Clinical Cardiology Frontiers

Reversal of Coronary Atherosclerosis
Clinical Promise as the Basis for Noninvasive Management of Coronary Artery Disease

K. Lance Gould, MD

Coronary heart disease remains widely prevalent and is the leading cause of mortality and morbidity in the United States, with an estimated half-million deaths and $56 billion expended for hospital, physician, and medical-surgical costs associated with this disease.1,2 In war casualties of Korea and Vietnam, 12% to 20% of young men averaging 26 years old had coronary artery stenoses of 50% diameter narrowing or greater.3-6 It is therefore a conservative current estimate that 10% to 13% of middle-aged individuals in the United States have coronary heart disease,7-10 with up to 60% of heart attacks or sudden death occurring without prior warning symptoms sufficient to incur medical evaluation or treatment.11-14

For diagnosis of coronary artery disease, current cardiovascular practice focuses principally on ECG exercise testing, stress perfusion imaging, and coronary arteriography. For treatment, current cardiovascular practice focuses principally on antianginal drugs, percutaneous transluminal coronary angioplasty (PTCA), or bypass surgery. This review analyzes the basis for an alternative, comprehensive, noninvasive management of coronary artery disease using positron emission tomography (PET) perfusion imaging and vigorous risk factor modification aimed at regression of coronary atherosclerosis and stabilization of plaque to prevent the clinical events of myocardial infarction, sudden death, and unstable coronary syndromes requiring PTCA or bypass surgery. The diagnostic and therapeutic components of this approach, PET, and vigorous risk factor modification are analyzed separately and then integrated into a practical paradigm or protocol for the principally noninvasive management of coronary atherosclerosis as currently practiced by the author.

New concepts introduced into scientific literature are by definition only partially validated. When completely documented by multiple confirmatory studies, extensive data and wide acceptance, the concept is no longer new or even publishable. Therefore, to some extent this analysis reflects the author's personal perspective on current medical literature, on some data not yet published, and on his personal experience in clinical practice. While a randomized clinical trial of the approach described here in comparison to mechanical revascularization would be ideal, it is germane to point out that the most widely used elective cardiology therapeutic procedure, PTCA, has never been subjected to a randomized trial of its benefits in patients with stable coronary artery disease compared with medical therapy. In contrast, vigorous risk factor modification and/or lipid lowering in several randomized trials have demonstrated partial regression of stenoses and major reduction of cardiac events as detailed subsequently. This review goes beyond the traditional summary of what has been substantially proven. Rather, it is a rational synthesis of what is feasible, strongly supported by current medical literature, and demonstrated by the author's personal clinical practice as an example beyond mere academic conjecture. While many points will be challenged as inadequately validated, the purpose of this synthesis is to detail an alternative way of thinking about the primarily noninvasive management of coronary atherosclerosis that is as rational, clinically feasible, and no less validated than current more invasive practice paradigms.

Pathophysiology

The explanation for sudden death, myocardial infarction, or unstable coronary syndromes after a prolonged silent phase of coronary atherosclerosis is most commonly rupture of an atherosclerotic plaque associated with localized coronary thrombosis and/or spasm.15-21 Plaque rupture typically occurs at milder stenoses of 40% to 60% diameter narrowing or less15-21 that may not cause symptoms or ischemia on treadmill testing, which, therefore, may not predict future coronary events.8-10,22

Quantitative coronary arteriography of the entire coronary vascular tree indicates that patients with segmental coronary artery narrowing, even mild narrowing, have coronary artery lumen diameters that are diffusely 30% to 50% smaller than normal subjects' for the size of the regional distal myocardial mass.23,24 Quantification of focal stenoses on coronary arteriograms does not account for the cumulative effects of diffuse coronary atherosclerosis or multiple stenoses on the maximum perfusion capacity of the integrated arterial/arteriolar vascular system.25,24 Intracoronary ultrasound also demonstrates in vivo the presence of diffuse coronary atherosclerosis in patients with risk factors, even in the absence of segmental stenoses by arteriography.25-29

Thus, either with or without significant or symptomatic segmental coronary artery stenoses, coronary athero-
sclerosis is a diffuse process in the entire epicardial coronary artery tree, subject throughout to the risk of plaque rupture and associated coronary events in the absence of vigorous risk factor management.

Functional vasomotor abnormalities of the coronary arteries appear with both early and established coronary atherosclerosis and with or without hemodynamically significant segmental coronary narrowing.5-49 In experimental animals,42-50 coronary artery disease and/or hypercholesterolemia alone impair coronary arterial and distal arteriolar vasodilation mediated by endothelium, commonly in a regionally heterogeneous pattern.48 Atherosclerosis of proximal conduit epicardial coronary arteries impairs endothelium-mediated vasodilation of the distal microcirculation.30,34,41,43 Thus, the functional endothelium-mediated vasomotor abnormalities of epicardial coronary arteries also extend into the microcirculation despite absence of anatomic atherosclerosis in the coronary microcirculation. In both experimental animals and humans, cholesterol lowering improves the endothelium-mediated dilatatory capacity of both coronary arteries and distal arterioles.33,35,36,41,50 In women with coronary artery disease, estrogens acutely improve abnormal coronary vasomotor response to intracoronary acetylcholine.50

