Burgeoning Dilemmas in the Management of Diabetes and Cardiovascular Disease

Rationale for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

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Abstract—A paradoxical increase in mortality attributable to diabetes has occurred, particularly during the last decade, despite the overall decrease in mortality attributable to coronary artery disease in patients without diabetes. Insulin resistance with or without frank type 2 diabetes has emerged as a major determinant of accelerated coronary artery disease and its sequelae. The advent of insulin sensitizers enables clinicians to target treatment of insulin resistance, as well as hyperglycemia and dyslipidemia. The prevalence of diabetes in the United States is enormous and is increasing rapidly. Patients with diabetes respond less favorably to percutaneous coronary interventions and surgery compared with nondiabetic patients. These considerations led to the initiation of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. It is designed to determine whether treatment targeted to attenuate insulin resistance can arrest or retard progression of coronary artery disease compared with treatment targeted to the same level of glycemic control with an insulin-providing approach. It is designed also to determine whether early revascularization reduces mortality and morbidity in patients with type 2 diabetes whose cardiac symptoms are mild and stable. Despite challenges in study design and enrollment, intensive follow-up, and the long duration of follow-up planned, the questions being addressed are compelling and seem to merit the effort. (Circulation. 2003;107:636-642.)

Key Words: diabetes mellitus ■ angioplasty ■ revascularization ■ cardiovascular diseases

Over the past 2 decades, age-adjusted mortality, especially cardiovascular mortality, has declined precipitously in the United States (Figure 1). Paradoxically, mortality attributable to diabetes has increased sharply, particularly in the last decade. These opposing trends are surprising, given that the leading cause of death in patients with diabetes is cardiovascular disease. Thus, persons with diabetes have not experienced the favorable decline in cardiovascular mortality seen in those without diabetes and in the US population at large.1

In addition to the increase in cardiovascular mortality associated with diabetes, the incidence of diabetes itself is increasing markedly. Nearly 16 000 000 Americans are presently thought to have diabetes, and 26 000 000 have the metabolic syndrome associated with insulin resistance.2 Because 90% to 95% of diabetes is type 2,2 we shall be referring to type 2 diabetes when the term “diabetes” is not qualified.

Type 2 diabetes and its antecedents, including impaired glucose tolerance and syndromes of insulin resistance, are powerful risk factors for premature and accelerated cardiovascular disease.3 Mortality attributable to coronary artery disease is 4.3-fold higher in patients with diabetes defined by hemoglobin A1C levels >7% compared with that in nondiabetic subjects. In a study from Finland, a region with very high cardiovascular disease event rates, performed at a time when revascularization was not widely available, the risk of any cardiovascular event was 2.2-fold higher.4 Furthermore, cardiovascular risk associated with diabetes in patients without overt cardiovascular disease was comparable to that in nondiabetic patients with a history of cardiovascular disease.4 Although these results cannot necessarily be extrapolated to all populations, they are striking. They indicate that the combination of diabetes and coronary artery disease is a major and still growing public health problem.

Numerous factors may contribute to the association between diabetes and cardiovascular disease, including decreased high-density lipoprotein and elevated low-density lipoprotein (LDL) cholesterol, especially small, dense LDL cholesterol, high triglycerides, increased VLDL, nephropathy, hypertension, obesity, altered coagulation and platelet function, impaired fibrinolysis, and hyperglycemia. Even with normalization for all conventional cardiovascular risk factors, diabetes remains a major independent risk factor for cardiovascular disease.
Rationale for Testing a Metabolic Control Hypothesis

Until relatively recently, macrovascular risk associated with diabetes was thought, in perhaps overly simplistic terms, to be attributable exclusively to hyperglycemia and the conventional risk factors hypertension and dyslipidemia. It is now believed that this interpretation is incomplete.

