EDITORIAL COMMENT
Optimization of Glycemic Control and Restenosis Prevention in Diabetic Patients Undergoing Percutaneous Coronary Interventions*

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Diabetes mellitus is associated with major cardiovascular morbidity and mortality, mostly related to diffuse atherosclerosis. Although substantial progress has been made in the prevention and treatment of cardiovascular diseases over the last two decades, the age and co-morbidity adjusted death rate among diabetic patients undergoing percutaneous catheter-based interventions still remain higher than the general population (1,2). Furthermore, tight glycemic control, a principal factor in the prevention of microvascular complication (e.g., retinopathy), was shown to have a limited effect on the development of macrovascular (e.g., atherosclerotic) disease (3,4). The limited therapeutic achievement in reducing cardiovascular complications among diabetics, together with the increased worldwide prevalence of diabetes mellitus, result in overall augmented fraction of diabetic patients who are likely to undergo percutaneous coronary intervention (PCI) (5,6).

The clinical outcome after PCI among patients with diabetes is less favorable than the outcome among non-diabetic patients, and it is dominated by higher rate of restenosis after balloon angioplasty (7,8) and coronary stenting (9–12). The increased risk of restenosis after angioplasty and/or stenting in diabetic patients is primarily due to an exaggerated reactive intimal hyperplasia that causes increased late lumen loss and decreased vessel lumen area (13). In a recent pooled analysis of several major recent stent trials, Cutlip et al. (14) found diabetes to be the strongest clinical predictor for restenosis, with almost 50% increased risk for target lesion revascularization at one-year follow-up. Considering the higher rate of restenosis and the current prevalence of diabetes among patients who undergo PCI (e.g., a prevalence of 18% to 30% in most series), a simple calculation would show that 30% to 40% of the patients who sustain clinical restenosis and eventually undergo target vessel revascularization are those with diabetes mellitus. Thus, reduction of restenosis rate among diabetic patients will have a major favorable impact on the global outcome of catheter-based coronary interventions.

In this issue of the Journal, Corpus et al. (15) assessed the effect of glycemic control on target vessel revascularization at the time of coronary intervention among a group of 179 diabetic patients as compared with 60 non-diabetic control patients. Patients who had optimal diabetic control, defined as HbA1C ≤7%, had a target vessel revascularization rate of 15%, compared with 34% among counterparts with a HbA1C >7%. By multivariate analysis, poor glycemic control, defined as a HbA1C >7%, was a major independent predictor for target vessel revascularization with an odds ratio = 2.87. These results are in accord with a recent study of 75 diabetic patients that identified poor glycemic control as a significant predictor for angiographic restenosis with an odds ratio = 3.0 (16). Another important finding of the current study is the observation of similar repeat revascularization rates among both diabetic and non-diabetic patients with optimal glycemic control.

The increased restenosis rate among patients with diabetes has been attributed to various physiological mechanisms, including accelerated neointimal responses, impaired vessel remodeling, exaggerated thrombus formation, and persistent endothelial dysfunction (17–19). Experimental models have shown that the combination of hyperglycemia and arterial injury induces expression of multiple inflammatory cytokines that interact with the vessel wall to enhance atherogenesis and/or neointimal formation by accelerating smooth muscle proliferation (20,21). These observations are in accord with animal and human studies suggesting that arterial injury and accompanied inflammatory responses are associated with exaggerated in-stent restenosis (22,23). It has been thus hypothesized that pharmacologic interventions aimed at improving glycemic control, via recovered endothelial function, decreases in inflammatory responses, and other yet-unrecognized mechanisms, may result in reduced restenosis (24,25). An indirect support for the potential benefit of optimal diabetic control may also be derived from a recent report from the Diabetes Control and Complications Trial (26). In this study that examined only patients with type I diabetes, the progression of the intima-media thickness of the carotid artery was significantly reduced in the group that had received “intensive” compared with the group receiving “conventional” hypoglycemic treatment. Mean HbA1c levels were 7.2% and 9%, respectively, and HbA1c level was found to be an independent predictor for progression of intima-media thickness (26). Interestingly, the differences between groups were noted at six years but not at one-year follow-up, indicating a late effect (i.e., years rather than months) of diabetes control on macrovascular complications. Progression of carotid intima-media thickness was also associated with other risk factors such as hypertension and elevated low-density lipoprotein (LDL)
levels. Also, in a recent study, the degree of oxidative stress and monocyte activation at a time of coronary intervention was greater in patients with restenosis than in those without restenosis and significantly correlated with the pre-procedural levels of LDL (27). In the current study, hypertension was more frequent, and the need for insulin was twice as high among patients with elevated HbA1c levels compared to normoglycemic patients, although LDL levels were similar. It is possible that HbA1c, a marker for glycosylation and/or glycemic control, may also mirror the overall severity of diabetes by reflecting the overall risk factor profile of the disease.

Several important issues are yet to be examined before practical implications can be drawn concerning peri-procedural optimal glycemic control. First, the study by Corpus et al. does not establish a “dose response relationship” between the levels of glycemic control and restenosis prevention. In other words, it is unclear how strict glycemic control should be and what is the optimal duration needed to affect restenosis in the context of PCI. Second, because the study population included mostly patients with Type II diabetes, it is important to further examine whether a similar beneficial effect will be obtained among patients with Type I disease and/or those who are receiving long-term insulin treatment. Moreover, a question still remains as to whether post-procedural glycemic control also plays a role in the process of restenosis. Unfortunately, HbA1c was not recorded at follow-up, and currently no data are available to address this question. The non-enzymatic process associated with the formation of advanced glycosylation end products is complex and involves large numbers of proteins and lipoproteins being exposed to hyperglycemia for months to years. Thus, achieving optimal glycemic control might be an impractical approach for most patients being referred for coronary angiography and in need of an urgent revascularization procedure. Nonetheless, the current study underscores the potential significance of an “aggressive” metabolic normalization approach as part of a comprehensive therapeutic strategy aimed at inhibiting atherosclerotic progression and preventing restenosis among diabetic patients. This approach should be evaluated in a large cohort of patients wherein several preprocedural aggressive metabolic modification strategies should be examined.

Finally, drug-eluting stents were recently introduced into the clinical practice with most impressive effects on restenosis prevention via local suppression of neointimal formation (28,29). This approach may diminish the importance of systemic optimization of glycemic control at the time of coronary intervention for the purpose of restenosis prevention. Nonetheless, the importance of a long-term comprehensive therapeutic approach directed toward metabolic normalization should be emphasized, using optimal glycemic control, adequate lipid-lowering strategy, aggressive blood pressure management, and other risk-factor modification. Currently, those therapeutic means may reduce the risk of long-term microvascular and macrovascular complications among diabetic patients regardless of restenosis prevention.

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