Reversal of Coronary Atherosclerosis

In recent randomized trials,51-64 vigorous cholesterol lowering by moderate low fat diet and cholesterol-lowering drugs or intensive lifestyle change resulted in stopping progression or partial reversal of coronary artery disease in up to 80% of treated subjects. The regression in these recent trials was only modest, 3% to 10% diameter stenosis units, depending on stenosis severity at baseline, but was consistently observed and statistically significant. There was a proportionately larger, major decrease in clinical events of myocardial infarction, death, bypass surgery, or balloon angioplasty in up to 80% of the treatment groups undergoing vigorous cholesterol lowering compared with control groups in several of these studies, including patients with severe coronary artery stenoses.15,16,18,22,55-58,59,62,63 This reason for proportionately greater clinical benefit than extent of anatomic regression appears to be plaque stabilization and reduction in the risk of plaque rupture, which leads to acute unstable coronary syndromes, particularly at sites of relatively mild narrowing in diffusely atheromatous coronary arteries.15-21 There is also a marked decrease in angina pectoris in parallel with decreased coronary events. Therefore, dietary and pharmacological cholesterol lowering provides an alternative approach to the treatment of coronary atherosclerosis that substantially reduces the necessity for balloon angioplasty or bypass surgery.

Several methods for lowering cholesterol demonstrate these benefits, including very low fat, low cholesterol diet alone (less than 10% of calories as fat), moderate low fat diet combined with cholesterol-lowering drugs, and ileal bypass surgery. Those studies with more vigorous cholesterol lowering of 35% or more or very low fat diets tend to show greater benefit on regression or prevention of events than studies with less vigorous intervention.15,16,62,63 Control groups in recent randomized trials on an American Heart Association diet of 20% of calories as fat show substantial progression of coronary artery disease and coronary events. In contrast, patients on diets of less than 10% of calories as fat showed regression or no progression.55,52 With a large number of food products made with no fat or low fat content, adhering to a very low fat diet is readily achievable with only moderate effort, even for tightly scheduled working individuals as subsequently discussed.

The combination of low fat diet of less than 10% fat as calories combined with cholesterol-lowering drugs has a more profound cholesterol-lowering effect than either of these treatment approaches alone and readily decreases cholesterol to 140 mg/dL or below in most patients, even with modest doses of an HMG CoA reductase inhibitor (statin) as the only drug. For individuals with very high density lipoprotein (HDL), the addition of smoking cessation, adequate dietary protein, exercise, and/or gemfibrozil or niacin usually normalizes HDL.

In patients with coronary artery disease and relatively normal levels of cholesterol at baseline, lowering cholesterol to well below normal ranges has substantial benefit,15,16,52,63,64 probably more than in patients with very high cholesterol levels.16 In the correlation of coronary-related deaths to cholesterol levels in the 10-year follow-up of 361662 men screened for the MRFIT program,63 mortality decreased continuously and was directly related to decreasing cholesterol down to levels of 140 mg/dL. Based on these reports and the author's personal experience, achieving lean body mass and a total cholesterol of 140 mg/dL or below with an HDL of 45 mg/dL or greater using a very low fat diet and lipid-altering drugs increases to over 90% the probability of partial regression or no progression of disease and absence of clinical events. Partial reversal of coronary artery stenosis and protection from clinical events occurs even in patients with initially normal cholesterol levels if these targets are reached.15,16,52,63,64

The essential major advance derived from these multiple cholesterol-lowering trials is the demonstration of partial regression or no progression by vigorous cholesterol lowering with an associated major decrease in clinical events proportionately larger than might be expected on the basis of the modest anatomic regression observed. These new approaches to the treatment of coronary atherosclerosis provide a relatively low-cost alternative to traditional invasive approaches that markedly decreases myocardial infarction, death, balloon angioplasty, or bypass surgery in patients with moderate or severe coronary artery stenoses. Finally, healthcare costs are substantially reduced with optimal outcomes.

Although used as a measure of changing stenosis severity in lipid-lowering trials, percent diameter narrowing by coronary arteriography does not account for the complex shape changes of stenoses,54 is poorly related to flow capacity or coronary flow reserve,55-71 and fails to account for diffuse disease present in most patients with or without localized coronary artery narrowing.23-29 The degree of improvement of percent stenosis in regression trials is quite modest, ranging up to 5% diameter stenosis units for all stenoses and up to 10% diameter stenosis units for more severe stenoses.51-64 Based on automated, objective, quantitative analysis of PET images before and after vigorous cholesterol lowering, the size and severity of myocardial perfusion abnormalities by PET after dipryidamole stress decrease or improve in patients undergoing in-
tense dietary changes and being treated with cholesterol-lowering drugs in comparison to an increase or worsening in patients treated with standard antianginal therapy alone.\textsuperscript{65,72,73} The improvement in perfusion abnormalities on PET images after vigorous cholesterol lowering demonstrates the functional changes in the atherosclerotic coronary arterial tree associated with the modest extent of anatomic regression by arteriography after cholesterol lowering. We have also demonstrated that vigorous cholesterol lowering by extreme dietary restriction or cholesterol-lowering drugs over a relatively short time of 90 days improves myocardial perfusion in patients with coronary artery disease before anatomic regression occurs, thereby suggesting improved vasomotor function.\textsuperscript{72}

