

Continuing aspirin before coronary artery bypass grafting surgery: old fears challenged by new evidences

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“The patient is scheduled for coronary artery bypass graft (CABG) surgery. He is taking aspirin 100 mg/die for secondary prevention of coronary artery disease. Should aspirin be continued, discontinued or replaced before surgery?”

This question might afflict hundreds of cardiac surgeons worldwide, and the decision about the preoperative drug regimen might rely more on surgeon's preference rather than on evidence-based approach. A thorough assessment of this topic would have required a multicenter double-blind randomized trial, and such evaluation has been performed by Myles *et al.* in their article recently published in *New England Journal of Medicine* (1).

In this article, authors treated 2,100 patients over 7 years with either aspirin or placebo on the day of coronary surgery. Primary outcome (a composite of death and major thrombotic complications) did not differ significantly between groups ($P=0.55$), as well as reoperation for bleeding ($P=0.75$). Besides the caveat that this study included patients undergoing redo cardiac surgery, off-pump CABG, combined procedures, and local practices might have influenced surgical management, authors concluded that aspirin use before CABG resulted in neither a lower risk of death or thrombotic complications nor a higher risk of surgical bleeding or transfusion requirement. Notably, among 5,784 patients eligible for the study, 1,143 of them had their referring surgeon who declined to participate in the study. This reflects the profound concern about intraoperative bleeding associated with aspirin use among surgeons worldwide. In fact, conflicting guidelines and lack of reliable recommendations make ambiguous the preoperative aspirin administration before elective CABG (1,2). Current opinions about antiplatelet management before CABG could be summarized into three different views.

- (I) “Aspirin haters”. About 10 years ago, a consistent body of evidences pointed out that aspirin is associated with an increased risk of postoperative bleeding after elective CABG, with greater blood products use (3). Therefore, preoperative aspirin withdrawal was initially considered as a consistent alternative before elective surgery (4). However, studies on acute coronary syndromes found that aspirin withdrawal was an independent predictor of death (5), and those results were translated to cardiac surgery. Aspirin withdrawal was found to increase cardiac and cerebral complications among patients undergoing CABG (6,7), and therefore this strategy was gradually abandoned towards alternative routes;
- (II) “Alternatives”. Considering the risks associated with aspirin withdrawal, an alternative treatment has been investigated to reduce preoperative adverse events, and pharmacologic treatment of acute coronary syndromes was translated into the management of cardiac surgery. Aspirin might be replaced before surgery with low molecular weight heparin (LMWH), such as enoxaparin. These compounds exert their action over 12–24 hours, are more manageable than unfractionated heparin, and do not impair platelet function. Such strategy would maintain a certain degree of preoperative protection against adverse events with reduced intraoperative bleeding risk (8). Therefore, preoperative aspirin replacement with LMWH as a bridge to intervention has been advocated by many centers as a compromise. However, LMWH were found to be unable to protect from major cardiac events

when used as a replacement therapy before cardiac surgery (9). Also, our group found that preoperative replacement of aspirin with enoxaparin increased the risk of bleeding after coronary surgery and of postoperative thrombosis-related complications (10). Those results can be interpreted considering our proposed “inflammatory theory” of post-operative bleeding: continued aspirin treatment until the time of CABG, reducing oxidative stress, and inflammatory responses might reduce postoperative bleeding. The reduction in inflammatory response is suggested by the reduction in postoperative C-reactive protein levels, as well as by the protective role of statins against postoperative major bleedings. LMWH lacks pleiotropic anti-inflammatory properties, and therefore might be even harmful in this surgical context considering both the higher risk of bleeding and the inability to protect from major cardiac events before surgery (9,10).

- (III) “Aspirin lovers”. Aspirin continuation was shown to reduce postoperative myocardial infarction, improve myocardial oxygenation and increase survival (11), and platelet inhibition was found to prevent acute bypass graft occlusion early after CABG (12). Further studies proved that aspirin treatment was associated with reduced operative morbidity and cardiac complications (6,7,12,13), with no increase in blood product use (14). Most importantly, aspirin use was proven to be safe before CABG compared to placebo, with no increased risk of bleeding or hemorrhagic complication. The presumed risk of bleeding associated with aspirin among patients undergoing cardiac surgery appears to be definitely confuted by Myles *et al.* (1).

Results from Myles *et al.* and other studies can also support other speculative hypotheses. As far as coronary surgery after recent acute coronary syndromes or coronary stent implantation is concerned, the adequate timing of the double antiplatelet therapy withdrawal is crucial for preventing post-operative bleeding, and generally aspirin treatment is continued while the other antiplatelet agent (e.g., clopidogrel) is replaced by LMWH. However, heparins seem not to provide a valuable protective effect against platelet aggregation, and might be associated with more adverse events and increased bleeding (10). Therefore, to reduce bleeding risk and provide an adequate platelet anti-aggregation, the concept of replacing the non-aspirin

antiplatelet agent with newer antiplatelet compounds such as tirofiban or other Glycoprotein IIb/IIIa receptor inhibitors (GPRI) is gradually entering into the show. These considerations could be translated to the elective scenario: it would be interesting to compare bleeding and complications after elective CABG in patients taking aspirin until surgery or after its replacement with GPRI 5 days before surgery. Despite the higher costs compared with aspirin, GPRI provide an adequate antiplatelet effect and due to their pharmacokinetic features platelet function becomes restored early after withdrawn. Therefore, a patient could be protected against preoperative thrombotic events without increased risk of intraoperative bleeding. Platelet functional evaluation would help heart team in assessing platelet function before surgery, in order to choose the most appropriate compound and infusion rate to minimize bleeding risk.

In conclusion, the management of this important topic remains debated; many other factors and patient-specific situations should be taken into account. Good quality evidences, such as the study from Myles and coworkers, are warranted to shed some lights on this highly relevant issue in cardiac surgery.

At present, the continuation of aspirin therapy before elective CABG is recommended by many US and European guidelines (15,16) considering that this practice has beneficial effects on coronary-graft flow, reduced the risk of graft thrombosis (11,17) and resulted in a similar risk of bleeding or death compared to placebo (1). Aspirin replacement with LMWH may result in increased postoperative bleeding and overall complications, and therefore this practice should be abandoned (10). Bridging strategy with newer antiplatelet agents are an intriguing alternative, but should be carefully evaluated for their cost-effectiveness.

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Footnote

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