Diabetes mellitus (DM), which is an increasingly important issue worldwide, threatens the life expectancy of patients largely by coronary artery disease (CAD). The burden of CAD is anatomically much greater in diabetic patients than in the nondiabetic population, which makes greater the need for coronary revascularization, including coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), among DM patients. The recent advent of drug-eluting stents (DES) and off-pump CABG (OPCAB) together improved the outcome of advanced revascularization therapy, but the unique pathophysiological features of DM, such as hyperglycemia, insulin resistance, dyslipidemia, inflammation, and thrombophilia, contribute to a specific response to coronary revascularization, eventually result in a worse clinical outcome of PCI in diabetic patients than in nondiabetics.

Further, regarding the prognosis of DM patients presenting with macrovascular disease, the burden of CAD is anatomically much greater in diabetic patients than in the nondiabetic population, which makes greater the need for coronary revascularization, including coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), among DM patients. The recent advent of drug-eluting stents (DES) and off-pump CABG (OPCAB) together improved the outcome of advanced revascularization therapy, but the unique pathophysiological features of DM, such as hyperglycemia, insulin resistance, dyslipidemia, inflammation, and thrombophilia, contribute to a specific response to coronary revascularization, eventually result in a worse clinical outcome of PCI in diabetic patients than in nondiabetics.

In the context of hyperglycemia, a growing body of evidence has shown that optimal glycemic control improves the long-term prognosis of DM subjects, as demonstrated in large-scale prospective cohort studies such as UKPDS80 and the Framingham Heart Study. On the other hand, it is yet to be defined whether intensive glucose lowering is appropriate for the prevention of macrovascular disease. Results of landmark large-scale randomized controlled trials (RCTs), ACCORD, ADVANCE, and VADT, together suggest that intensive glucose lowering may not be beneficial for all DM patients, so the American Diabetes Association states that HbA1c should be the current goal for glycemic control to prevent major adverse cardiac events (MACE).

Further, regarding the prognosis of DM patients presenting with macrovascular disease requiring revascularization, it is totally unclear whether glycemic control affects the prognosis after the revascularization procedure and to what extent glycemic control should be targeted. PCI is a procedure by which myocardial ischemia is minimized at the expense of vascular injury. The subsequent vascular healing process is known to be greatly influenced by hyperglycemia and hyperinsulinemia via vasomotor dysfunction, increased cellular proliferation, and altered inflammatory response caused by advanced glycation endproducts. Thus the specific topic of what intensity of glucose control should be achieved to better perform PCI remains unresolved, although the importance of the subject has been raised.

In fact, very few studies have dealt with this particular but important issue. A medium-scale prospective study (n=239) conducted by Corpus et al is a noteworthy one, comparing clinical outcome after PCI among 3 groups based on the HbA1c at the time of the procedure. They found that the rate of performing target vessel revascularization (TVR) was significantly lower in patients with HbA1c ≤7.0% at the time of PCI than in those with HbA1c >7.0%, and that TVR was similar between the nondiabetic group and the optimal control group (HbA1c <7.0%). They provide enough notable evidence to attract attention to this specific focus of glycemic control before PCI, even though there were several study limitations. Clinical follow-up was performed by telephone interview and hospital records without routine coronary angiography, and they did not examine the glucose levels after the procedure. Consequently, the question remains as to whether post-procedural glycemic control plays a role in the process of restenosis. In addition, there is a hypothetical theory that hyperinsulinemia itself is responsible for restenosis after vascular injury in PCI by a variety of mechanisms of action of insulin. They also tested this hypothesis in their study and found that the association of insulin use with clinical outcome had borderline significance, leaving the question still unanswered.

Hage et al investigated the impact of baseline fasting plasma glucose (FPG), HbA1c, and glucose control methods (intensive insulin therapy, or medical therapy) on target lesion restenosis after PCI at 6 months in a relatively small RCT (n=93). After 6 months, there was no significant change in HbA1c, FPG, or restenosis rate between the 2 groups. Interestingly, univariate analysis showed that baseline FPG was the only predictor of the restenosis rate after PCI at 6 months, suggesting that the main contributing factor is not the method of controlling the glucose level, but the glucose level per se.

In this issue of the Journal, Ike et al shed light on this currently unresolved problem by a retrospective study using their registry database from a single center. They success-
fully demonstrate that good glycemic control at the time of PCI is significantly associated with the clinical outcome post-PCI in terms of MACE, including target lesion revascularization (TLR) (18.4% in ≤6.9 group vs. 26.2% ≥6.9 group, P<0.05). They also compared the incidences of in-stent restenosis and TLR, and late loss at stent/lesion based on angiographic data between the ≤6.9 group and ≥6.9 group. Further comparison was performed between the DM control group and poor control group within the ≥6.9 group. This study has several remarkable advantages of scientific value compared with previous studies, albeit its limitation of a retrospective study design. Angiographic assessment is a highly qualified method, with accuracy based on QCA and IVUS and complete angiographic follow-up rate, as is characteristic of angiographic studies in Japan. Another point is that as many as 50% of lesions were treated with DES. In particular, the most notable result of this study is that glucose levels before and at the time of PCI, not those after PCI, were significantly associated with a lower incidence of TLR as well as MACE. This evidence arouses us to pay more attention to the glycemic control status at the time of PCI rather than the chronic control status of DM patients. Another potentially crucial point is that the cutoff level of HbA1c: 6.9% (based on NGSP) is almost consistent with the current glycemic control goal of 7.0% to prevent macrovascular disease, which has not only been adopted in many significant large-scale trials such as COURAGE, but also presented in the American Diabetes Association statement, as well as in the ACC/AHA secondary prevention guideline, irrespective of differences in ethnic and lifestyle background. During their editing of the paper, authors also tested the cutoff value of 6.5% (equivalent to current HbA1c: JDS 6.1%) by applying it to the current study model and found no significant results, implying that the HbA1c (NGSP) cutoff value of 6.9–7.0% might be universally important in terms of preventing cardiovascular events around the time of PCI. Accordingly, their results are of substantial importance, particularly for Japanese, in respect of the clinical compatibility of DM diagnostic criteria with worldwide guidelines, in the face of possible confusion caused by the ongoing shift towards NGSP HbA1c usage for years. The authors provide evidence to support the emphasis on the importance of normalizing the plasma glucose levels particularly at the time of PCI, but in doing so raise many questions. Are their conclusions reproducible and robust enough? What are the appropriate plasma glucose levels instead of using HbA1c? How long should DM patients undergo intensive glucose normalization to achieve as good an outcome as nondiabetes after PCI? Should normalization of plasma glucose also be achieved even by insulin injection, with the possibility of the unfavorable effect of hyperinsulinemia? These questions, as well as the precise underlying pathophysiological mechanisms, need to be elucidated by further clinical investigations.

In conclusion, glycemic control status before an interventional procedure in a DM patient should be a previously unrecognized but promising target for improving the overall effectiveness of PCI in these patients. It is crucial for their long-term clinical outcome to scientifically research and develop efficacious modifications of current therapies. For this extreme goal, a move toward more well-designed RCTs for DM patients with CAD is particularly required.

References