The improvement in size and severity of myocardial perfusion abnormalities after dipyridamole stress in patients undergoing cholesterol lowering in comparison to worsening in control subjects most likely involves two mechanisms. The first, occurring over 1 or more years, is partial anatomic regression of localized coronary artery stenosis, as previously demonstrated by quantitative coronary arteriography. A second mechanism for decreased size and severity of perfusion abnormalities by dipyridamole PET is improved endothelium-mediated coronary artery and arteriolar vasodilation\textsuperscript{33,35,38,41,50} in response to high flows after initial direct arteriolar vasodilation induced by dipyridamole. In primates with coronary atherosclerosis, this improvement in endothelium-mediated vasomotor function of the coronary vasculature after cholesterol lowering precedes anatomic regression.\textsuperscript{74} Our observations of improved perfusion and smaller abnormalities by PET imaging after dipyridamole stress in humans relatively rapidly after cholesterol lowering\textsuperscript{65,72,73} are consistent with experimental studies in animals showing restoration of endothelium-dependent vasodilation by dietary fat restriction and/or cholesterol lowering.\textsuperscript{33,35,38,41}

With the modest changes in anatomic severity of coronary artery stenoses after lipid lowering, the commonly used terms regression and reversal might be questioned. The process of atherosclerosis in the coronary arterial wall consists of a complex mix of cholesterol deposition, cellular proliferation, inflammation, and calcification. With vigorous cholesterol lowering, lipid content and inflammatory cells in the wall decrease,\textsuperscript{15-17,19,74-76} but cellular and fibrotic elements remain with calcification. The lumen becomes somewhat larger, due in part to diminution of lipids and inflammation and in part due to structural remodeling of the artery,\textsuperscript{77} which remains scarred and smaller than normal.\textsuperscript{78} With diminution of lipids and inflammation, plaque stabilization occurs with a decrease in unstable coronary syndromes or coronary events.\textsuperscript{15-21} These pathological correlates with coronary events or lack of events parallel the clinical observation that progression of stenosis severity on arteriograms is associated with subsequent coronary events, whereas stabilization or partial regression by arteriography is associated with low risk of coronary events.\textsuperscript{15,16,19,21,78,79} Thus, the terms reversal and regression as used clinically incorporate the spectrum of beneficial changes in plaque composition and pathology, compensatory arterial structural changes, arteriographic severity, vasomotor function, flow capacity, symptoms, and prognosis. Certainly, regression back to normal in all of these processes does not occur. However, these terms appropriately characterize the cumulative benefits seen clinically as a symptom-free individual at low risk of coronary events with continuing lifelong risk factor modification.

### Comprehensive Noninvasive Management of Coronary Artery Disease

In clinical application, treatment regimens to partially reverse or stop progression of coronary atherosclerosis predictably with high probability of success involve substantial commitment to a very low fat diet, moderate exercise, smoking cessation, and cholesterol-lowering drugs, in addition to good control of hypertension, if present. Of patients with risk factors for coronary artery disease, approximately two thirds may not develop the disease, while the remainder do.\textsuperscript{8-10,22} Consequently, a firm diagnosis of coronary artery disease is essential as the basis for undertaking a vigorous, lifelong reversal regimen, as for example documentation by prior myocardial infarction, coronary arteriography, previous PTCA, or coronary artery bypass surgery. Most such patients should be on a reversal regimen due to the benefits of decreasing symptoms and coronary events.

For individuals without an established diagnosis of coronary artery disease, standard noninvasive testing does not appear to provide adequate diagnostic certainty for identifying the presence and severity of coronary artery disease as the basis for lifelong reversal treatment. For example, as shown in Table 1, in eight publications since 1983 involving over 4000 patients, the

---

**Table 1. Sensitivity and Specificity of Thallium Exercise Testing**

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>No. of Patients</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>71%</td>
<td>210</td>
<td>DePasquale. Circulation. 1988;77:316.</td>
</tr>
<tr>
<td>94%</td>
<td>52%</td>
<td>81</td>
<td>Bungo. Chest. 1983;83:112.</td>
</tr>
<tr>
<td>75%</td>
<td>53%</td>
<td>845</td>
<td>Schwartz. Circulation. 1993;87:165.</td>
</tr>
</tbody>
</table>

Average, 86% Average, 54% Total, 4064
TABLE 2. Sensitivity and Specificity of Cardiac Positron Emission Tomography

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>No. of Patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>84%</td>
<td>88%</td>
<td>81</td>
<td>Stewart. Am J Cardiol. 1991;67:1303.</td>
</tr>
<tr>
<td>97%</td>
<td>100%</td>
<td>60</td>
<td>Yonekura. Am Heart J. 1987;113:645.</td>
</tr>
</tbody>
</table>

Average, 95% Average, 95% Total, 855

diagnostic sensitivity and specificity of thallium stress testing averaged 86% and 54%, respectively. If corrected for referral bias, the specificity increases to 68% and the sensitivity falls to 70%. In asymptomatic subjects with risk factors, where exercise testing is commonly used, the diagnostic specificity of standard perfusion stress imaging is less than in those clinical populations, falling to 40% or less.

