

# Platelet Inhibition and Bleeding Risks in Patients Undergoing Non-Cardiac Surgery

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While there have been substantial advances in the use of anti-platelet therapies (APTs) in many conditions such as acute coronary syndrome and coronary interventions,<sup>1</sup> the appropriate management of APT for patients undergoing non-cardiac surgery continues to remain a topic of discussion. With as many as one-fifth of the patients requiring non-cardiac surgery within 1 year after coronary stent implantation,<sup>2</sup> weighing the risk of haemorrhagic complications in the peri-operative period against the possible ischaemic complications, especially stent thrombosis after recent coronary stenting, is a critical decision for every physician involved.

Our current guidelines generally do not recommend the use of aspirin peri-operatively.<sup>3</sup> The Perioperative Ischemic Evaluation 2 trial randomized over 10,000 patients undergoing non-cardiac surgery to aspirin or placebo before surgery. Rates of myocardial infarction and death were not reduced by use of aspirin 30 days after surgery, whereas major bleeding did increase.<sup>4</sup> However, considering only 23% of included patients had known coronary artery disease and all patients undergoing carotid endarterectomy were excluded in the trial, it is possible that patients with low peri-operative bleeding risk and high thromboembolic risk, might benefit from aspirin peri-operatively.<sup>3</sup> For patients on dual APT (DAPT) undergoing surgery, it is indeed recommended to perform surgery without discontinuation of aspirin or P2Y12 inhibition if surgery is performed within 1 month after bare-metal stent implantation and 3 months after drug-eluting stent implantation. If surgery is planned outside these timeframes, current guidelines uphold a universal approach of 5 days withdrawal for clopidogrel and ticagrelor, and 7 days for prasugrel prior to surgery and to continue aspirin.<sup>3,5</sup> For all patients who are at especially high risk for stent thrombosis, bridging strategies can be contemplated.<sup>3,5</sup>

As it is widely known that individual responses to clopidogrel and platelet function recovery after clopidogrel withdrawal highly vary,<sup>6,7</sup> determining the right timing for surgery might be more appropriate with platelet function

testing (PFT) that monitors the response of the patient to the withdrawal of clopidogrel exclusively.

In patients undergoing coronary revascularization surgery by coronary artery bypass grafting (CABG), platelet function monitoring is recommended in current guidelines as an option for timing of surgery instead of the standard withdrawal period of 5 days for clopidogrel.<sup>5,8</sup> Assessment of platelet function predicts peri-operative bleeding in patients undergoing cardiac surgery, as well as reduces blood transfusions and hence might decrease transfusion-related complications, although clinical trials in various settings do not report a beneficial effect on post-operative mortality and surgical re-exploration rates.<sup>9–12</sup> In a prospective, single-centre non-randomized study, pre-operative PFT by thrombelastography in order to determine the timing of CABG in patients treated with clopidogrel, was associated with no excess bleeding when compared to clopidogrel-naïve patients, and led to pre-operative waiting time reduction of 50% as compared to what is recommended in the current guidelines.<sup>13</sup> However, although PFT is endorsed as a useful tool to determine appropriate timing of cardiac surgery, more research in this field is urgently needed as there is still much uncertainty about the optimal tests and cut-off values for determining the timing of surgery.

In the previous issue of *Thrombosis and Haemostasis*, Mahla et al present the BIANCA study, a prospective study that examines the association between platelet reactivity to adenosine diphosphate (ADP) and bleeding complications in non-cardiac surgery.<sup>14</sup> In cardiac surgery, mechanisms of bleeding involve a complex interaction involving among others, hypothermia, excessive fibrinolysis, haemodilution from pump priming and, most importantly, platelet function defects due to cardiopulmonary bypass. While this effect might be absent in non-cardiac surgery, still the assessment of pre-operative platelet function may optimize the timing of non-cardiac surgery, and therewith minimize both bleeding and thrombotic complications, as Mahla et al suggest in their article.<sup>14</sup>

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Of the 197 patients included in this study, 84% underwent surgery within 48 hours after the last clopidogrel dose. Several platelet function tests were used to assess platelet reactivity pre-operatively, namely, light transmittance aggregometry (LTA), vasodilator stimulated phosphoprotein (VASP) assay, Multiplate Analyzer and Innovance PFA-200. Of these tests, the LTA-assessed platelet reactivity was independently associated with bleeding complications.

