Fractional Flow Reserve–Guided Intervention of Angiographically Nonsignificant Coronary Stenoses

We read with interest the recent DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) study by Pijls et al. (1) comparing results of percutaneous coronary intervention (PCI) with medical therapy in patients with stable coronary artery disease and angiographically intermediate stenotic lesions. The study demonstrated no beneficial effects of PCI in stenosis with fractional flow reserve (FFR) $>0.75$ (performance group) as compared with medical therapy (defer group) and increased major adverse cardiac events (MACE) in lesions with $\text{FFR} < 0.75$ (reference group) during 5 years of follow-up.

It is interesting to note the high frequency of coronary artery bypass grafting (CABG) during 5 years of follow-up in the reference group (10.4%), especially given the fact that two-thirds of the patients had single-vessel disease, with normal left ventricular ejection fraction (68 ± 9), and few with diabetes (13%). This figure is definitely high as compared with that seen in concurrent studies such as COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) (2) and MASS II (Second Medicine, Angioplasty, or Surgery Study) (3), with the majority of their patients having multivessel coronary artery disease. Seventy-seven patients (6.7%) in the PCI arm of the COURAGE study underwent CABG after median 4.6 years, whereas MASS II reported 9.3% during 5 years of follow-up.

The DEFER study defined myocardial infarction using a 2-fold elevation of creatinine kinase, which is not a standard definition as reported by the joint committee of European Society of Cardiology/American College of Cardiology (4). Furthermore, the definition of acute myocardial infarction after PCI requires at least 3 times elevation above the upper limit of the normal (ULN) and another study reported 5 to 8 times the ULN (5). We believe that the definition used in the present study significantly increased the events of myocardial infarction both in hospital and during follow-up and might have led to increased MACE in the reference group (FFR < 0.75).

*Umamahesh C. Rangasetty, MD
Charles Y. Lui, MD

*Division of Cardiology
University of Texas Medical Branch Galveston
301 University Boulevard
Galveston, Texas 77555
E-mail: cylui@utmb.edu

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Reply

We do not believe that the rate of coronary artery bypass grafting in the reference group of the DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) study was high compared with that seen in other studies.

Although in the DEFER study the majority of patients had single-vessel disease, the reference group only consisted of those patients with proven ischemia (1). This is in contrast to the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial and many other trials. In those trials (2), patients were classified according to angiographic criteria, and it is well known that a significant number of angiographic stenoses in those patients is not functionally important (i.e., not responsible for reversible ischemia) and that from the functional point of view, angiographic 2- or 3-vessel disease often becomes 1-vessel disease in terms of inducible ischemia (3,4).

In fact, one of the reasons why outcome after medical treatment was reasonable compared with that seen with percutaneous coronary intervention (PCI) in the COURAGE trial has been the fact that in the PCI group, intervention was often performed on relatively mild lesions, many of them most likely not functionally significant. Performing PCI of such lesions (fractional flow reserve [FFR] > 0.75) creates a negative bias for PCI as demonstrated in the performance group of the DEFER study. In contrast, also in the COURAGE trial, PCI of ischemia-related stenosis (equivalent of FFR < 0.75 in a study) was significantly better than medical treatment.

At the time when the DEFER study was performed (1997 and 1998), no consistent definition of myocardial infarction in enzymatic terms existed, and an increase to more than twice the normal upper limit was often used. Nowadays, we would have taken a 3-fold increase as standardized in the recent guidelines of the European Society of Cardiology (5). This would not have made any fundamental difference for the outcome of the study.

CORRESPONDENCE

Letters to the Editor
Drug-Eluting Stent Implantation May Not Affect Vasomotor Function in Early Phase

The study by Obata et al. (1) demonstrates that drug-eluting stents (DES) adversely affect endothelium-dependent vasomotor function with a reduction in vascular endothelial growth factor (VEGF). This report addressed a very important issue because it has been reported that endothelialization and its function are impaired following DES implantation (2,3). However, we are not convinced by the findings in the present study that DES affect vasomotor function 2 weeks after implantation. As we have previously reported (4), there is no histologic difference between DES and bare-metal stents (BMS) within 2 weeks following implantation. Moreover, vascular healing of the stented segment in acute myocardial infarction generally takes a much longer time to complete than stable plaques do in the case of both DES and BMS because these lesions generally contain large necrotic cores. Therefore, it is surprising that the authors report differences in response to intracoronary acetylcholine because the extent and functionality of endothelium for lesions stented with either DES or BMS lesions is not different 2 weeks after implantation. Furthermore, angiography cannot detect the underlying atherosclerotic disease in the distal segments where vasomotor function was assessed, and it is possible that the differences observed were due to differences in atherosclerotic burden between the 2 groups because endothelial function has been shown to be heavily influenced by the presence of underlying atherosclerotic disease.

The authors also speculate that lack of VEGF in DES might be responsible for impaired endothelialization or its function. As the authors mentioned in the introduction, a compensatory up-regulation of VEGF is usually observed when endothelium is denuded, whereas VEGF is down-regulated upon complete re-endothelialization (5). We do agree that high blood concentrations of sirolimus at an early time point could impair endothelial cells in the portion distal to the stent and be responsible for vasomotor dysfunction. However, the sirolimus concentration in the anterior interventricular vein is far below its IC50 (1.0 to 1.5 nmol/l) even at 3 days (0.5 nmol/l) and even further below at 2 weeks (0.2 nmol/l) following implantation. Even if sirolimus had a detrimental effect on endothelial cells in the distal vessel, the VEGF level should be higher in the presence of active ongoing arterial repair. In fact, our in vitro and in vivo data clearly showed VEGF up-regulation after endothelial injury. In our own assays, human umbilical vein endothelial cells are grown under its IC50 (1.0 to 1.5 nmol/l) even at 3 days (0.5 nmol/l) and even further below at 2 weeks (0.2 nmol/l) following implantation. Even if sirolimus had a detrimental effect on endothelial cells in the distal vessel, the VEGF level should be higher in the presence of active ongoing arterial repair. In fact, our in vitro and in vivo data clearly showed VEGF up-regulation after endothelial injury. In our own assays, human umbilical vein endothelial cells are grown under its IC50 (1.0 to 1.5 nmol/l) even at 3 days (0.5 nmol/l) and even further below at 2 weeks (0.2 nmol/l) following implantation. Even if sirolimus had a detrimental effect on endothelial cells in the distal vessel, the VEGF level should be higher in the presence of active ongoing arterial repair. In fact, our in vitro and in vivo data clearly showed VEGF up-regulation after endothelial injury. In our own assays, human umbilical vein endothelial cells are grown under its IC50 (1.0 to 1.5 nmol/l) even at 3 days (0.5 nmol/l) and even further below at 2 weeks (0.2 nmol/l) following implantation.