News and Views from the Literature

Coronary Artery Disease

Percutaneous Transluminal Coronary Angioplasty and Diabetes

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Patency of Percutaneous Transluminal Coronary Angioplasty Sites at 6-Month Angiographic Follow Up. A Key Determinant of Survival in Diabetics after Coronary Balloon Angioplasty

Van Belle E, Ketelers R, Bauters C, et al.
Circulation. 2001;103:1218–1224.

This study by Van Belle et al,[1] which makes an important contribution to the literature dealing with percutaneous transluminal coronary angioplasty (PTCA) and diabetics, analyzed 513 diabetic patients undergoing PTCA in whom angiographic follow-up was obtained at 6 months. The diabetics were categorized according to therapy, namely, diet alone, diet and oral hypoglycemic drugs, and the use of insulin. On the basis of the angiographic findings, three groups were identified: Group 1: 162 patients (32%) without restenosis; Group 2: 257 patients (50%) with nonocclusive restenosis (defined as greater than 50% stenosis); Group 3: 94 patients (18%) with coronary occlusion at the site of the PTCA and another 18 patients (3%) occlusion at 6 months was noted at untreated sites. Of the patients with occlusive restenosis, approximately one third were asymptomatic, one third had stable angina, and one third had unstable angina or an acute myocardial infarction at the time of angiography.

Overall actuarial mortality was 36%—this was 24% in Group 1, 35% in Group 2, and 59% in Group 3 ($P < .0001$). Among patients without restenosis or in those with nonocclusive restenosis, ejection fraction at 6 months was basically unchanged from baseline, whereas this was significantly reduced (4.8% ± 12.6%) in patients with occluded vessels. Multivariate analysis demonstrated that coronary occlusion was a strong and independent correlate of long-term total mortality and cardiac mortality. Other correlates of late cardiac mortality were a fall in ejection fraction as well as baseline ejection fraction, age, end-organ damage, the presence of multivessel disease, hypertension, and occlusion at untreated sites.

This study clearly demonstrates the high frequency of restenosis in diabetics and a disturbing incidence of occlusive restenosis of 18%. Moreover, the data suggest a marked adverse impact of restenosis (particularly in its occlusive form) on long-term mortality in diabetic patients undergoing PTCA. The authors were careful to point out that occlusive restenosis was "a correlate" of long-term mortality as opposed to calling this a "determinant," because it is possible that the occlusive restenosis may have been a consequence of the restenotic lesion rather than or as well as a phenomenon of the occlusion itself.

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The diabetes–PTCA interaction has been a source of considerable controversy since the publication of the 5-year outcomes of the Bypass Angioplasty Revascularization Investigation (BARI) Trial in 1997.[2] This report from the largest trial of PTCA and coronary artery bypass graft (CABG) in multivessel disease demonstrated no difference in death or myocardial infarction in nondiabetics (a finding consistent with all the other trials),

but in diabetics on treatment, the 5-year survival with CABG was far better than among patients assigned to PTCA, in both diabetics receiving insulin and those receiving oral hypoglycemic agents. A similar trend has been noted in other trials of PTCA/CABG, but the number of diabetic patients in these studies was considerably less than in BARI.

The issue is not whether CABG is superior to PTCA in diabetics, but why? Diabetes currently represents 15% to 25% of patients undergoing coronary revascularization, and this proportion is likely to increase substantially in the future as the full weight of the growing epidemic of type II diabetes mellitus begins to be felt. Consequently, explanations for this apparent difference between the two forms of revascularization are needed, because this is an important clinical issue that requires clarification.