Even though Himsworth, as early as in the 1930s, recognized that 2 types of diabetes existed, one of which reflected insulin insufficiency and the other which reflected impairment of the action of insulin, it was not until much later that type 2 diabetes was recognized to be the tip of an iceberg in which the antecedent condition and perhaps primary derangement was insulin resistance. Hyperglycemia appears in patients with type 2 diabetes only when pancreatic β cell function can no longer compensate for insulin resistance by progressively increasing insulin output. Insulin resistance per se is a marker and perhaps determinant of macrovascular disease. Thus, spearheaded by the seminal work of Reaven, our concept of the nature of diabetes has changed, as has our view of its optimal medical management. With the advent of insulin-sensitizing pharmacological agents such as the thiazolidinediones that enhance insulin sensitivity in liver and skeletal muscle directly and the biguanides that enhance insulin sensitivity indirectly by diminishing hepatic glucose output and hyperglycemia, therapy has been directed toward amelioration of insulin resistance in addition to and as a means for achieving glycemic control.

Metabolic derangements associated with diabetes may compromise efforts to intervene to ameliorate coronary disease. Adverse responses to percutaneous coronary intervention (PCI) in patients with diabetes are prominent. This may reflect differences in the nature of restenosis in this population compared with that in nondiabetic subjects undergoing comparable interventions. Blood vessels in nondiabetic experimental animals subjected to stenting exhibit neointimal formation attributable to migration and proliferation of vascular smooth muscle cells, as well as to a change in their phenotype from contractile to proliferative. A paradoxical decrease in atherosclerotic plaque mass has been seen in patients with diabetes treated with insulin and is considered to reflect "impaired adaptive remodeling or shrinkage of arterial wall, of plaque, or both." "Intimal hypercellular tissue content is reduced in restenotic tissue" in diabetic patients exhibiting restenosis after PCI consistent with phenomena other than proliferation of vascular smooth muscle cells. These observations are compatible with the increased intramural synthesis of plasminogen activator inhibitor type-1 (PAI-1) that is typical of diabetes. Such changes have been implicated to be mediated in part by hyperinsulinemia. They may contribute to alterations in the compositional nature of evolving lesions in the setting of insulin resistance predisposing to plaque rupture, restenosis, or both.

The association of adverse outcomes with diabetes is consistent with compelling information indicating that deleterious effects of insulin or proinsulin on vessel walls may contribute. In several small studies, the use of insulin sensitizers resulted in favorable effects on carotid intimal medial thickness in patients with diabetes and improved the outcome after coronary stenting as judged from a preliminary report. Subjects with insulin resistance who do not have diabetes, including women with the polycystic ovarian syndrome and those with syndromes of insulin resistance characterized by hypertriglyceridemia, hypertension, abdominal obesity, increased intra-abdominal fat, and impaired fibrinolytic system capacity, are at increased risk of coronary events despite the absence of diabetes manifested by hyperglycemia.

In concert these observations and considerations suggest 2 potentially important postulates: (1) coronary atherosclerosis associated with diabetes is particularly prone to become generalized and to manifest itself by evolution of vulnerable plaques, with consequent predisposition to rupture and precipitation of acute coronary syndromes; and (2) the response of coronary vessels in patients with diabetes to PCI is likely to be intrinsically less favorable and less sustained than that in patients without diabetes. In view of these postulates and the basis for them, it is not surprising that overall long-term outcomes in subsets of patients with diabetes treated with either medical management alone or revascularization proce-
dures coupled with medical management have not differed consistently (Figure 2).

No clinician would presently question the necessity of relieving obstructive coronary lesions that may precipitate acute coronary events or account for refractory symptoms in patients with type 2 diabetes. What is not clear in the setting of diabetes with stable coronary artery disease, however, is whether PCI or coronary surgery improves survival when the disease present represents the tip of an iceberg of generalized coronary arterial disease. Despite the very favorable results that have been achieved with coronary surgery entailing left internal mammary arterial grafting to the left anterior descending coronary artery, such disease is likely to progress regardless of whether or not an intervention is interposed unless factors underlying its progression can be ameliorated.

