

A Perspective on Coronary Revascularization in the PROactive 05 Study

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events before randomization and was based upon a liberalized version of the inclusion criteria of the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial (3). Of course, any subgroup needs to be interpreted with caution before the results are applied broadly and we went to great lengths in the paper to interpret our findings very conservatively and with the appropriate caveats. The subgroup as defined is one that represents a population in which it is biologically plausible that there might be benefit, and the findings are in keeping with and an extension of several other clopidogrel trials, such as the CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy), COMMIT (Randomized Placebo-Controlled Trial of Adding Clopidogrel to Aspirin in 46,000 Acute Myocardial Infarction Patients), and CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) studies (4–6). Importantly, we conclude by stating that further study is necessary to validate our findings.

Dr. Gebel's comparisons of our results to the CAPRIE trial, as well as to the MATCH (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) trial, are flawed (7). In the CHARISMA study, the comparison was clopidogrel to placebo, with a background of aspirin therapy. In the CAPRIE trial, the comparison was clopidogrel versus an active control, aspirin, with no placebo arm. The MATCH trial was essentially a comparison of aspirin versus placebo, with a background of clopidogrel. Thus, interpretation of these trials and cross-comparison is not as simple as Dr. Gebel portrays.

He concludes by stating that he does not think the findings would be replicated if the trial were repeated. Indeed, one trial has already been announced that will test the hypothesis of whether adding a novel antithrombotic to aspirin is superior to aspirin alone in patients with prior myocardial infarction, stroke, or peripheral arterial disease. Likely, other trials will also test the value of additional antithrombotic therapy in this patient population, such that we will ultimately have further data to guide decision making about optimal antithrombotic strategies for patients with prior ischemic events.

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A Perspective on Coronary Revascularization in the PROactive 05 Study

Erdmann et al. (1) should be applauded for their recent contribution entitled “The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction”. The PROactive 05 study is a post hoc exploratory analysis of patients enrolled in the main PROactive study that entered the study with a previous myocardial infarction (MI) (2). The investigators conclude that in high-risk patients with type 2 diabetes and previous MI, pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and acute coronary syndrome (1). These results provide critically important clinical data for pioglitazone, in light of Nissen and Wolski's (3) recent analysis suggesting increased risk of MI with rosiglitazone use.

In the PROactive 05 study, cardiac intervention is defined as coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) (1). Approximately 40% of the patients at baseline had a previous PCI/CABG (1). In Table 5 under the heading for individual end points, the investigators reported that coronary revascularization (CABG and PCI) demonstrated a nonsignificant absolute risk reduction (ARR) of 2% (1). This is the most dynamic ARR among any of the individual end points. This finding may be supported by the results of a recent meta-analysis. That meta-analysis evaluated the effect of thiazolidinediones (TZDs) on reducing the risk of repeat target vessel revascularization (TVR) after PCI (4). The results suggested that TZDs, in fact, significantly reduce repeat TVR after PCI (4). Although relative risk is reduced regardless of the TZD used or the presence of diabetes, patients with diabetes and studies evaluating pioglitazone seemed to show the most robust benefit (4).

Because a large portion of patients at baseline had undergone a previous coronary intervention, it would be interesting to evaluate these patients separately to determine if this subgroup would demonstrate a significant reduction in any coronary revascularization. Additionally, it may be compelling to evaluate pioglitazone's effect on CABG and PCI separately. We suspect that the majority of the absolute risk reduction for this end point is driven by the PCI subset of patients. Such a finding could substantiate the results reported in the meta-analysis by Riche et al. (4) and may cast a new light on the darkening link between TZDs and MI.

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Reply

We thank Drs. Riche and Dale for their letter commenting on the PROactive 05 subanalysis in patients with myocardial infarction (MI) at baseline. In that prespecified analysis, we reported that pioglitazone reduced the occurrence of adverse cardiac outcomes, including recurrent MI, in the 2,445 patients with previous MI (1).

Drs. Riche and Dale suggest that it would be useful to look specifically at any reductions in cardiac revascularization in the subgroup of patients who had had a previous cardiac intervention (coronary artery bypass graft [CABG] or percutaneous intervention [PCI]). We found that, in the full PROactive analysis set, pioglitazone was equally effective in reducing the occurrence of first revascularization relative to placebo in patients with a prior history of cardiac intervention compared with those without such a history (hazard ratio 0.88 in both patient groups; *p* for interaction between subgroup and treatment = 0.9960). Thus, in the total PROactive

population, there did not appear to be any extra benefit of pioglitazone in the group with a prior history of coronary intervention.

Looking at the same end point in those with both a history of MI and cardiac intervention at baseline, there was again no evidence of a treatment subgroup interaction (hazard ratios 0.86 in those with and 0.75 in those without prior PCI/CABG; *p* for interaction between subgroup and treatment = 0.6013). Only 140 patients had a prior CABG at baseline, but an analysis of those with PCI (*n* = 214) yielded a similar outcome.

One major limitation to these analyses is the high correlation between the end points of MI/acute coronary syndrome (ACS) and PCI/CABG. However, any direct effect on the risk of PCI/CABG should be reflected in elective PCI/CABG rates. Using the definition of elective PCI/CABG as occurring without MI or ACS or occurring >30 days after MI/ACS, there were 123 events in the pioglitazone group and 132 in the placebo group (hazard ratio 0.94; *p* = 0.6135).

Taking all of the above information together, we conclude that, in the PROactive study, pioglitazone reduced MI relative to placebo and this was reflected in PCI/CABG rates, but there was no conclusive evidence that pioglitazone influenced revascularization rates differently.

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