The explanations for the diabetes–PTCA interaction are multifactorial and relate partly to the 1) *vascular biology of diabetes*[3–5] and partly to 2) differences in *selection criteria*[6–9]

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for PTCA/CABG in the randomized trials, in comparison with community studies. What needs to be emphasized, however, is that the diabetic milieu is characterized by an enhanced prothrombotic, proliferative, and inflammatory state; all these factors increase the severity and progression of atherosclerosis and have an adverse impact on the long-term results of *both* percutaneous coronary intervention (PCI) and CABG. Nonetheless, there is evidence that, at least in the intermediate term (5 to 7 years), the vascular biology of diabetes may exert a particularly severe detrimental impact on patients undergoing PCI as opposed to patients treated surgically. It has been postulated that in diabetics the deleterious effects of hyperglycemia, insulin, proinsulin, or both (which cause microangiopathy in association with increased concentrations of free fatty acids) may be linked to abnormalities in platelet activity, the coagulation and fibrinolytic systems in blood, and proteo(fibrino)lytic systems in the vessel wall.[3,5] Given this milieu, it is not surprising that diabetics are more prone to restenosis and progressive, diffuse atherosclerosis.[3]

Vascular Biology of Diabetes—Pathogenetic Implications

Several studies, including the current study by Van Belle and colleagues, have demonstrated increased rates of restenosis in diabetics.[1,4,10] In addition, this and a prior study from the same group of investigators demonstrated that restenosis was likely to lead to occlusion in a much higher proportion of diabetics compared with nondiabetics.[1,10] Moreover, late reocclusion is a powerful correlate of long-term mortality. In addition, another study from Israel drew attention to the increased progression of disease in nondilated vessels in diabetics compared with nondiabetics.

Because diabetics are more likely to have diffuse disease, left ventricular dysfunction, reduced collaterals, and severe ischemia in comparison with nondiabetics, one would expect that such patients would be in greater need of "complete revascularization," which is more likely to be achieved by CABG. The target for PCI is usually single or multiple "culprit" lesions within a vessel, whereas the target for CABG is the entire epicardial artery including "future culprit lesions," which may not be a site of significant stenosis at the time of the procedure.

In summary, the diffuseness of disease in diabetics, the increased incidence of occlusive restenosis, and the progression of disease in the setting of severe derangements in endothelial stability are likely to favor the use of CABG (vessel directed) over PTCA (lesion directed), at least in the intermediate term. Eventually, however, some of the same factors will have an adverse effect on the long-term outcomes after bypass surgery.

Patient Selection Criteria

An established tenet of the randomized controlled trials of coronary bypass surgery versus medical therapy is that "the sicker the patient," the greater the survival benefit of CABG over medical therapy alone.[9] In this context, "sicker" is defined by the severity of ischemia, the presence of left ventricular dysfunction, the number of vessels diseased, and their location, eg, involvement of the left main coronary artery or proximal left anterior descending coronary artery.[9] Subsequent database studies including a large study from the Duke University Database demonstrated a similar trend in regard to the 5-year outcomes after CABG versus PTCA. In patients with single-vessel disease there was a trend toward a better survival with PTCA, whereas among patients with double-vessel disease, outcomes were similar between the two techniques.[9] In contrast, among patients with triple-vessel disease and some subsets with severe double-vessel disease, 5-year survival following CABG was markedly superior to that found with PTCA, results similar to those noted in the BARI Trial in diabetics.[2,9]

The picture becomes clearer when one compares diabetics and nondiabetics in the BARI Trial.[8] Not unex-

pectedly, diabetics had a higher frequency of three-vessel disease, diffuse disease, proximal left anterior descending coronary artery involvement, and left ventricular dysfunction. In this respect, diabetics comprise a subset previously shown in the Duke Database to experience a greater benefit from CABG; perhaps, therefore, the results of the randomized trial should not have come as such a surprise.

Further clarification comes from two studies in the community and an analysis of the BARI Registry,[6-8] which included patients who were clinically eligible for randomization but declined to be randomized, based on either patient or physician preference. In all these studies, the results of both CABG and PTCA were poorer in diabetics than in nondiabetics, but in each group, survival following CABG was almost identical to that following PTCA. This contrasts markedly with the findings among diabetics in the randomized control trials. The explanation is, I believe, fascinating and tells us much about differences between randomized trials and a community experience. In the community and in the registry, the overwhelming majority of patients with more severe forms of disease, such as triple-vessel disease, disease involving the proximal LAD, and diffuse disease were treated with bypass surgery. In contrast, the process of randomization resulted in an equal proportion being treated with both CABG and PTCA in the trials. In other words, patients in the randomized control trials were treated with PTCA, whereas in clinical practice the likelihood is that they would have been treated surgically.