An analogous conundrum exists with respect to the nature of medical management of diabetes in patients with coronary artery disease. Insulin is often lifesaving for patients with type 1 diabetes. In type 2 diabetes, metabolic control is essential and often requires insulin. Glycemic control is imperative for retardation of neuropathy, nephropathy, and microvascular disease. Control of dyslipidemia and probably hyperglycemia as well is likely to attenuate progression of macrovascular disease. Despite striking advances in the achievement of glycemic control, however, coronary artery disease remains the leading cause of death in patients with type 2 diabetes. Myocardial infarction occurs remarkably often in such patients. Coronary risk is increased in patients with syndromes of insulin resistance even when diabetes is absent. Even modest elevations of fasting insulin portend increased risk in apparently normal subjects. Normalization of covariates known to confer coronary risk does not eliminate the powerful association between diabetes and coronary artery disease. Glycemic control targeted to lower median hemoglobin A1C to 7% over 10 years induced significant and clinically important reductions in microvascular complications of diabetes in the United Kingdom Perspective Diabetes Study (UKPDS). However, the magnitude of reduction of the risk of occurrence of myocardial infarction was modest and not statistically significant. Several observations suggest that treatment targeted to attenuate insulin resistance may arrest or retard progression of coronary artery disease. Derangements in fibrinolysis and coagulation are well recognized in association with type 2 diabetes. One factor implicated is elevated concentrations of PAI-1 in blood, atheroma, and vessel walls, with consequent limitation of fibrinolytic system capacity in blood and proteo(fibrino)lysis in vessel walls. The elevations have been linked to hyper(pro)insulinemia on the basis of studies of cells in culture, concentrations of PAI-1 in blood in patients with diabetes and other insulin resistant syndromes, and concentrations of PAI-1 in atheroma and arterial walls of vessels from patients with diabetes compared with those from patients with comparably obstructive coronary artery disease. Diminution of insulin resistance induced by treatment with thiazolidinediones or metformin exerts favorable effects on concentrations of PAI-1 in blood. In addition, these agents can induce favorable modification in concentrations of lipids in blood and endothelial function. Thus, by normalizing fibrinolytic system capacity in blood and perhaps altering the evolution of atherosclerotic plaque composition such that vulnerability to rupture is reduced, attenuation of insulin resistance and the consequently increased synthesis of PAI-1 may decrease coronary risk. To the extent that adverse effects on vessel walls do result from insulin resistance, medical management targeted to reduce it may be particularly important in retarding the progression of coronary disease associated with diabetes.

**Rationale for Testing an Early Revascularization Hypothesis**

Until relatively recently, the conventional wisdom has been that treatment of coronary artery disease should focus on relieving obstruction within epicardial arteries sufficient to induce myocardial ischemia under basal conditions or with physiological stress. Remarkable progress has been made in
ameliorating lesions responsible through coronary artery bypass grafting, percutaneous transluminal coronary angioplasty (PTCA), and PCI including the use of atherectomy, stents, brachytherapy, and drug-eluting stents. These interventions indubitably improve myocardial perfusion and reduce morbidity in patients with unstable coronary syndromes or severe stable symptoms, and in limited subsets of patients, mortality has been reduced. Their use has been engrafted on vigorous treatment of metabolic determinants of the progression of coronary artery disease, such hypercholesterolemia and hypertension. The result has been a remarkable decrease in age-adjusted cardiovascular morbidity and mortality (Figure 1) despite a continuing increase in the overall incidence of coronary disease due to the graying of the population. Sadly, however, persons with diabetes have not experienced decreased age-adjusted cardiovascular morbidity and mortality. The lack of benefit has been especially evident in minority populations (Figure 3).

These trends provide the impetus for ascertaining whether a strategy of early revascularization reduces mortality and morbidity in patients with type 2 diabetes whose cardiac symptoms are mild and stable. Historically, revascularization has been shown to improve survival over medical therapy alone in selected high-risk subsets of patients, including those with the most severe forms of 3-vessel disease and depressed left ventricular function or left main coronary artery disease. In the Bypass Angioplasty Revascularization Investigation 1 (BARI 1) study, patients with diabetes had higher mortality rates compared with those without diabetes despite revascularization in all in each group. However, coronary bypass surgery with the use of an arterial graft equalized the 5-year mortality risk from cardiac causes but did not attenuate the elevated risk of myocardial infarction.22 No trials to date have been designed to compare revascularization with medical therapy in patients with diabetes, and results from unpublished post-hoc subgroup analyses are equivocal (Figure 2).

