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EDITORIAL COMMENT

Pioglitazone to Reduce Restenosis After Bare-Metal Stent Placement?*

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In this issue of *JACC: Cardiovascular Interventions,* Takagi et al. (1) report the results of a small, multicenter, randomized trial suggesting that pioglitazone might reduce the risk of restenosis in diabetic patients who receive a bare-metal stent. The study design was simple and elegant. The authors randomized a typical population of type II diabetes patients with stable or unstable angina to pioglitazone versus other oral hypoglycemic agents after bare-metal stent placement for a single culprit lesion. The results are consistent with a favorable effect of pioglitazone on neointimal proliferation and clinical restenosis, although the statistical significance of these findings was marginal. Target lesion revascularization, the most clinically relevant measure of restenosis, was reduced from 29.8% to 12.5%, p = 0.04. The neointimal index (the percent of the stent volume occupied by neointima), the most clinically relevant intravascular ultrasound (IVUS) measure of neointimal proliferation, was reduced from 40.5% to 31.1%, p = 0.01.

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Several aspects of this study are notable. The success of the study reminds us that, in an era of $100 million "mega-trials", important scientific observations can be accomplished by dedicated investigators performing a meticulous, small randomized trial with a limited budget. The authors succeeded in this endeavor by applying many of the best practices of large randomized trials in conducting their small study. They enrolled a fairly homogeneous patient population, thereby avoiding the confounding effects of patient variability. The investigators used a core laboratory to perform IVUS and angiographic measurements to avoid the variability inherent in "locally" measured images. They managed the randomization process well, with no clinically relevant differences observed in baseline characteristics between the 2 study groups (Table 1 in Takagi et al. [1]). They enrolled patients undergoing intervention on a single discrete coronary lesion, avoiding the confounding effects of treatment of multiple lesions. Commendably, the investigators prospectively performed formal power calculations to determine the optimal sample size.

There were a few aspects of the study conduct that were suboptimal. To keep the sample size low, the study was powered at 80% (not the more typical 90%), and the authors used very aggressive assumptions in their power calculations, postulating a reduction in restenosis rate from 43% to 17% for the pioglitazone treatment group. They actually observed a 17% restenosis rate in the pioglitazone group but a better-than-expected 35% restenosis rate in the control group, resulting in a p value that fell just short of conventional levels of statistical significance, p = 0.06. Repeat IVUS measurements were obtained in only 56 of 97 patients (58%). As a consequence, 1 measure of proliferation, absolute in-stent neointimal volume, was substantially smaller in the pioglitazone group (48.0 mm^3 vs. 62.7 mm^3), but again, the statistical significance was marginal, p = 0.07. Thus, the small study size resulted in findings that were not statistically robust, particularly without a statistical correction for the multiplicity of end points. This potential for type I error imposes limitations on interpretation. Therefore, the findings must be considered hypothesis-generating rather than hypothesis-proving.

Despite these limitations, the potential importance of the current findings should not be underestimated. In the 4 decades since the first coronary angioplasty, the quest to develop a systemic therapy to reduce restenosis has been fraught by frustration and failure (2). Nearly all pharmacological efforts to limit restenosis were abandoned after the successful development of drug-eluting stents (DES). Perhaps, termination of such efforts was premature. Recently, the emergence of concerns about potentially catastrophic late stent thrombosis and the need for 12 months of dual antiplatelet therapy have exposed some critical weaknesses in the DES approach. Clearly, for some patients, DES is not an option, including patients awaiting urgent planned major surgery or those who face increased bleeding hazards. We must view any systemic therapy that shows a favorable effect on restenosis as a welcome addition to the therapeutic armamentarian. Furthermore, it must be emphasized that restenosis still occurs in >10% of patients who receive DES, particularly in patients with diabetes (3). Although the authors did not study patients receiving DES, the potential of this approach to further reduce restenosis, if confirmed, would be a valuable addition to current therapy.

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From Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio. Dr. Nissen reports that he has received research support to perform clinical trials through the Cleveland Clinic Coordinating Center for Clinical Research from Pfizer, AstraZeneca, Novartis, Roche, Daiichi-Sankyo, Takeda, Sanofi-Aventis, Resverlogix, and Eli Lilly. Dr. Nissen consults for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction.

This study also provides interesting insights into the biological effects of a controversial group of drugs, the thiazolidinedione (TZD) class. Introduced with great fanfare in the late 1990s, the TZDs are peroxisome proliferator-activated receptor (PPAR)-gamma agonists. The PPAR-gamma agonists modulate the activity of a wide array of genes affecting a large number of biological processes (4). At the time of introduction, TZDs seemed to have many desirable properties for treatment of diabetes mellitus, including a robust and durable reduction in glycosylated hemoglobin, potent anti-inflammatory properties, and antithrombotic effects. Then came disquieting findings; these drugs could cause fluid retention and precipitate congestive heart failure in susceptible individuals (5). A closely related drug, muraglitazar, was not approved by the Food and Drug Administration after we published a pooled analysis of Phase II and III data showing a significant increase in ischemic cardiovascular events (6). In 2007, we published a meta-analysis of the most widely used TZD, rosiglitazone, that showed a significant increase in the incidence of myocardial infarction and possibly cardiovascular death (7). These revelations have created an atmosphere of concern and suspicion about the entire class.

In the setting of a drug class currently undergoing reconsideration, how do we explain the current favorable findings? It is important to understand that TZDs are unlike most typical drug "classes." Each TZD is a unique PPAR agonist that upregulates and downregulates somewhat different genes (8). Accordingly, the biological effects of the TZDs differ considerably. For example, rosiglitazone increases low-density lipoprotein cholesterol (LDL-C) and shows minimal effects on triglycerides, whereas pioglitazone has minimal effects on LDL-C and lowers triglycerides (9). We recently published, as noted by the authors, an IVUS regression–progression trial that showed slowing of disease progression in diabetic patients treated with pioglitazone, compared with glimepiride (10). A large clinical outcomes trial showed a strong trend toward reduction in major adverse cardiovascular events with pioglitazone treatment (11). A meta-analysis of Phase II, III, and IV trials of pioglitazone also showed a favorable effect on cardiovascular outcomes (12). Accordingly, despite concerns about other drugs in the "class," the hypothesis that pioglitazone might reduce restenosis is biologically plausible.

Regardless of mechanism of benefit, the results of this study are notable. Systemic therapy to prevent restenosis is not a futile endeavor. The current results must be replicated in a larger trial with greater statistical power, and the hypothesis should be explored in separate study of patients receiving DES. Nonetheless, the current study represents a good start.

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Key Words: diabetes mellitus ■ ultrasound ■ stent ■ restenosis.