EDITORIAL COMMENT

Don’t Blame the Stents*

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Diabetes mellitus portends excessive adverse clinical outcomes for coronary artery disease (CAD) patients, including those undergoing percutaneous coronary intervention (PCI) (1–5). Causes for adverse outcomes in diabetic patients include more stent hyperplasia (3), smaller vessels, greater vascular inflammation, a higher thrombotic state, type of diabetic treatment (oral vs. insulin), and severe diffuse vascular disease promoted by more risk factors, with a marked increase in the relative adverse impact on outcome for each risk factor. Furthermore, the outcomes of diabetic patients with CAD indicate that eliminating ischemia caused by a finite number of focal stenoses is not sufficient. Revascularization reduces angina as well as morbidity and mortality, particularly in high-risk patients. However, future events are more often related to progressive CAD, often the result of non-critical lesions observed during earlier angiography (1).

The potential for multivessel PCI to be a competitor of coronary artery bypass grafting (CABG) early on led to randomized trials demonstrating equivalent survival outcomes for balloon PCI compared with CABG. However, patients undergoing PCI frequently required additional revascularization later in the year compared with CABG patients. However, the Bypass Angioplasty Revascularization Investigation (BARI) (4,5) and Emory Angioplasty versus Surgery Trial (EAST) (6) trials demonstrated that balloon angioplasty in treated diabetic patients was associated with increased mortality at five and eight years, respectively, compared with CABG. These results form the basis for the generally accepted recommendation that, when feasible, CABG is preferable to PCI in treated diabetic patients with multivessel CAD.

More recently the impact of coronary stents, with their potential for more durable revascularization, has been investigated. Data from the Arterial Revascularization Therapies Study (ARTS) trial (7), which randomized over 1,200 patients with multivessel disease to stenting or CABG, demonstrated a nearly 20% absolute reduction in the need for late revascularization in the stented patients compared with earlier balloon PCI studies. Overall, one-year mortality was not different between PCI using one or more stents and CABG. In a sub-analysis, diabetic patients (not prospectively randomized) had a higher rate of repeat revascularization compared with CABG or non-diabetic stent patients (8). However, mortality at one year tended (but not significantly) to be greater for diabetic (6.3%) versus CABG patients (3.1%). However, the ARTS trial also emphasizes the overt risk of diabetes regardless of the form of revascularization. Patients undergoing CABG had a significantly increased risk of peri-surgical events, markedly affecting clinical outcome and cost. Re-hospitalizations for diabetic CABG patients were significantly increased, relating to non-revascularization events such as sternal infection, stroke, renal insufficiency, and pulmonary embolism. Thus, the net cost advantage at one year was still in favor of coronary stenting, partly related to morbid CABG complications despite more revascularization procedures in the stent PCI diabetic group. These results re-emphasize the adverse effects of diabetes on both CABG and stent PCI outcome.

LIMITS OF FOCAL REvascularization

The complexity of diffuse diabetic CAD on the outcome of PCI versus CABG was described in the diabetic subgroup of the randomized CABG versus balloon angioplasty trial (Coronary Angioplasty vs. Bypass Revascularization Investigation [CABRI]) (9). In this trial, although mortality was significantly higher for the balloon PCI group compared with the CABG group, the mortality for the diabetic versus non-diabetic patients who underwent CABG was also twice as high. Of note, the number of successfully revascularized lesions was nearly twice as great for the CABG population compared with the angioplasty group. Reasons for less complete revascularization in angioplasty patients is partially technical, although this limitation continues to decline with advances in equipment. Conversely, a bypass graft that covers multiple lesions of varying severity, including the most critical lesion, which may have been the only lesion treated with the angioplasty, “protects” a longer segment of the artery at risk for future coronary events. The extent of “vascular protection” may account for a significant component of the CABG advantage in diabetics who tend to have more diffuse disease. Again, in the more recent ARTS trial (7), complete revascularization was more commonly observed with CABG than with stenting (10). Although the extent of revascularization at one year did not predict event-free survival, stented patients with less complete revascularization were more likely to need subsequent CABG. Thus, completeness of revascularization, including both significant lesions as well as multiple, often non-critical lesions, appears to affect late outcome.

CONTEMPORARY STENTING

In the report by Mehran et al. (11) published in this issue of the Journal, the authors describe the short-term and one-
year outcomes for patients undergoing multivessel native vessel stenting, specifically comparing diabetic with non-diabetic patients. In this report, the authors included a small number of non-treated diabetic patients in the non-diabetic group as reported in the BARI trial (6). Overall, the population included 689 patients with 1,639 native coronary lesions, including 188 diabetic patients with 439 treated lesions. Short-term outcomes were similar between the diabetic and non-diabetic groups, except for a higher incidence of CABG in the insulin-dependent diabetic group (3.5%) versus 1% or less for non-diabetics or oral treatment diabetics. However, CABG risk represents only 3 patients of 86; and such small numbers could easily explain this difference. More importantly, the one-year results demonstrate a 10% lower survival in treated diabetic patients compared with non-diabetic patients. Likewise, the incidence of target lesion revascularization for the oral agent and insulin-dependent diabetic groups was 26% and 35%, respectively, compared with 16% in non-diabetics, a number consistent with what would be predicted for a multivessel stent population.