After the seminal work of Falk and Davies et al,23,24 it has become increasingly clear that morbidity and mortality associated with coronary artery disease are often associated with lesions that are not obstructive until they rupture and precipitate clinical events. Abluminal lesions are frequently present. They may be detectable by intravascular ultrasound (IVUS), magnetic resonance imaging (MRI), and possibly other modalities such as positron emission tomography (PET). Their presence and impact are consistent with the prescient thinking of Glagov et al.25

The clinical importance of plaques prone to rupture has been well established. Such so-called vulnerable plaques are characterized by lipid-laden cores, thin fibrous caps, and a relative paucity of vascular smooth muscle cells. Their rupture is the proximate pathophysiological event most commonly responsible for acute coronary syndromes and their sequela. Accordingly, treatment of obstructive lesions alone cannot solve the problem of coronary artery disease. Attention must also be directed toward retarding or arresting abluminal coronary atherosclerosis, the evolution of vulnerable plaques, and factors precipitating plaque rupture, such as activation of macrophages associated with inflammation,26 mechanical stress, thrombosis, attenuation of fibrinolysis, hypertension, and neurohumoral stimulation.

Unfortunately, it is not clear whether immediate revascularization in patients with type 2 diabetes with mild symptoms diminishes morbidity and mortality compared with that seen with vigorous medical management of ischemic heart disease without immediate revascularization. Extrapolation of results from nondiabetic subjects, which are also equivocal, is not well justified because of inherent differences in the nature of atherosclerosis, subjective perception of ischemia, and/or the progression of coronary artery disease and its outcomes in patients with and those without type 2 diabetes. This was apparent in analysis of results obtained in the BARI 1 trial. Among patients who underwent initial PTCA, those with diabetes experienced a greater increase in the percentage of myocardium jeopardized at the time of follow-up angiographic assessment than patients without diabetes.27 The greater increase occurred even though patients with and without diabetes had, on average, virtually the same minimal amount of residual myocardium jeopardized after the initial PTCA. The results are consistent with the particularly high long-term mortality in patients with diabetes treated with PTCA in the BARI 1 trial.28,29 Although the BARI 1 results did show that use of an arterial graft in patients with diabetes seemed to be life-protecting after the occurrence of acute
myocardial infarction, the overall higher incidence of infarction in patients with diabetes was not reduced with the use of this strategy.

In another analysis of consecutively treated patients with diabetes undergoing PTCA, the 10-year mortality rate was 36% overall and 59% in the 50% of patients who manifested early nonocclusive restenosis. The authors concluded that restenosis was prominent and a major determinant of long-term mortality.

The advent of stents has improved outcomes after PCI in patients with and without diabetes. Specifically, in patients with diabetes, the use of abciximab has been demonstrated to reduce mortality after PCI. Nevertheless, results of the intervention are less salutary in patients with diabetes than in nondiabetic patients, even in patients undergoing contemporary PCI with stenting. The increased rates of restenosis and repeat revascularization in patients with diabetes, including those with stented and non-stented lesions, are attributable to exaggerated intimal hyperplasia. Testing of drug-eluting stents in patients with diabetes undergoing PCI is of critical importance. Their use will be included in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial when they become generally available.

**Brief Description of the BARI 2D Trial**

The BARI 2D study was designed and implemented in the context of consideration of the principles deduced from the observations noted above. The primary objective of the BARI 2D trial is to simultaneously test with the use of a 2×2 factorial design 2 clinically-discrete hypotheses regarding the efficacy of treatment in patients with type 2 diabetes and stable coronary artery disease who may be candidates for coronary revascularization. Patients will be identified early in the course of their coronary artery disease by more aggressive screening according to recommended guidelines of the American Diabetes Association for screening of patients with type 2 diabetes mellitus. Those type 2 diabetic patients with mild or no symptoms of angina who are being referred to coronary angiography for risk stratification in the setting of documented myocardial ischemia by noninvasive testing will also be eligible for participation after definition of coronary anatomy suitable to either an initial strategy of aggressive medical management or invasive revascularization (PCI or coronary artery bypass grafting [CABG]).