In cholesterol-lowering trials to date, coronary artery disease documented by quantitative coronary arteriography has been the basis for both diagnosis and follow-up of changes in severity of disease. However, reliance on an invasive diagnostic test for noninvasive reversal treatment precludes consideration of a principally noninvasive alternative approach to managing coronary artery disease. Although the data are less extensive than for single-photon imaging, cardiac PET detects coronary artery disease and assesses its severity with a diagnostic sensitivity and specificity of 95%, as shown in Table 2, thereby providing a noninvasive, reliable diagnosis of coronary artery disease as the basis for reversal treatment. PET identifies which coronary arteries are involved65,86 and the qualitative severity of disease65,86-89 is as accurate in asymptomatic as in symptomatic subjects in one study,87 and is as good or better than arteriography for following changes in stenosis severity in our experience.65,73 Since myocardial perfusion reflects the integrated effects of single or multiple stenoses, diffuse atherosclerosis, and vasomotor dysfunction on coronary flow,23,24,54,65-71,86-90 quantitative PET imaging indicates severity of coronary artery disease beyond a single-dimension percent stenosis of a single localized coronary arterial narrowing by arteriography. In addition, since perfusion is related to lumen radius raised to the fourth power, small changes in arteriographic lumen diameter that are difficult to see or measure on an arteriogram produce proportionately greater changes in perfusion that are visually obvious and easily quantified on a PET scan.

With currently commercially available generator sources of radionuclides that do not require a cyclotron, the total component costs of a cardiac PET scan at $2200 per study (including amortization for equipment costs and interpretation) are the same as or less than standard perfusion imaging stress tests at $2500 (all costs per study in some large American cities); for these similar costs per study, PET has an accuracy of 95% compared with 50% to 60% for the standard tests. Individuals definitely identified as having coronary artery disease by noninvasive PET may then undergo a vigorous reversal program, with changes in severity of disease followed by dipyridamole PET.65,72,73 Therefore, although they are separate, independent tools in our diagnostic-therapeutic armamentarium, the combination of PET and reversal treatment applied together are powerful as the basis for noninvasive management of patients with symptomatic or asymptomatic coronary artery disease.

As examples, Fig 1 shows the orientation of three-dimensional PET images of the heart in relation to coronary anatomy. Fig 2 illustrates an example of the baseline, control, resting PET (upper row), and dipyridamole PET images (lower row) in right (septal), anterior, left lateral, and inferior views (left to right, respectively) of a patient with a moderate inferior resting defect that was larger and more severe after dipyridamole. Fig 3 illustrates the dipyridamole PET image before treatment (upper row) and the dipyridamole PET image of this same patient (lower row) after 2 years of intense lipid-lowering treatment on a very low fat diet and on statin without mechanical revascularization. The PET image shows a markedly smaller, less severe inferior perfusion abnormality at the end of the 2-year treatment period compared with the larger, more severe abnormality at baseline. Perfusion was improved and more uniform throughout the heart, particularly in border-zone areas of defects, thereby making them smaller. Completely automated computerized measurements of size and severity of the perfusion abnormalities on dipyridamole PET of the above studies were made without operator interpretation or drawing regions of interest.65,72,73,90 Percent of the left ventricle outside of 2.5 standard deviations of normal was 26% at baseline and 15% on the follow-up dipyridamole image after 2 years of reversal treatment. The changes in quantitative severity paralleled the visual appearance. By comparison, Fig 4 shows the dipyridamole PET image at baseline (upper row) and the dipyridamole PET image 13 months later (lower row) of another patient showing progression of atherosclerosis in all three coronary arteries in the absence of adequate reversal treatment.

Fig 5 illustrates a clinical pathway or algorithm relying principally on noninvasive PET and reversal treatment for the comprehensive management of coronary artery disease.
artery disease other than acute unstable syndromes. For patients who do not choose reversal treatment or prefer the immediate results of PTCA or coronary artery bypass surgery, or if the reversal program is not successful, these invasive procedures are backup alternatives in this clinical algorithm. This approach parallels conclusions of the CASS study demonstrating the appropriateness and safety of antianginal medical treatment with deferral of invasive revascularization. However, in this algorithm, the principally antianginal treatments used in the CASS study are augmented by reversal regimens that stabilize plaque, partially reverse stenoses, and prevent...
myocardial infarction, sudden death, and unstable coronary syndromes requiring bypass surgery or PTCA even for patients with severe stenoses. \textsuperscript{15,16,19,52,55,58,59,62,63,78,90}

Consequently, even for severe perfusion abnormalities by dipyridamole PET, reversal treatment is indicated with PTCA or bypass surgery being options.

Since cardiovascular disease is a major cause of mortality and disability, for highest probability of successful outcome as an alternative to invasive procedures, a coronary disease reversal program requires a vigorous approach combining concurrently all the major therapeutic steps available, including very low fat food, cholesterol-lowering drugs (and/or HDL-increasing drugs), smoking cessation, exercise, antianginal drugs, and vitamin antioxidants in order to optimize regression or stop progression and to minimize the risk of future clinical events. As an alternative approach competitive with elective bypass surgery or PTCA, how much should cholesterol be reduced? Is the percent decrease in cholesterol or the absolute lowest level of cholesterol more important? The literature supports both points of view. Most recent arteriographic trials have involved secondary intervention in patients with established coronary artery disease and hypercholesterolemia in whom cholesterol was significantly lowered but remained above normal levels. Several of these studies included subsets of patients with coronary artery disease and mild hypercholesterolemia or with normal cholesterol levels and reported significant benefit of further lowering of cholesterol to lower than normal levels. \textsuperscript{15,16,63,64} Relatively greater lowering of cholesterol confers relatively greater benefit, \textsuperscript{15,16,63,64} and the lowest absolute

levels of cholesterol and lowest incidence of coronary events are associated with the lowest mortality at cholesterol levels of 140 mg/dL or below. \textsuperscript{63} In the recent SCRIPT trial,\textsuperscript{52} there was a modest decrease in coronary events but no regression—only slowed progression of arteriographic disease. However, the extent of cholesterol lowering was also modest, with cholesterol levels in the treated group not decreasing to the levels of even 160 mg/dL recommended by the NCEP guidelines. Therefore, although incomplete, existing data suggest that lowering cholesterol as much as possible by diet and drugs to levels below normal or below consensus levels recommended by the American Heart Association may be beneficial, particularly in patients with coronary artery disease and relatively normal cholesterol levels.

