS 2-year IMT group means, 0.09 mm, is comparable to that from CLAS (0.13 mm).

CLAS results are in accord with a report by Salonen and Salonen,100 that for each 0.1-mm increase in IMT, the risk of acute myocardial infarction increases by 11% (95% confidence interval, 6% to 16%; P<.001). This observational study suggests that CCA IMT is potentially predictive of clinical coronary events. However, before the change in CCA IMT can be accepted as a surrogate end point for coronary events in clinical trials, it must be verified by longitudinal measurements within individuals to determine its predictive validity. Since sequential coronary angiographic determination of progression predicted subsequent clinical coronary events in CLAS and since distal CCA far-wall IMT correlates with coronary angiographic measurements of atherosclerosis, CCA IMT will potentially be predictive of coronary events in CLAS. This is actively under investigation in our laboratory.

There are several advantages of a noninvasive surrogate end point for clinical coronary events. High-resolution B-mode ultrasonography has the advantage that it can be performed at any frequency in symptomatic or asymptomatic subjects of any age, can be used to quantify arterial wall changes in superficial vessels, and carries negligible risk. As demonstrated in CLAS and MARS, repeated measurements of IMT as a quantitative variable greatly reduce the sample size necessary for study. Additionally, all of the ultrasound studies discussed in this section were conducted with clinically available ultrasound imagers and low-cost image processing equipment. If it were desired to deploy instruments for wide-scale carotid arterial wall measurements, an off-the-shelf, single-purpose measurement system could be assembled for approximately $50 000. Furthermore, equal quality images can be obtained by portable ultrasound imagers, broadening the capability of this procedure relative to other noninvasive techniques, such as MRI.

Cost-Effectiveness of Noninvasive Peripheral Vessel Screening

Atherosclerosis is a multifactorial disease, and balance between importance of factors is bound to vary over time. For example, when smoking prevalence is reduced, the importance of smoking in atherogenesis will be reduced. Risk factors not previously recognized have been discovered when their prevalence increased or the prevalence of other risk factors decreased. As an example, before World War II, florid atherosclerosis of the aortic aneurysmal formation. These advanced forms of atherosclerosis disappeared with widespread penicillin treatment of syphilis. More recent examples of this concept can be found in CLAS and MARS, in which LDL-C was aggressively reduced. Once LDL-C was effectively reduced as a risk factor for lesion progression in the drug-treated groups of CLAS and MARS, triglyceride-rich lipoproteins became important risk factors for continued lesion progression. It follows that the goal for treatment may be a moving target.

To augment the current trend of progressively increasing cost that accompanies advancing technology in arterial imaging in tertiary centers, we need to deploy low-cost, noninvasive imaging capability in centers for
primary patient care. Cost/benefit analyses of coronary risk reduction indicate that costs are reduced by early identification of high-risk subjects. An early case finding and treatment strategy modeled on tuberculosis control, for example, could be applied to the prevention of coronary atherosclerosis and myocardial infarction with the use of noninvasive imaging. Coronary atherosclerosis is ubiquitous, but we know that some individuals develop more severe coronary atherosclerosis at an earlier age than others. A case finding and treatment strategy based on noninvasive imaging would benefit those with premature atherosclerosis who are not recognized with current risk factor screening until they develop symptoms. Screening for peripheral vessel changes indicative of high risk is possible and cost-effective with procedures now available.

Author’s Note
On November 16, 1992, Dr Blankenhorn presented the Duff Memorial Lecture at the American Heart Association’s 65th Scientific Sessions. At that time, he was in remission from prostate cancer. Unfortunately, a complete for my friend, mentor, and colleague.

Duff Memorial Lecture article, which would be our final writing effort together. Three days before his death on May 9, 1993, my last conversation with Dr Blankenhorn included a promise to complete this article. It has been, to say the least, one of the most emotionally difficult tasks I have undertaken but one that I am proud to complete for my friend, mentor, and colleague.

Howard Hodis, MD

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Abstract.

not with new lesion formation.

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