Randomization will be stratified in the revascularization arm consistent with a decision before angiography such that if a given patient is randomized to the invasive strategy arm, the procedure will be either PCI or CABG in keeping with results from the BARI Registry and other observational studies providing guidance for selection in patients with diabetes for an appropriate revascularization procedure. The primary end point is 5-year mortality, with a major secondary combined end point of death, Q-wave myocardial infarction, or stroke. All patients entered into BARI 2D will have been identified after clinically indicated noninvasive screening and coronary angiography. Patients on insulin-sensitizing drugs already will be included as well as those on insulin. Specific algorithms delineated in the protocol are designed to produce the desired separation of treatment regimens such that patients will be differentiated into insulin-sensitizing and insulin-providing treatment groups. Randomization will be stratified in the revascularization arm (PCI or CABG) according to the procedure chosen on the basis of the clinical profile and coronary angiographic findings in each individual patient. The rationale for allowing attending physician/patient choice of the revascularization procedure is based on the following:

1. This is a trial to compare the best revascularization procedure for an individual patient combined with aggressive medical management, with an initial strategy of aggressive medical management of ischemic heart disease alone. The BARI Registry and other observational studies have demonstrated that physicians can identify those patients with diabetes who will do well with PTCA.
2. The original BARI trial demonstrated an advantage of CABG with an internal mammary graft compared with PTCA. It included patients with multivessel disease, the majority of whom had unstable coronary disease that required revascularization. BARI 2D will recruit patients who have stable coronary disease and who have mild or no angina, including those with single vessel disease.
3. Improved outcomes of PCI in patients with diabetes have been reported with the use of abciximab and stents. Thus, the applicability of the results of the original BARI trial, which included patients treated with PTCA without stents or glycoprotein IIb/IIIa inhibitors, to current practice is not necessarily valid.
4. The BARI 2D Revascularization Working Group concluded that CABG with arterial grafts is the preferred procedure for revascularization for patients with severe proximal triple vessel disease.

One hypothesis being tested in the trial concerns the nature of the treatment of diabetes. Two modalities are being tested: (1) pharmacological therapy designed to induce glycemic and metabolic control by provision of endogenous or exogenous insulin; and (2) pharmacological therapies designed to induce comparable glycemic and metabolic control by amelioration of insulin resistance. The target for glycemic control in both groups is reduction of hemoglobin A1C concentrations to ≤7.0%.

Another hypothesis being tested in the trial concerns treatment of the coronary artery disease itself. The 2 strategies being compared are intensive pharmacological management of coronary artery disease (including the use of β-blockers, angiotensin-converting enzyme inhibitors, anti- lipemic agents, and aspirin) and intensive pharmacological management plus initial coronary revascularization by either percutaneous coronary intervention or coronary bypass grafting as selected by the patient in consultation with the attending physician. Both treatment arms include lifestyle monitoring and strict management of all conventional, modifiable risk factors. Patients assigned to the intensive medical management arm may undergo revascularization during follow-up as clinically necessary consistent with the rationale for allowing attending physician/patient choice of CABG or PCI delineated above.

The anticipated sample size for BARI 2D is 2800 patients with mild stable angina or no symptoms but with documented...
ischemia and at least 1 major coronary artery judged to have luminal diameter narrowing of at least 50% at the time of coronary arteriography. Patients with unstable or acute coronary syndromes and those with severe symptoms or coronary anatomy indicating the need for immediate coronary revascularization are not eligible for the trial. Examples include patients with unstable angina and those with left main or critical proximal 3-vessel disease and depressed LV function. By design, 50% of all patients will be randomized to initial coronary interventional therapy plus medical management and 50% to initial medical management only of the coronary artery disease. Within each of these 2 randomized groups, additional randomization to the 2 types of medical management of diabetes will be implemented.

What Can We Expect From BARI 2D?

The BARI 2D trial was initiated to resolve the ambiguity confronting us. Its randomization scheme and factorial design are being implemented so that 2 fundamental questions can be answered: (1) are the progression of coronary artery disease and some implicated pathophysiological determinants altered favorably, regardless of whether or not a coronary intervention is implemented, in patients with type 2 diabetes with treatment targeted to reduce insulin resistance compared with those with treatment targeted to augment endogenous insulin secretion; and (2) does the implementation of a coronary intervention favorably alter the clinical course of patients with type 2 diabetes whose coronary lesions are not immediately life-threatening or responsible for refractory signs and symptoms indicative of cardiac impairment? Both questions surface every day in clinical practice. Neither can be answered definitively on the basis of the information presently available. An urgent need exists for definitive answers given the alarming increase in the prevalence of obesity and diabetes in the United States and the failure, to date, to reduce overall cardiovascular mortality in persons with diabetes.