Due to the association of low HDL with future coronary events,\textsuperscript{63,92} substantial efforts are appropriate for normalizing HDL by smoking cessation, increasing exercise, and use of HDL-raising drugs such as niacin, gemfibrozil, and estrogens in women. Because of the direct relation between body mass and mortality, with the lowest mortality in lean individuals,\textsuperscript{93} and the effect of achieving lean body mass on lowering cholesterol, another important part of a reversal program is reducing weight to approximate lean body mass by appropriate carbohydrate restriction in addition to fat restriction. Thus, for optimal probability of partial reversal and preventing coronary events with a certainty comparable to or better than invasive alternatives, a reversal regimen should achieve lean body mass, total cholesterol of 140 mg/dL or below, low-density lipoprotein
below 80 to 90 mg/dL, HDL 45 mg/dL or above, and absence of smoking. At these goals, coronary events are simply uncommon.

For consistent patient acceptance, these components of our program are individually planned for each patient, depending on his or her time constraints, work demands, prior lifestyle, and personal preferences, thereby increasing compliance. They are adapted for each patient with emphasis on developing knowledge, motivation, and active self-maintenance of reversal treatment for coronary artery disease. The principles of reversing coronary heart disease are emphasized and adapted for each individual's application with follow-up reinforcement, motivation, and monitoring by a variable mix of outpatient clinic visits, home lifestyle rehabilitation, intensive telephone, fax, or written follow-up locally or at long distance and/or exchange with the private physician. Individuals are carefully informed about all aspects of their lipid-altering drugs, particularly how to check their own lipid and liver profiles along with the physician as an active participant in their own care. There is no single fixed or rigid regimen, diet, or method to which all individuals must conform because the needs and preferences of individuals are highly varied. Multiple subspecialty consultations, special equipment or facilities, group interaction, classroom meetings, excessive clinic visits, time demands, or disruption of busy schedules are avoided in this program.

**Fig. 4.** Positron emission tomography after dipyridamole in a hyperlipidemic patient at baseline (upper row) and after 13 months without appropriate diet or cholesterol lowering (lower row) demonstrates characteristic worsening seen commonly in patients not on a reversal regimen.

**Fig. 5.** Algorithm for the comprehensive noninvasive elective management of coronary artery disease based on positron emission tomography (PET) and reversal treatment with revascularization as a backup alternative for those unable to adhere to a successful reversal program. CAD indicates coronary artery disease; Cath, catheterization; PTCA, percutaneous transluminal coronary angioplasty; and CAGB, coronary artery bypass grafting.
in favor of integrating essential lifestyle changes and medical management into the individual's daily life at home and at work.

Table 3 outlines the essential components of a program aimed at reversing or stopping progression of coronary artery disease. For optimal results as an alternative to PTCA or coronary artery bypass surgery, a reversal program does require the strong input of a physician or cardiologist comparable to time spent performing an invasive procedure. The influence of a committed, interested physician is an essential part of developing patient self-motivation that becomes subsequently internalized with successful achievement of goals and/or relief of symptoms. In initially stable patients with coronary artery disease who adhere to the program, balloon dilation or bypass surgery is usually not necessary because the response to this treatment regimen is so consistent and effective. The abnormal endothelial function caused by elevated cholesterol and/or coronary artery disease starts to heal within 3 months after undertaking vigorous cholesterol lowering,72 usually with decreased symptoms, increased exercise capacity, and increased sense of well-being within weeks followed by marked, sustained improvement in myocardial perfusion by 2 to 4 years, as shown in the above example (Fig 3). On a combined regimen of very low fat diet (less than 10% of calories as fat) and cholesterol-lowering drugs together, reversal or cessation of progression and decrease of clinical events exceeds 90% in the author's current practice. However, a small percentage of patients may still develop unstable coronary syndromes despite very low cholesterol and smoking abstinence and may require PTCA or bypass surgery. In the author's experience, such patients usually have persisting low HDL with low total cholesterol and often have ongoing work stress imposed by job circumstances.

Is reversal treatment suitable only for patients with mild to moderate severity or extent of coronary artery disease? Most lipid-lowering trials14-16 report that the most severe stenoses show the greatest regression. Since coronary atherosclerosis is a diffuse process25-29 subjecting the entire epicardial coronary tree to plaque rupture, reversal treatment is beneficial for preventing future sudden death, myocardial infarction, or unstable coronary syndromes requiring PTCA or bypass surgery.15,16,19,52,55,58,59,62,63,78,91 Based on the author's anecdotal experience with individual patients who have severe coronary artery disease, particularly unstable coronary syndromes, but have refused PTCA or bypass surgery, very aggressive lipid-lowering and antianginal treatment usually controls or eliminates angina and allows long-term noninvasive reversal treatment. However, in the absence of systematic data for unstable syndromes, revascularization by PTCA or bypass surgery may be necessary or preferable.

