Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 35, No. 5, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00532-5

EDITORIAL COMMENT

Diabetes and the Cardiologists: A Call to Action*

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Two articles in this issue of the *Journal* persuasively emphasize the importance of diabetes in the long-term outcome of coronary heart disease (CHD) after revascularization procedures (1,2). These two randomized controlled trials comparing coronary artery bypass grafting (CABG) and

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percutaneous transluminal coronary angioplasty (PTCA) in patients with multivessel disease clearly demonstrate the adverse effects of diabetes. It has long been appreciated that diabetes is a major risk factor for the development of atherosclerosis resulting in a wide variety of cardiovascular dysfunction and complications, including renal disease with hypertension, diastolic dysfunction, platelet abnormalities, abnormal vascular reactivity, etc. (3,4). During the last several decades, other major risk factors, particularly hypertension, smoking and lipid abnormalities have been the targets for intensive efforts at risk reduction, but diabetes has received scant specific attention, especially by cardiologists. In three leading textbooks, pages devoted to diabetes are limited: 11 of 2,602 (5), 5 of 1,996 (6) and 23 of 2,641 (4) text pages. The sections devoted to lipid abnormalities and hypertension each contain many more pages (2 to 10 times as many). The landmark Diabetes Control and Complications Trial (DCCT) convincingly demonstrated that fastidious control of blood glucose can delay or prevent complications in type 1 diabetes mellitus (T1DM) (7). Similar studies are ongoing in reference to the much more common type 2 diabetes (T2DM).

The Bypass Angioplasty Revascularization Investigation (BARI) (1) and Emory Angioplasty vs. Surgery Trial (EAST) (2) have many similarities in reference to study design. Both studies enrolled symptomatic patients with multivessel coronary atherosclerotic disease who were eligible for either CABG or PTCA as their first revascularization procedure. Differences in patient selection and protocols exist but are not critical to the discussion in this editorial. Emory Angioplasty vs. Surgery Trial is a single center trial involving 392 patients while BARI enrolled 1,829 patients from 18 centers. The current reports describe long-term follow-up at seven to eight years after first intervention. The BARI trial is more informative in reference to the role of diabetes in the long-term outcome. In both studies, the long-term follow-up (seven to eight years) demonstrates that diabetic patients who had PTCA as their first revascularization procedure had a significantly higher mortality than nondiabetic patients. There was no significant mortality difference related to the choice of first revascularization procedure in the nondiabetic patients.

The BARI trial involves not only a larger number of patients but more detailed data, which permits more sophisticated analyses. There was a statistically significant survival benefit for patients who had CABG as the first procedure (84.4% vs. 80.9%, $p = 0.043$) at the seven-year follow-up. The entire mortality benefit derives from the drug treated (oral hypoglycemic or insulin) diabetic patients who constituted 19.3% of the sample. There was no mortality difference in the remainder of the patients, nondiabetics and diabetics not on drug treatment. Coronary artery bypass grafting resulted in better survival in all a priori subgroups, which included severity of angina, left ventricular function and angiographic characterization of vessel disease, including number of vessels involved, presence of proximal left anterior descending artery (LAD) disease and lesion characteristics. Although drug treated diabetic patients had more severe overall disease than the rest of the patients (and a poorer outcome regardless of treatment), the randomization process assured equal distribution of these more severe attributes in both the PTCA and CABG treatment arms. The conclusion is inescapable; diabetes is an independent determinant of adverse outcome in this trial.

The smaller single center EAST also had a lesser percentage of drug-treated diabetic patients, 15%, versus 19.3% in BARI. The overall eight-year mortality demonstrated no statistically significant difference relative to the first revascularization procedure selected, but the CABG group had a better survival (82.7% vs. 79.3%, $p = 0.40$). Hence, three lives would be saved per 100 patients treated if the study had been powered to detect such a difference statistically. However, the eight-year survival difference in the 59 drug-treated diabetic patients (30 in the CABG group and 29 in the PTCA group) was highly disparate (82.6% in nondiabetic patients and 60.1% in drug-treated diabetic patients) and statistically significant ($p = 0.02$). The remaining 333 nondiabetic patients demonstrated no difference in survival relative to initial revascularization procedure selected: 84.9% in the PTCA group versus 82.6% in the CABG group ($p = 0.7$). The difference in mortality in diabetic patients in reference to the first selected revascularization procedure was not significantly different at the five-year follow-up

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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(although major difference was seen), undoubtedly reflecting the small number of diabetics in the EAST. This observation emphasizes the importance of a longer follow-up when dealing with a small number of patients in a chronic disease.