Importantly, in this study, the diabetic patients, particularly the insulin-dependent patients, experienced more renal failure than did non-diabetic patients, which is a known predictor of high, short-term risk after PCI and CABG. Other characteristics increasing the overall risk of the diabetic population included relatively small vessels based on pretreatment reference vessel size, with more insulin-dependent diabetic patients having more than three lesions stented. The diabetic patients had more incidents of hypertension, peripheral vascular disease, a higher incidence of prior cerebrovascular events, and greater clinical congestive heart failure. The increased risk profile of the diabetic population was further supported by a comparatively high incidence (33%) of patients with a reduced left ventricular ejection fraction (<50%), a rate that is higher than in the BARI trial (6).

Although the diabetic patients in this study had greater restenosis, this may be related to smaller vessel size, greater risk factors, but also to the independent effect of diabetes (1–5). Furthermore, the need for late target lesion revascularization in the treated diabetic patients may be related to disease progression other than in the stented segments. Comorbidities may have increased target vessel, not target lesion risk, because the event rate for renal failure patients was increased, whereas the target lesion revascularization was not.

**CONFOUNDING CLINICAL ISSUES**

Prospective registry studies have the advantage of real-world outcomes because they represent practice reality, but they also have the limitation of uncontrolled and undocumented real world inconsistencies in practice, some of which may represent less than optimal risk management by multiple practitioners involved in the long-term medical care. Conversely, the outcomes reported may have been benefited by the decision-making capability of the operators (12,13). For example, in the EAST trial (13), operator decisions in the registry population were associated with better outcomes than in randomized patients.

Although PCI was performed by experienced operators in the current report, the outcome may have been affected by uncontrolled technical aspects, such as variable stent design use and deployment methods, including maximum inflation pressures, predilation, and so forth. The inconsistent application of multiple stent designs and techniques over six years may have had an unknown effect, particularly in higher-risk lesions, which may be more responsive to specialized stent characteristics or procedure-related techniques. Thus, technical variability may have produced either a positive or negative advantage in some patient populations.

**ADJUNCTIVE MEDICAL TREATMENT**

The authors (11) report a <10% use of IIb/IIIa antagonists, which may relate to the high (28%) incidence of periprocedure myocardial infarction. Abciximab use has been shown to significantly reduce acute and long-term events for diabetic patients undergoing stent placement (14). Systematic use of IIb/IIIa antagonists might have significantly narrowed the gap between diabetic and non-diabetic patients.

Another factor not reported is the overall use of statin therapy, which became more recognized for its benefits over the time of the study. Although the LIPS trial (15) did not show a difference in outcome for patients after angioplasty treated with fluvastatin at one year, favorable effects were evident beginning at 1.5 years, particularly in diabetics and patients with multivessel disease. Furthermore, although patients with acute myocardial infarction within 48 hours were excluded from the Mehran et al. report (11), the percentage of patients with acute coronary syndromes was not defined. Statins improve outcomes in acute coronary syndromes, as evidenced by the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) (16) trial. Although the MIRACL trial did not address coronary intervention specifically, the favorable effect on short-term outcome further suggests that statins can significantly impact vascular inflammation, which appears to be one of the hallmarks of diabetic vascular disease.

Relative to other risk factors, hypertension was higher in the diabetic population. Again, given the time frame of the study, the unknown degree of hypertension control (current guidelines call for blood pressures of <130/80 mm Hg for diabetes) may have had an important adverse impact on outcome.

Another issue under intense current investigation is the optimal drug treatment of glucose control in diabetes to optimize late outcome. In the current registry, diabetes management was uncontrolled regarding type of treatment...
and/or effectiveness in the absence of the hemoglobin A1C levels achieved.

Finally, recently reported one-year results of the CREDO trial (17) demonstrated a 26.9% (absolute 3%) reduction in combined death, myocardial infarction, or stroke for continued clopidogrel treatment beyond one month after PCI. Similar results applied to the Mehran et al. (11) population could have further improved outcome had this information been available during the study period.

In summary, clearly defined, standardized adjunctive medical therapy might have had significant impact on the outcome of described patient population, partially relating to the stent vascular response, but more likely directed at blunting the generalized adverse vascular effects associated with diabetes.

THE FUTURE

Drug-eluting stents should further improve the late outcomes of patients undergoing multivessel coronary intervention. On the other hand, data from the Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery (SIRIUS) trial (18) indicates that although diabetic restenosis is reduced significantly compared with a control restenosis with the DES stent tends to still be higher than for non-diabetic patients. Furthermore, in the SIRIUS trial, nine-month follow-up showed a 7% to 8.6% risk in the sirolimus and control stent groups, respectively, for non-restenotic events, such as in-hospital major adverse coronary events and out-of-hospital myocardial infarction, mortality, and late non-target lesion revascularization.

In the era of drug-eluting stents, there is no doubt that better outcomes will be seen as a result of more durable revascularization, but the need for targeted adjunctive medical therapy for the entire vasculature remains crucial for optimal outcomes. Diabetics will be the major group to benefit from a better understanding of vascular disease management, including risk factors, thrombosis, and platelets as well as optimal methods for glucose control.

In summary, the data presented by Mehran et al. (11) are encouraging in that stents did improve the outcome for multivessel PCI compared with prior balloon trials. The results also emphasize that optimal diabetic management is complex and incompletely treated by stent revascularization therapy. This is not a failure of stents as much as it is a failure of our understanding and application of effective adjunctive vascular therapy. However, the future is bright with drug-eluting stents poised to markedly limit restenosis while the application of medical vascular management continues to expand.

References