### Economics of Reversal Treatment for Coronary Artery Disease

Although medical care in the United States is considered optimal for those with access to it, the cost for achieving optimal outcomes is high. This inefficiency of high cost for good outcomes involves not only high-cost procedures but excessive diagnostic tests that are not definitive, unnecessary interventional procedures, and the practice pattern of "doing everything to all patients," so that overall costs are high to produce good outcomes in some individuals.94-98 Current reimbursement policies and insurance coverage provide definite economic incentives for such inefficient practice patterns. The field of healthcare is therefore focusing on containment of costs, effectiveness of outcomes, elimination of unnecessary tests or procedures, alternative less-expensive but effective treatment modalities, and alternative less-costly clinical pathways. These issues in healthcare reflect a fundamental problem long familiar to industry and business, i.e., the problem of cost versus quality of product: in this case, healthcare.

Most current approaches to this problem in healthcare have used potentially counterproductive strategies of discounted fees, restricted access, second-opinion requirements, preapproval programs for many services, precertification for diagnostic testing and hospital admission, omission of services (particularly new services or new technology), and coercive forces for early discharge from hospital care. These "clamp-down" approaches may ultimately hinder optimal solutions to the problem because they disallow innovation, flexibility of developing basic, new clinical practice strategies, protocols, and technologies that provide better answers with high quality at lower cost than heavily discounted traditional practices. It is therefore important to consider reversal treatment as an alternative to the current standard practice of PTCA or bypass surgery in the management of stable coronary artery disease. However, currently only 15% to 25% of patients who have established coronary artery disease documented by PTCA or coronary bypass surgery undergo intensive cholesterol-lowering and risk management programs despite the benefits of decreased cardiac events and partial regression of disease.99,100 Analyzing why regression treatment is not more widely used requires consideration of broad practice patterns in cardiovascular medicine now being scrutinized in an environment of cost and outcome consciousness.

The most common algorithm or pathway for evaluation and treatment of coronary artery disease currently includes (1) exercise treadmill testing, (2) stress perfusion imaging, (3) coronary arteriography, (4) antianginal drugs, and (5) PTCA or coronary artery bypass surgery. Table 4 lists some of the documented limitations
TABLE 4. Published Problems of Standard Technology for CAD

<table>
<thead>
<tr>
<th>Problem</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error in standard exercise tests</td>
<td>46%</td>
</tr>
<tr>
<td>Coronary arteriograms without significant CAD</td>
<td>25%</td>
</tr>
<tr>
<td>Visual overestimates of severity</td>
<td>30%</td>
</tr>
<tr>
<td>Overestimates of improved severity by PTCA</td>
<td>180%</td>
</tr>
<tr>
<td>Recurrence of narrowing after PTCA</td>
<td>30%</td>
</tr>
<tr>
<td>Potential overutilization of CABG, PTCA</td>
<td>44%</td>
</tr>
<tr>
<td>Patients after CABG/PTCA on reversal treatment</td>
<td>17%</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass grafting.

of this approach when applied broadly. These limitations arise from multiple complex causes including inherent biological limitations and complexity of pathophysiology, past practice traditions, clinical approaches ingrained during training, and strong economic incentives for procedures in the current reimbursement system.

Since cost is an important issue currently, Table 5 lists the total cost of a reversal program over a 5-year period as follows: all costs of a diagnostic PET scan including interpretation, $2200; costs for cholesterol-lowering drugs, $1200 per year for 5 years; clinic visits, laboratory monitoring of lipid and liver profiles, and all costs associated with noninvasive medical management, $1160 per year for 5 years, giving a total cost of $14,000 over a 5-year period. Based on published cost data, the total component costs of PTCA and bypass surgery are also shown for comparison calculated as follows: all costs for standard stress perfusion imaging including interpretation, $2200; coronary arteriography including professional fee, $9000; PTCA including professional fee, $15,000 plus a times 1.3 factor for 30% restenosis (actually 40%, Reference 95), plus another times 1.3 factor for 30% repeat restenosis gives a total cost of $35,000 over a 5-year period without clinic fees. Total costs for diagnostic studies and bypass surgery including professional fee were calculated as follows: standard stress perfusion imaging, $2200; coronary arteriography, $9000; bypass surgery, all costs, $41,000 plus a times 1.15 factor for 15% graft failures requiring repeat surgery over 5 years, for a total of $60,000. Thus, the comprehensive noninvasive management of coronary artery disease by PET and reversal treatment provides substantial reductions in costs of cardiac care compared with traditional invasive approaches but with comparable optimal outcomes for stable coronary artery disease as reported in lipid-lowering trials.

Limitations to Reversal Treatment

Potential limitations to reversal treatment for coronary atherosclerosis include inadequate long-term adherence to risk factor modification, the risk of interim coronary events, the side effects and expense of cholesterol-lowering drugs, and poor clinical recognition of the benefits of reversal treatment, particularly the decreased need for PTCA and coronary artery bypass grafting and associated costs. To some extent or in some individuals, these limitations are valid. However, in comparison to the documented limitations of current practice patterns of cardiovascular medicine outlined in Table 4, the limitations of reversal treatment are greater in perception than in fact and are readily managed in daily practice. In the author’s experience, there is a large number of patients who are able and who want to undergo reversal treatment including the lifestyle changes but are not able to obtain appropriate guidance and medical management from the cardiology profession oriented toward principally invasive alternatives.