The screening and enrollment process required for the BARI 2D trial are challenging. Patients with diabetes, often asymptomatic, must be evaluated to determine whether or not they have coronary artery disease. Unfortunately, ascertainment of its presence is difficult even with procedures such as exercise stress testing because even advanced atherosclerotic disease may be largely abluminal. Surprisingly, stress tests are positive in only 30% to 50% of patients with diabetes, even when symptoms compatible with coronary artery disease are present. In those patients with positive stress tests, specificity is less than optimal. If coronary disease is documented by stress testing, patients must then agree to undergo coronary arteriography. If arteriography demonstrates lesions other than clinically trivial ones mandating no intervention or unequivocally life-threatening or highly obstructive lesions mandating coronary intervention, patients must consent to a randomization scheme that assigns them to either coronary intervention with intensive medical management of ischemic heart disease or to intensive medical management alone.

With respect to glycemic control, patients may be required to substantially alter their current treatment regimens to near-complete or complete use of either insulin-providing or insulin-sensitizing agents, depending on their assigned randomization. Moreover, follow-up for 5 years and frequent clinic visits are required to ensure achievement of glycemic control and risk factor modification targets. Thus, enrolling patients into BARI 2D is difficult, participation by patients and investigators is demanding, expense entailed is considerable, and the duration of a study with 5 years of follow-up required for acquisition of definitive information is projected. The pivotal nature of the answers to be obtained is such, however, that the investment seems to be merited.

Acknowledgments

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References


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In the Current Perspectives article, “Burgeoning Dilemmas in the Management of Diabetes and Cardiovascular Disease: Rationale for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial” by Sobel et al, which appeared in the February 4, 2003, issue of the journal (Circulation. 2003;107:636–642), the Acknowledgments section should have read as follows:

“The sponsors of the BARI2D study are the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases in the National Institutes of Health. Other contributors providing support are Abbott Laboratories; Bayer Diagnostics; Becton Dickinson; Centocor, Inc; Bristol-Myers Squibb Medical Imaging (formerly DuPont); Eli Lilly and Co; Fujisawa Healthcare, Inc; GlaxoSmithKline; Merck & Co; and Pfizer, Inc.”
In the article, “Enzymatically Modified Nonoxidized Low-Density Lipoprotein Induces Interleukin-8 in Human Endothelial Cells: Role of Free Fatty Acids” by Suriyaphol et al, which appeared in the November 12, 2002, issue of the journal (*Circulation*. 2002;106:2581–2587), two errors require correction.

In the table on page 2583, the word “Concentration” should be removed. The corrected table appears below.

<table>
<thead>
<tr>
<th>Fatty Acid Constituents of E-LDL</th>
<th>nmol/mg Cholesterol</th>
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<tbody>
<tr>
<td>Fatty Acids</td>
<td>E-LDL (Unfloated)</td>
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<td>Myristic 14:0</td>
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<td>Palmitic 16:0</td>
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<tr>
<td>Palmitoleic 16:1</td>
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<tr>
<td>Linoleic 18:2</td>
<td>1277</td>
</tr>
<tr>
<td>Arachidonic 20:4</td>
<td>172</td>
</tr>
</tbody>
</table>

On page 2586, the first sentence of the last paragraph of the article should be replaced by the following: “Our hypothesis proposes that enzymatic modification of LDL is a meaningful process that triggers physiological events leading to the removal of stranded cholesterol. Atherosclerosis develops only when the normal transport system is overloaded.”

In the article “Common Estrogen Receptor Polymorphism Augments Effects of Hormone Replacement Therapy on E-Selectin but Not C-Reactive Protein” by Herrington et al, which appeared in the April 23, 2002, issue of the journal (*Circulation*. 2002;105:1879–1882), and the editorial, “Hormone Replacement Therapy and Heart Disease: Replacing Dogma With Data” by David M. Herrington, MD, MHS, which appeared in the January 7/14, 2003, issue of the journal (*Circulation*. 2003;107:2–4), a citation was erroneously inserted giving the impression that the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) found no evidence of benefit of hormone replacement therapy on atherosclerosis in women with established cardiovascular disease.

The correct citation in both articles should have been: