Platelet function testing to time surgery in patients on dual antiplatelet therapy?

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Summary
In patients pretreated with P₂Y₁₂ receptor inhibitors who need to undergo non-emergent cardiac or major non-cardiac surgery, current guidelines of the European Society of Cardiology recommend postponing surgery for at least five days after last intake of clopidogrel or ticagrelor, and for seven days after last intake of prasugrel, unless there is high risk of ischemic events. However, a fixed five to seven days preoperative waiting period may be challenged, in the presence of inter-individual variability in on-treatment platelet reactivity. Therefore, Society of Thoracic Surgeons guidelines suggest to base decisions about a surgical delay on platelet function although both, the optimal platelet function assay and a bleeding cutoff have not yet been defined by large scale multicenter trials. This review aims to provide an overview on current knowledge of P₂Y₁₂ receptor induced platelet inhibition and surgery related bleeding and the potential role of platelet function analysis to time surgery.

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Dual antiplatelet therapy (DAPT) with aspirin and a P₂Y₁₂ receptor blocker is a cornerstone to reduce platelet reactivity and to prevent ischaemic cardiovascular events in patients with acute coronary syndrome (ACS) and after percutaneous coronary intervention (PCI). Current guidelines recommend maintenance of DAPT for up to 12 months, unless contraindicated by excessive bleeding, followed by lifelong therapy with aspirin (21, 46).

- 10 to 15% of patients with ACS need urgent coronary artery bypass grafting (CABG) and
- 5% percent of patients need non-cardiac surgery during the first year after PCI (11, 22, 47).

While premature discontinuation of DAPT in this setting may result in stent thrombosis associated with up to 50% mortality, perioperative continuation of these drugs may increase surgery-related bleeding (21, 38, 45). Major bleeding and transfusion have been demonstrated to dose-dependently increase early and long-term morbidity and mortality both, after PCI, cardiac and non-cardiac surgery (9, 13, 20, 25, 30).

This review aims to provide an overview on current knowledge of P₂Y₁₂ receptor induced platelet inhibition and surgery related bleeding and the potential role of platelet function analysis to time surgery.

European cardiological guidelines

In patients pretreated with P₂Y₁₂ receptor inhibitors who need to undergo non-emergent cardiac or major non-cardiac surgery, current guidelines of the European
Because of their high negative predictive value, preoperative point-of-care testing to assess 2
2
2
For patients who require urgent operation while on dual antiplatelet therapy, delay of even a day
For patients on dual antiplatelet therapy, it is reasonable to make decisions about surgical delay
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CABG: coronary artery bypass grafting surgery
Tab. 1

A “sweet spot” to reduce the risk of ischaemia and bleeding?
The benefits and risks of current P2Y12 receptor blockers were recently compared in large clinical trials. Both, TRITON TIMI 38 (prasugrel versus clopidogrel in patients with ACS) and PLATO (ticagrelor versus clopidogrel in patients with ACS) demonstrated that newer, more potent P2Y12 inhibitors reduce the risk of thrombotic events at the cost of an increased bleeding risk (48, 51). Based on this cardiologic knowledge, it is tempting to speculate that during preoperative withdrawal of P2Y12 receptor blockers and subsequent gradual recovery of platelet function, a “therapeutic window” balancing the risk of bleeding and ischaemia may be present. Surgery within this “therapeutic window” may represent the safest approach regarding patient outcome.
In patients undergoing PCI the presence of such a “therapeutic window” was suggested for the first time by Sibbing et al. (43). Using the Multiplate® analyzer the authors demonstrated a remarkably low ~ 1% incidence of both 30-day ischaemia and bleeding in 2533 patients within the range of 189–467 AU × min after pretreatment with 600 mg clopidogrel for PCI (42, 43). Similarly, the presence of a “sweet spot” was proposed by Bonello et al. using the vaso dilator-stimulated phosphoprotein (VASP) assay in 301 patients who underwent successful PCI for ACS and received a 60 mg prasugrel loading dose. Importantly, a platelet reactivity index (% PRI) outside a range of 16 – 53.5 was associated with a 2.92-fold (95% CI: 1.37–62; p = 0.006) increased risk of thrombotic and bleeding events during 1-year follow up after adjustment for platelet count (6).
Whether the concept of a “therapeutic window” as suggested for the patient undergoing PCI can be transferred to the cardiac and non-cardiac surgical setting needs to be proven by large scale multi-center studies employing standardized bleeding definitions, strict transfusion triggers, and accounting for relevant covariables, known to affect bleeding.