Strict dietary reduction of fat to 10% or less of calories is commonly regarded as not attainable by most patients with coronary artery disease. However, a diet of less than 10% of calories as fat has been previously reported in the Life Style Heart Trial. These results are consistent with the finding that a low fat diet combined with lipid-lowering drugs is associated with relief of angina, partial reversal or stopping progression of stenoses, and prevention of clinical events such as death, myocardial infarction, bypass surgery, or balloon angioplasty in most patients. This approach nearly always combines both very low fat diet and cholesterol-lowering drugs to achieve optimal results. When it is presented appropriately and adapted to individual needs, the majority of patients will succeed in maintaining a reversal program.

While the risk of coronary events is always a concern, cholesterol-lowering trials have shown a remarkable decrease in coronary events. Moreover, in patients with new-onset angina, in asymptomatic or mildly symptomatic patients, or even in patients with severe exercise-induced ischemia, ischemic episodes during daily life or with exercise do not predict future coronary events. If restenosis is considered a coronary event after PTCA and graft closure after bypass surgery, coronary events after these procedures are quite common in up to 40% of patients. However, in the author’s experience, these observations in parallel with the CASS study suggest that it is appropriate and safe to pursue a medical regimen, such as antiplatelet and reversal treatment with deferral of revascularization in most patients having stable coronary artery disease, where revascularization is an option if reversal treatment is not successful. It is therefore appropriate to treat such patients initially with reversal regimens using diet, cholesterol-lowering and antiangiinal drugs, antioxidants, and exercise as an alternative to PTCA or bypass surgery.

Use of cholesterol-lowering drugs requires that liver enzymes be checked monthly for 3 months after starting or changing dose of an HMG CoA reductase inhibitor (statin) and every 3 to 4 months thereafter. It is there-
after occasionally necessary to discontinue drugs because of side effects, but such instances are not common and substantially less than the 40% restenosis rate documented after PTCA.101–105 The expense of cholesterol-lowering drugs is also a valid limitation but is substantially less than the cost of PTCA, more so if the cost of repeat procedures due to restenosis is accounted for.

Regarding adequacy of evidence documenting benefits of reversal treatment, further studies and more data would always be of interest. However, publications since 1990 consistently show benefits of vigorous lipid management. The benefits of these more recent trials compared with less convincing results in trials before 1990 are probably due to more vigorous cholesterol-lowering measures and/or lower fat diets in studies published since that time. In comparison, despite the current widespread use of PTCA, there are no randomized trials of elective PTCA in stable coronary artery disease compared with medical antianginal or reversal treatment. Furthermore, in long-term follow-up, coronary bypass surgery does not appear to decrease incidence of myocardial infarction or death.111 Therefore, on balance in the literature, there are more trials showing decreased coronary events by reversal treatment than reports on decreased coronary events by elective PTCA or bypass surgery in stable coronary artery disease.

Whether marked cholesterol lowering causes increased deaths due to suicide or trauma has been a concern. For example, in the LRC-CPPT and Helsinki trials involving several thousand patients, there were 12 accidental or suicidal deaths in the treated group and 8 in the control group; of those individuals in the treated group dying of accidental deaths or suicide, 4 were not taking the cholesterol-lowering drug but were included in the treatment group based on the intent-to-treat principle in the study design.112 Therefore, in these trials, there is no evidence for increased accidental or suicidal deaths associated with cholesterol-lowering treatment. In large population studies, there may be an association between low cholesterol and accidental death, suicide, or cancer. This association can be explained by the likelihood that psychiatrically depressed individuals prone to accidental or suicidal death are often anorexic and therefore have low cholesterol. Similarly, individuals with undiagnosed cancer may have low cholesterol, with a subsequent diagnosis of cancer thereby making an association. However, prospective trials of low fat or low calorie diets do not show these associations. In the Multiple Risk Factor Intervention Trial,113 no excessive traumatic deaths were observed. In the Family Heart Study,114 the group on the low fat diet of a cholesterol-lowering program showed a reduction in depression and aggressive hostility paralleling lowered cholesterol as compared with the control group on a standard high fat “American diet.” Even very low calorie diets in addition to low fat diets are not associated with adverse violent events.115 Therefore, in prospective trials there is no identifiable risk of increased suicide, traumatic deaths, or cancer.

### Other Noninvasive Technologies for Identifying Coronary Artery Disease

Other noninvasive technologies have been tested for identifying coronary artery disease. Magnetic reso-

nance imaging holds promise for measuring myocardial perfusion and imaging coronary arteries.116–119 However, imaging or measuring myocardial perfusion has not been clinically satisfactory to date. Imaging the coronary artery lumen has been accomplished by magnetic resonance techniques for identifying flowing blood in the lumen. However, the apparent lumen size imaged depends on the characteristics of the flow profile. Small, localized areas of turbulence or disordered flow appear as the inner lumen border and therefore as apparent stenosis or as apparent worse stenosis than is anatomically present. The reliability of this approach, particularly for quantifying severity of narrowing or for following changes in severity, remains to be developed.

Fast computed tomography has been used to identify coronary calcification as reflecting the presence of coronary artery disease.120–124 However, the specificity of this approach for coronary artery narrowing is low because many individuals over 50 years old have coronary calcification without coronary artery narrowing. A recent publication suggests that the sensitivity of fast computed tomography for identifying coronary artery disease is also limited.124

Stress echo and stress gated blood imaging have been used to indirectly identify coronary artery disease by monitoring abnormal left ventricular function under stress conditions. The diagnostic accuracy of these indirect methods is not sufficient or direct enough to provide the basis for lifelong drug treatment and risk factor alterations essential for reversing coronary atherosclerosis. These technologies also do not provide measures of severity of stenoses or changes in severity for following regression or progression.

### Role of Coronary Arteriography, Intracoronary Doppler/Echo, PTCA, and Bypass Surgery in Noninvasive Management of Coronary Artery Disease Based on Reversal Treatment

Current invasive diagnostic technology of arteriography, intracoronary Doppler, and intracoronary echo provides powerful insights into coronary anatomy and function not previously possible except experimentally. Analysis of the pressure gradient–flow characteristics of coronary artery stenoses that was first done only in experimental animals65–69 is now routinely feasible in humans.125,126 Coronary flow reserve initially described in animals as an integrated measure of stenosis severity65,127–131 is now routinely measured by intracoronary Doppler for absolute coronary flow reserve71,132,133 and from intracoronary pressure measurements for relative coronary flow reserve.134,135 Structure of the arterial wall visualized by intracoronary echo, with or without coronary artery stenoses, may show atherosclerosis in vivo, previously identifiable only in pathological specimens.25–29 Functional responses of coronary blood flow and/or lumen diameter after intracoronary vasoactive drugs provide insights into regional endothelial function for clinical purposes.136 Finally, coronary arteriography has evolved to a quantitative integrated analysis of the entire coronary arterial tree for multiple segmental stenoses or diffuse coronary artery disease, reflecting the interrelations and integration of anatomy and function.25,26 Thus, invasive evaluation of the coronary ar-
teries has progressed far beyond visual interpretation of regional narrowing on an arteriogram.

For noninvasive management, the identification of stable coronary artery disease and qualitative assessment of its severity provided by visual interpretation of a coronary arteriogram can now be provided by PET (Table 2). For following changes in disease severity, either progression or regression, PET is as good or perhaps better than coronary arteriography because the changes in perfusion reflect flow effects that depend on the fourth power of lumen diameter. Small changes in arteriographic lumen size that are difficult to measure reliably even by quantitative coronary arteriography are quite apparent by PET imaging of myocardial perfusion after dipyridamole.\(^{65,72,73}\) As important, the PET perfusion images show the cumulative effects on flow of diffuse disease and endothelial function of the macrocirculation as well as recently demonstrated abnormalities of the microcirculation in the presence of epicardial coronary artery disease. Whereas percent diameter fails to account for other stenosis geometry, diffuse disease, or functional pressure-flow characteristics of coronary artery stenoses, these newer invasive diagnostic modalities provide a wide range of sophisticated anatomic and function measurements that completely characterize the coronary artery tree for both research investigation and as the basis for procedures such as PTCA, atherectomy, lasers, and coronary bypass surgery.

In this scheme of principally noninvasive management of coronary atherosclerosis, the complete characterization of the arterial wall, pressure gradient-flow characteristics, flow reserve, and integrated analysis of the entire arteriographic coronary tree have become the raison d’être for carrying out invasive diagnostic studies. In essence, these new diagnostic procedures provide the basis of new knowledge. As noninvasive diagnostic imaging such as PET advances to the accuracy and clinical utility of a visually interpreted arteriogram for noninvasive treatment, the invasive diagnostic procedures need to advance to a quantitative accuracy and clinical utility of characterizing the functional and anatomic characteristics of the entire coronary artery tree, including the arterial wall.

In this algorithm for the principally noninvasive management of coronary artery disease, reversal treatment is not antithetical to invasive treatment. Rather, reversal treatment is a valid, safe, effective alternative that requires patient and physician preference. In the author’s experience, the majority of patients will pursue an effective reversal regimen when it is presented and managed appropriately. However, a minority will not alter risk factors despite predictable future events, morbidity and mortality. For such patients, catheter procedures or coronary bypass surgery are appropriate. Many patients and physicians may choose both invasive procedures and reversal treatment for a complex variety of reasons, depending on personal preference of the patient and clinical judgment reflecting the training, skills, personal preference, community standards, and economic incentives influencing the physician.

Conclusions

Current knowledge and practical experience demonstrate that the comprehensive noninvasive management of coronary artery disease based on PET and reversal treatment is a valid, safe, and effective alternative to traditional invasive approaches for diagnosing and treating coronary heart disease at potential cost reductions of 20% to 50% compared with standard cardiology practice emphasizing coronary arteriography, balloon dilation, and bypass surgery.

Acknowledgments

This study was supported in part by National Institutes of Health grants RO1-HL-26862, RO1-HL-26885, and RO1-HL-28356.

References

17. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994;89:36-44.
57. Singh RB, Rastogi SS, Verna R, et al. Randomised controlled trial of cardioprotective diet in patients with recent acute myo-


KEY WORDS • atherosclerosis • coronary disease • tomography • angioplasty
Reversal of coronary atherosclerosis. Clinical promise as the basis for noninvasive management of coronary artery disease.

K L Gould

_Circulation_. 1994;90:1558-1571
doi: 10.1161/01.CIR.90.3.1558

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/3/1558.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/