Unfortunately, in neither study are we given any information about how effectively the diabetic patients' glycemic state was controlled. It can be assumed this is an important issue in reference to outcome, especially in light of the information from the DCCT trial (7).

The approach to catheter-based interventions has changed in major ways since the EAST and BARI trials were started more than 10 years ago. Stents, and a variety of devices, have been introduced and, in many laboratories, are used in the majority of patients with generally overall improved outcomes when compared with PTCA. Pharmacological therapy with IIb, IIIa glycoprotein receptor antagonists are now routine adjunctive therapy and result in improved procedure outcomes. Ongoing studies will clarify further how much these newer approaches improve outcomes in diabetic patients. However, we need not await the outcome of these (and undoubtedly yet to come) additional trials to conclude that diabetic patients deserve a much more assertive approach in recognizing the adverse outcomes related to the diabetic state (at least if drug therapy is indicated) and the need for fastidious control of glycemia.

The growing body of evidence in support of decreased CHD risk and improved outcomes for patient with manifest disease with better glycemic control in diabetic patients is compelling. Clinical interventional trials, including the DCCT (7) and the United Kingdom Prospective Diabetes Study (UKPDS) (8) have demonstrated that attainment of average blood glucose of around 150 mg/dl or hemoglobin A1c (HbA1c) levels of 7.0% result not only in profound reductions of the microvascular complications of eye, kidney and nerve disease, but, likewise, results in reductions of cardiovascular disease risk factors and cardiac event rates. Additional cross-sectional and epidemiologic studies report similar findings. Data from Kuusisto et al. (9) in studies on elderly Finnish patients with T2DM demonstrated that the lowest CHD mortality and event rates were observed at HbA1c levels of $<6\%$, while the highest rates were encountered at levels $>7.9\%$. Similar relationships between lower glucose levels and reduced CHD risk were observed in the Honolulu Heart Study (10) and the Islington Diabetes Survey (11). A report from the registry portion of the BARI trial also contains the strong suggestion that overall characteristics of the diabetic patient, including compliance with treatment, influenced the outcome (12). The principle emphasized in all of these studies is that aggressive treatment of diabetes with focus on glucose lowering to levels of HbA1c of $\leq 7.0\%$ must assume high priority by cardiologists, who should feel increasingly obliged to become involved in the diabetic care of their patients.

It is, unfortunately, not possible to discern how intensively treated the subjects with diabetes were in the BARI and EAST trials because no HbA1c or other glycemia-related data were included. It is possible that the outcome differences might have been muted in the treated diabetics had their glucose control achieved the currently recommended treatment goals. This is an issue that needs critical study. It is assumed that diabetic patients not on drug treatment had less hyperglycemia. They had better outcomes since they were indistinguishable from nondiabetic patients; however, we are given no specific information about the number or characteristics of the diabetic patients who were not on drug treatment.

It is also clear that control of the hyperglycemic state in diabetes has a major effect on outcome in the management of acute myocardial infarction. This is demonstrated in the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (13–15). This Randomized Control Trial of 620 diabetic patients with acute myocardial infarction evaluated the use of insulin-glucose infusion to lower blood sugar during the acute phase followed by prolonged multidose insulin therapy for more intense post-MI glucose control. The intervention group had a one-year mortality of 8.6% compared with an 18.0% one-year mortality in the conventionally treated group. This is an area of continuing research and interest (16,17). Thus, the benefits of improved diabetic control are evident from short-term and long-term interventions.