The short withdrawal period before surgery and non-adherence to current guidelines is remarkable in itself and probably worthy of further investigation, inasmuch as that the large majority (82% of all patients) underwent elective surgery.

Furthermore, the short withdrawal period ensures pre-operative variability in platelet inhibition, showing once again the variable recovery of platelet function and responsiveness to clopidogrel, as the authors stated. Unfortunately, this might have resulted in not being able to state conclusive correlations regarding Multiplate Analyzer and Innovance PFA-200 platelet inhibition testing and bleeding complications. General platelet reactivity even in the third tertile for Multiplate testing was well below the level of 'high platelet reactivity', and made it impossible to set a cut-off value for Innovance PFA-200 platelet inhibition closure time in order to reflect normal platelet reactivity.

However, being the first prospective study evaluating the relationship between platelet function and bleeding complications conducted in patients undergoing non-cardiac surgery, the BIANCA study gives us some well-needed direction that the 'one-size-fits-all' approach in patients with DAPT undergoing non-cardiac surgery might not be the best approach.

Furthermore, the concept of platelet function-guided timing of surgery needs deliberation. The test that will eventually be used in clinical practice, will ideally be easily (and quickly) applicable, have low inter- and intra-variability and will not be too costly. There are also multiple clinical risk scores of varying complexity that have been used to predict bleeding in various clinical settings,<sup>15,16</sup> but such clinical scores will usually have their predictive value improved by biomarkers, such as platelet function tests. Ultimately, more focus on simple assessments and modifiable bleeding risk factors has been advocated.<sup>17</sup> These requirements make deciding for the most suitable approach for platelet function-guided timing for surgery difficult.

An abundance of potential tests are available that could be used to monitor platelet function. Point of care platelet function tests differ in their assay principle, and results are almost impossible to compare. Thus, very little consensus exists on the optimal test on determining platelet function. The classical platelet function test is LTA. Notwithstanding, as Mahla et al indicate, the LTA needs extensive work and expertise and is difficult to reproduce due to lack of standardization. This makes it probably less suitable for the repeated testing that is required in platelet function-guided timing of surgery. Of the tests used in this study, the VASP is also time-consuming and needs experienced executors. The Innovance PFA-200 is easy to learn and semi-automatic, whereas the Multiplate needs some labwork. Another test

that might be considered to be used in platelet function-guided timing of surgery is the VerifyNow P2Y12 assay. The VerifyNow P2Y12 assay is a point-of-care test with results that are rapidly available, has good reproducibility and results of the assay have been shown to correlate well with the LTA.<sup>18</sup> Moreover, it is known that intraoperative platelet function testing in patients undergoing cardiac surgery may lead to costs savings, this effect being especially distinct in patients using ADP-receptor inhibitors.<sup>19</sup> Recent evidence appears to indicate that VerifyNow P2Y12 platelet function-guided timing of surgery in patients undergoing bypass surgery and/or valve replacement could also cause cost savings by reduced in-hospital waiting time and physician time management, outweighing the costs of the tests.<sup>20</sup>

Platelet function-guided timing of surgery in non-cardiac surgery patients on DAPT appears to be a promising method. Directing available resources from a 'one-size-fits-all' approach, which is still state of the art in both cardiac and non-cardiac surgery, to a more targeted approach, which is far more suitable for the individual patient, it might thereby be possible not only to limit cost-effectiveness of patients scheduled for surgery and after surgery, but, more importantly, also to curtail severe haemorrhagic and ischaemic complications for individual patients.

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