This does not in any way diminish the importance of randomized control trials like BARI. Indeed, it required a randomized trial to highlight and identify the problem in diabetics in the first place. Nonetheless, it is somewhat reassuring to see that the judicious selection of therapy in practice appears to have produced the optimal result for the individual patient.

Recommendation for Patients with Multivessel Disease

1) The first step is not whether to perform PTCA or CABG, but to decide whether the patient needs revascularization at all as opposed to medical therapy alone. In the event that revascularization is recommended, the randomized trials of CABG and PTCA have in the main been highly consistent and have provided us with an invaluable body of information upon which to base an educated opinion. 2) In general, the presence of severe three-vessel disease and diffuse disease (particularly in the setting of left ventricular dysfunction) and the presence of left main coronary artery disease warrant referral for bypass surgery. 3) Among patients with double-vessel disease, suitable anatomy, and (in particular) preserved left ventricular function, PCI is the preferred initial approach, in that the trials have demonstrated similar rates of mortality and late myocardial infarction, quality of life, and subsequent employment in patients undergoing PCI and CABG. In this situation, a less invasive approach, namely PCI, is the preferred option for both patients. 4) Where do diabetics fit into this algorithm? I believe that diabetics should be individualized according to the coronary anatomy, left ventricular function, comorbidities, and patient preference. It is clearly impractical and intellectually unjustified to refer all diabetics to CABG based on the results of the BARI Trial.

Preliminary data from the ARTS Trial of multivessel stenting versus CABG suggested that among diabetics, 1-year mortality is substantially higher after PTCA compared with CABG.

Future Directions

The use of stents in diabetics is promising, given the high rate of restenosis and late reocclusion demonstrated in this study. At least two studies have demonstrated a much lower rate of reocclusion (≤5%) in diabetics with stents compared with standard PTCA.[10] Nonetheless, preliminary data from the ARTS Trial of multivessel stenting versus CABG suggested that among diabetics, 1-year mortality is substantially higher after PTCA compared with CABG. These data have not yet been published but only presented.

Another area of interest relates to the use of platelet inhibitor therapy after PCI in diabetics. From the theoretical standpoint, one would expect a greater benefit in diabetics given the fact that abnormalities and platelet activation, the coagulation system, and the fibrinolytic system have been demonstrated in diabetics.[10] In this context, it is of interest that several subgroup analyses have suggested that the benefit of abciximab in regard to late major adverse coronary events is greatest in the diabetic population.[11]

Finally, the focus on revascularization should not overshadow the fact that diabetics have multiple risk factors for progressive coronary artery disease. Progressive risk factor reduction is a key component of whatever therapeutic strategy is undertaken. The recently initiated BARI-2 Trial will, in the future, provide further insights into coronary revascularization versus medical therapy in type 2 diabetic with stable coronary artery disease.

In addition, this trial will explore the *glycemic control hypothesis* by comparing drug therapy with the use of insulin providers versus insulin sensitizers. ■

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Diabetes

Managing Diabetes and CAD

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In patients with diabetes mellitus, the prevalence of coronary artery disease (CAD) is 55%, markedly higher than the 2% to 4% range in the general population. Mortality from CAD is 4 times higher among women and 2 times higher among men than among their counterparts without diabetes. With the prevalence of cardiovascular disease so high in diabetic patients, aggressive efforts to determine its presence should be considered, including the use of stress testing, carotid duplex imaging, and determination of the ankle:brachial indices. Aggressive treatment with lipid-lowering and antihypertensive agents to established treatment goals in addition to glycemic control have been proved to greatly benefit this patient population.

Management of Coronary Artery Disease: Therapeutic Options in Patients with Diabetes

Hammoud T, Tanguay J-F, Bourassa MG
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Diabetes is associated with a variety of risk factors that are responsible for the more diffuse nature of atherosclerosis and the poorer outcomes from both percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) in patients. The endothelial dysfunction, decreased coronary flow reserve, increased platelet activity, higher fibrinogen and factor VII levels, and lower plasma fibrinolytic activity associated with diabetes may be responsible for the extensive multivessel disease, smaller-vessel dimensions, and increased thrombus formation seen in diabetic patients.

