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Reply to Letters

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Reply to Letters: "Preoperative Aspirin Use and Outcomes in Cardiac Surgery Patients: A Role of Platelet Function Assessment" and "Preoperative Aspirin Use in Cardiac Surgery"

Reply to Petricevic et al:

Dr Petricevic and colleagues raise several important questions in their letter commenting on our article published in *Annals of Surgery*,[1] especially regarding "the lack of objective quantification of the antiplatelet effect of aspirin in group of patients taking aspirin within 5 days preceding surgery." First, our study is an observational retrospective cohort study in which we could trace only the data collected in the databases while platelet function tests were not there. Some of the data were also lacking in the database including the chest tube draining and preoperative MACE events, although we certainly would like have them for the study.

Second, the mechanisms responsible for the beneficial effects of aspirin in patients undergoing cardiac surgery remain unclear. The benefits we observed in our study could well be the results of the effects of aspirin other than just antiplatelet, such as anti-inflammation.

Third, Petricevic et al[2] quoted their study that used a point-of-care platelet function analyzer (multiple-electrode aggregometry) to determine whether the patient's platelet aggregation was inhibited and whether the patient was resistant to aspirin. However, platelet function testing has shown significant differences in responses in patients treated with aspirin and there is no "gold standard" laboratory test for assessing platelet function.[3] Besides noncompliance, multiple confounding factors could underlie incomplete platelet response to aspirin, including bioavailability (underdosing, poor absorption, interference with other drugs), platelet function (incomplete suppression of thromboxane A2 generation, enhanced platelet turnover), polymorphisms of thromboxane receptor, smoking, hypercholesterolemia, stress, and exercise.[4]

As previous reports have indicated, there is a well-documented variability between patients and normal volunteers with regard to laboratory test responses to aspirin,[5] which has also been termed as aspirin "resistance." Presently, the International Society on Thrombosis and Haemostasis Working Group on Aspirin Resistance (or nonresponse) do not recommend testing for aspirin resistance in patients taking aspirin for cardiovascular disease or to change therapy based on such tests.[4] As stated by the Working Group on Thrombosis of the European Society of Cardiology (in 2009), "An exact estimate of the prevalence of resistance or no-response to oral antiplatelet drugs (including aspirin) is at present impossible. Such impossibility is mainly due to the absence of a univocal definition and of established laboratory methods."[6(p431)] Thus, the limitations have already been set on studies from platelet function tests, we believe.

With respect to the use of clopidogrel, the patients were excluded in our study if taking preoperative antiplatelets (including clopidogrel), anticoagulants, adenosine diphosphate receptor inhibitors, and glycoprotein IIb/IIIa inhibitors because these drugs may have effects overlapping those of aspirin. We appreciate Dr Petricevic and colleagues greatly for their comments and interest in our article, and we would like to address the question of subgroup studies in our next response to Scherner et al.

Reply to Scherner et al:

Dr Scherner and colleagues raise important points regarding our study. They correctly point out that the potential beneficial effects of aspirin have to be analyzed with respect to the underlying pathophysiology and the procedure itself. As hypothesized in our article, preoperative aspirin use could benefit all types of cardiac surgery due to its broad cardiovascular protective effects, especially its anti-inflammatory effect. Inflammation is probably a major pathophysiological pathway underlying the body's response to various types of cardiac surgery.

We recognized that a sample size larger than the present one will be needed to appropriately study/analyze a subgroup of patients undergoing coronary artery bypass graft and valve surgery. We have moved one step further on a subgroup study: aspirin and nonemergent cardiac surgery.[7] Others have reported on aspirin and coronary artery bypass graft previously.[8] Nonetheless, as indicated before (by Yusuf et al), "the overall trial result is usually a better guide to the direction of effect in subgroups than the apparent effect observed within a subgroup."[9(p93)]

Scherner et al questioned that the comparison groups in our study may differ significantly with regard to several factors. Although STS- or Euro-Scores were not used in the comparison of this study, we did incorporate major risk factors into the risk and outcome analysis; these major risk factors are also used in calculating Euro-Scores. We did find that there was a major difference between the aspirin and nonaspirin groups, that is, the patients taking preoperative aspirin were significantly older and sicker, with more comorbidities including hypertension, diabetes, cerebrovascular disease, peripheral vascular disease, previous myocardial infarction, angina, left main and multiple coronary artery disease, and family history of coronary artery disease. However, the results from our studies still revealed a strong association between preoperative aspirin use and improved outcomes including mortality, indicating that aspirin oppose the most important confounding factors—comorbidities, and can be potentially applied to these high-risk patients.[1,7]

Scherner et al indicated that "a sensitivity analysis including matching and stratification would have been far more convincing than simply presenting uni- and multivariable odds ratios," which we disagree. As already pointed out in our article, there are several different options of how propensity scores can be used to control confounding, including regression adjustment (used in our study) versus stratification versus matching based on the propensity scores. Each of these approaches has its advantages and shortcomings. For example, as Winkelmayer and Kurth indicated,

> the remaining option is to match individuals from the two exposure groups on their respective propensity scores. This is maybe the most intuitive way to use the propensity scores. As it is important to match on propensity scores as closely as possible, some individuals may be lost which would lead to reduced sample size and power. However, those subjects that could not be matched may constitute extreme observations, and may not reflect typical care situations. If such situations are also strongly associated with the outcome, confounding is avoided. However, if the association between exposure and outcome is different in individuals that cannot be matched (i.e. an effect modification exists) then a potential important exposure effect is ignored.[10(p1672)]

In addition, in a systematic review article that included 43 observational studies, Shah et al concluded that "observational studies had similar results whether using traditional regression or propensity scores to adjust for confounding."[11(p550)] Obviously, how (or whether) to use propensity scores remains to be determined before one can say which way would be better suited for a certain study.

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This study was based on the database from our university hospitals. Unfortunately, the database did not provide the records regarding the duration and dose of aspirin use.

We recognized that some questions could be answered better via a randomized clinical trial. However, besides the limitation of external validity of the randomized clinical trial, it has become extremely difficult (if not infeasible) to conduct a randomized clinical trial on preoperative aspirin therapy and cardiac surgery because of ethical dilemmas in the United States. Because the latest guidelines (revised by the American College of Cardiology Foundation/American Heart Association in November 2011) recommend that aspirin should be administered preoperatively to patients undergoing coronary artery bypass graft,[12] thereafter, is the use of a placebo group unethical in such a study? We really appreciate the comments and interest Scherner et al gave to this article.

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