What now emerges for the cardiologist is the necessity to accord to the treatment of diabetes the same degree of rigor and urgency that has been applied to the management of dyslipidemia and hypertension. It will be just as important for the cardiologist to understand the pathophysiology of diabetes as hypertension, especially since both are examples of insulin-resistant states. However, diabetes must be understood in terms of the equal importance of insulin deficiency. It is important to note that insulin deficiency is the major problem in T1DM and is appropriately treated with insulin replacement. On the other hand, T2DM is a dual defect disease, comprising insulin resistance and insulin deficiency. These differences in underlying pathophysiology dictate differences in treatment strategies and in the attendant comorbidities. This means that patients with T2DM must receive treatments directed at both problems. Insulin resistance is reduced by weight loss and increased physical activity, which constitute the foundation of treatment for T2DM, no matter which adjunctive pharmacologic treatments may prove necessary. Knowledge of the underlying pathophysiology of T2DM makes it possible to select the pharmacologic treatment more effectively.

The available drugs conveniently target different defects that contribute to the hyperglycemia of diabetes. The alpha glucosidases (AGIs) reduce glucose absorption from the gut and thus lower postprandial hyperglycemia. The thiazolidinediones (TZDs) are insulin sensitizers that increase tissue sensitivity to insulin, especially muscle and fat, while the insulin sensitizer metformin is effective in suppressing

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liver glucose production, a source of the excess glucose seen in persons with diabetes. Metformin also has stimulatory effects in muscle and has been shown to be especially useful in overweight T2DM in reducing microvascular disease events (18). When the beta-cells begin to deteriorate, usually marked by progressive increases in fasting glucose despite other oral agent treatment, the secretagogues repaglinide or sulfonylureas help restore the sensitivity of the beta-cell to glucose and, thus, increase insulin release. When diabetes is diagnosed late, with serious elevations of FPG already evident, it is often necessary to begin treatment with an insulin secretagogue or insulin itself. The dual problems and progressive nature of T2DM predict that the vast majority of patients with this disorder will require combination therapy for glucose control and ultimately will include the need for insulin supplementation. Because T2DM may require insulin therapy (even initially in severe cases), the use of insulin for treatment does not establish whether a person has T1DM or T2DM. It is the underlying disease pathology that determines disease classification.

Hence, the critical features of treatment include individualization of treatment, achievement of the recommended goals, appropriate monitoring of glucose levels and the use of team members like diabetes educators, nutritionists, the primary care provider and the endocrinologist.

Although achieving the American Diabetic Association (ADA) recommended targets (19) for glucose (and other risk factors) is challenging, the process has been greatly aided by the demonstration that it can be done and by the availability of newer treatment options that have excellent efficacy, safety and synergism of actions when used in combination (20). The cardiologist should incorporate strategies for intensive glucose control as a linear process. This is remarkably analogous to the approach to the treatment of dyslipidemias and hypertension. An initial strategy of medical nutrition therapy is established as a foundation, to which is added a progressive array of pharmaceuticals designed to target the underlying mechanisms. In diabetes, like the other disorders, monotherapy should be used until goals are no longer reached or maintained, followed by the addition of other agents that will have synergistic or additive effects on glucose levels. When oral agents are ineffective in combination, the use of insulin is warranted and should be vigorously pursued in all insulin-requiring diabetics. These general principles constitute what should be a matter of growing importance to all cardiologists: optimal glucose control in persons with diabetes.

In summary, the BARI and EAST trials reemphasize the very important role of diabetes in the progression of CHD and make it abundantly apparent that cardiologists must become much more knowledgeable about the pathophysiology of diabetes and more persuasive in their own attitudes and actions in reference to glycemic control in diabetics. The analogy with hypertension and the dyslipidemias is quite close. It required many years before cardiologists, as a group, became convinced that fastidious control of blood pressure and dyslipidemia was of great importance to the long-term outcome.

Mechanisms to achieve greater involvement of cardiologists in diabetic therapy include systematically incorporating information about the management of diabetics into cardiology fellowship programs, emphasizing the importance of close collaborative efforts among physicians and other health care providers involved in diabetic management in specific patients and featuring more prominently the role of diabetes in a variety of educational formats available to the cardiologists, including a wide variety of meetings. The promulgation of guidelines, which includes the role of diabetic control, has already commenced (21–23), but this requires additional emphasis since treatment goals are usually not specifically stated. Much more data are needed and are accumulating at a rapid rate before optimum treatment of diabetic cardiology patients can be established. However, the currently available information makes a compelling argument for cardiologist to become more educated about diabetes and adopt an enthusiastic assertive attitude in reference to glycemic control.

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