Dyslipidemia and hyperglycemia, common in diabetic patients, play important roles in the development of atherosclerosis. Hyperglycemia itself adversely affects endothelium-dependent vasodilation as well as lipid profiles and coagulation factors. The glycosylation of low-density lipoprotein (LDL) leaves it more predisposed to oxidation and, therefore, more atherogenic. The lipid profile of diabetic patients often includes the small-dense atherogenic LDL, lower levels of high-density lipoprotein (HDL), and elevated triglyceride levels. This provides a milieu for greater accumulation of cholesterol within vessel walls, particularly through lower levels of HDL, which reduce the egress of cholesterol through the mechanism of reverse cholesterol transport. LDL seems to play a role in the inflammatory response, leading to macrophage activation and coronary plaque destabilization.

The discussion by Hammoud and associates on the management of CAD emphasized the current undertreatment of diabetic patients with lipid-lowering drugs and angiotensin-converting enzyme (ACE) inhibitors, despite clear evidence of their efficacy in this patient population. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S)[1] was reviewed; in this study, simvastatin was used to reduce cholesterol levels in patients with established CAD and hypercholesterolemia. The

reduction of 5-year mortality was 43% in diabetic patients and 29% in nondiabetic patients. The Cholesterol and Recurrent Events (CARE) trial[2] used pravastatin for patients with average cholesterol levels after myocardial infarction (MI). Although cholesterol reduction was similar in diabetic and nondiabetic patients, the benefit of reduction was greater in the patients with diabetes. Current guidelines recommend achieving LDL levels of less than 100 mg/dL in patients with diabetes.

The benefit of hypertension control to reduce the macrovascular and microvascular complications of diabetes is well established. Blood pressure control reduces the incidence of stroke and renal failure, whereas coronary artery–related mortality seems to be more impacted by cholesterol reduction. Recommended goals for diabetic patients are to achieve blood pressures no higher than 130/85 mm Hg.

Diabetic patients seem to benefit from antiplatelet therapy. The Antiplatelet Trialists' Collaboration[3] found that the reduction of the cumulative end point of vascular death, MI, or stroke was 22.3% in the control group and 18.5% in patients taking aspirin. A similar benefit was seen in the treated diabetic subgroup. Glycoprotein IIb/IIIa platelet receptor inhibitors have been important in reducing event rates in diabetic patients undergoing coronary interventions, including patients with acute coronary syndromes. In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT),[4,5] abciximab reduced the mortality rate in patients undergoing coronary stent implantation by more than 75% at 1 year, with a 50% reduction in 6-month restenosis. In the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study,[6,7] tirofiban reduced the risk of death and MI by 88% in diabetic patients versus 43% in the overall study population. In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial,[8] 30-day mortality was reduced in patients with insulin-dependent diabetes, compared with nondiabetic patients.

ß-Blockers and ACE inhibitors seem to have particular usefulness post-MI in diabetic patients.

ß-Blockers and ACE inhibitors seem to have particular usefulness post-MI in diabetic patients. Analysis presented demonstrated a 37% reduction in mortality in diabetic patients post-MI with the use of ß-blockers, compared with a 13% reduction in all treated patients. Inclusion of ACE inhibitors in the post-MI treatment of patients with left ventricular dysfunction reduced mortality and prevented the progression to severe heart failure. In some studies, the reduction of mortality and morbidity was greater in diabetic patients than in those without diabetes.

PTCA and coronary stent implantation in diabetic patients are associated with a high angiographic success rate; however, restenosis and in-hospital complication rates are higher in diabetic patients than in nondiabetic patients. Survival rates of diabetic patients in trials and registries comparing the results of CABG with percutaneous interventions are not consistent. Most recently, the 7-year results of the Bypass Angioplasty Revascularization Investigation (BARI)[9] showed no difference in the primary end point of 5-year all-cause mortality in the overall population. In patients with diabetes, however, the 5-year mortality rate was twice as high with PTCA as with CABG (34.7% vs 19.1%). The current applicability of published comparisons of PTCA with CABG may be limited, since the studies occurred during periods when the use of IIb/IIIa inhibitors and stents were not yet the standard therapy they are today. In general, the presence of diffuse CAD, particularly in the presence of left ventricular dysfunction, directs patients toward CABG rather than PTCA. Randomized trials comparing contemporary revascularization techniques would be useful.

In conclusion, strict lipid, hypertension and, to a lesser extent, glycemic control remains the mainstay of treatment for patients with diabetes and CAD.

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Cholesterol

C-Reactive Protein as a Predictor of Coronary Event Risk

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The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[1] has provided us another important lesson on preventing coronary heart disease events in healthy, middle-aged men and women with low high-density lipoprotein (HDL) cholesterol, this time about the clinical value of assessing inflammation by measuring C-reactive protein (CRP).[2]

Measurement of C-Reactive Protein for the Targeting of Statin Therapy in the Primary Prevention of Acute Coronary Events

Ridker PM, Rifai N, Clearfield M, et al.
N Engl J Med. 2001;344:1959–1965.

The AFCAPS/TexCAPS study assessed the effect of lovastatin 20 or 40 mg/day in 6605 men and women, 31 to 75 years of age, without clinically evident cardiovascular disease, low-density lipoprotein (LDL) cholesterol 130 to 190 mg/dL, HDL cholesterol less than 45 mg/dL in men and less than 47 mg/dL in women, and triglycerides less than 400 mg/dL. Lovastatin reduced mean LDL cholesterol from 156 mg/dL to 115 mg/dL. Researchers observed a 37% reduction (183 vs 116 first events) in myocardial infarction, unstable angina, or sudden death in the treatment group.

This was the first cholesterol-lowering trial to demonstrate a benefit for healthy individuals with near "average" LDL cholesterol and low HDL cholesterol. The vast majority of the enrolled subjects would not receive drug therapy under the current National Cholesterol Education Program (NCEP) guidelines.[3] Those with multiple risk factors appeared to have the greatest benefit from cholesterol lowering. This study found the same significant event reductions in subjects with initial HDL cholesterol between 35 and 39 mg/dL as those with initial HDL cholesterol levels less than 35 mg/dL, thus redefining the range of HDL cholesterol that benefits from treatment. The study also suggested that optimal LDL cholesterol is less than 115 mg/dL in healthy individuals with low HDL cholesterol, which makes up a large segment of the American (especially male) population.

In the current study, the value of high-sensitivity CRP was studied as a predictor of subsequent event risk and benefit from cholesterol-lowering therapy. CRP was assessed in 5742 participants of the AFCAPS/TexCAPS study at baseline and after 1 year of treatment or placebo, the levels of which were stratified into quartiles. Coronary event risk reduction was determined in subjects with above and below median LDL cholesterol (149 mg/dL) and LDL/HDL cholesterol ratios stratified by above and below median CRP values (0.16 mg/dL). Initial CRP levels predicted overall event risk, with a 21% increase in events with each increasing CRP quartile. Lovastatin decreased CRP 15% at 1 year, but the decrease did not correlate with the individual degree of cholesterol lowering. Subjects with above median initial LDL cholesterol or LDL/HDL cholesterol ratios benefited from lovastatin therapy irrespective of their initial CRP levels. Subjects with below median initial LDL cholesterol or LDL/HDL cholesterol ratios benefited from lovastatin therapy if their initial CRP values were above median, but not if their initial CRP values were below median. In those with below median LDL/HDL cholesterol ratios, 43 subjects needed to be treated to prevent one event if their initial CRP was above medial, but 983 subjects needed to be treated to prevent one event if their initial CRP was below median.

Clinical Implications

This analysis suggests that CRP is indeed a predictor of coronary event risk and that it may have value in determining the efficacy of cholesterol-lowering therapy in patients with borderline indications. These data suggest that CRP level is of no clinical value in subjects with clear indications for therapy, such as elevated LDL cholesterol or LDL/HDL cholesterol ratios, because all of these subjects benefited from therapy. In contrast, those with lower LDL cholesterol levels or ratios were reasonably stratified as to benefit by their initial CRP values. Similar value probably exists for other risk stratification tests, such as electron-beam computed tomography. The absence of coronary calcification should not be used to avoid proven therapy, but an unexpectedly high score might be used to suggest a need for cholesterol-lowering in those patients with borderline lipids. ■

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