Association between platelet inhibition and surgery-related bleeding?
The reported incidence of bleeding associated with non-cardiac surgery is 1–21% (24, 32, 35, 47) although large scale trials evaluating time of P2Y12 receptor inhibitor withdrawal and association to bleeding are currently lacking.
In cardiac surgery, four recent meta-analyses, including primarily non-randomized studies, demonstrated that, compared to control, exposure to a P2Y12 receptor inhibitor within 2 to 7 days preoperatively increased the relative risk of both mortality and reoperation for bleeding by 50 and 250%, respectively (2, 5, 29, 31). Two further retrospective studies suggested increased bleeding and transfusion in patients undergoing cardiac surgery within 24–48 hours after last clopidogrel intake (3, 23).
In addition, a subgroup analysis of the TRITON TIMI 38 trial revealed both an increased 12-hours chest tube drainage (ml mean ± SD 655 ± 580 versus 503 ± 378; p =

Tab. 1  Guideline based recommendations for preoperative platelet function monitoring

<table>
<thead>
<tr>
<th>guideline</th>
<th>class</th>
<th>level</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (21)</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>• In patients pre-treated with P2Y12 receptor inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischemic events should be considered.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• When it is considered appropriate to have a modest degree of P2Y12 inhibition it is reasonable to stop clopidogrel 5 days before surgery, or less, if a validated platelet function testing method shows a poor response to clopidogrel.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012 Update to the Society of Thoracic Surgeons Guideline on Use ofAntiplatelet Drugs in Patients having Cardiac and Noncardiac Operations (14)</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>
| • Monitoring platelet function  
  – Because of their high negative predictive value, preoperative point-of-care testing to assess bleeding risk may be useful in identifying patients with high residual platelet reactivity after usual doses of antiplatelet drugs, and who can undergo operation without elevated bleeding risk.  
  – Point-of-care testing to assess perioperative platelet function may be useful in limiting blood transfusion. |
| • Treatment options for patients on antiplatelet drugs who require urgent operations  
  – For patients who require urgent operation while on dual antiplatelet therapy, delay of even a day or two before operation is reasonable to decrease bleeding risk and minimize thrombotic risk in patients with acute coronary syndrome. |
| • For patients on dual antiplatelet therapy, it is reasonable to make decisions about surgical delay based on tests of platelet inhibition rather than arbitrary use of a specified period of delay. |

CABG: coronary artery bypass grafting surgery

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Tab. 2 Studies evaluating the association between measured platelet inhibition and surgery related bleeding

<table>
<thead>
<tr>
<th>study (ref.)</th>
<th>DAPT</th>
<th>type of surgery</th>
<th>platelet function test</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. (8)</td>
<td>prospective n = 90</td>
<td>clopidogrel ≤ 6 days preoperatively versus control</td>
<td>on-pump CABG</td>
<td>LTA part of an algorithm for treating bleeding</td>
</tr>
<tr>
<td>Mahla et al. (28)</td>
<td>prospective n = 180</td>
<td>clopidogrel versus clopidogrel naïve on background aspirin</td>
<td>on-pump CABG</td>
<td>TEG platelet mapping assay</td>
</tr>
<tr>
<td>Kwak et al. (26)</td>
<td>prospective n = 100</td>
<td>clopidogrel and aspirin up until the day before surgery versus 3 days before surgery</td>
<td>off-pump CABG</td>
<td>TEG platelet mapping assay</td>
</tr>
<tr>
<td>Ranucci et al. (37)</td>
<td>retrospective n = 87</td>
<td>clopidogrel or ticlopidine ≤ 7 days preoperatively</td>
<td>CABG and/or valves</td>
<td>ADP test, performed preoperatively</td>
</tr>
</tbody>
</table>

AUC: area under the curve; CABG: coronary artery bypass grafting; CI: confidence interval; LTA: light transmittance aggregometry; MA: maximum amplification; TEG: thromboelastography

0.05) and increased platelet transfusions (units; mean 0.78 vs. 0.39, p = 0.047; donor exposure 18% vs. 9.8%, p = 0.033) in patients undergoing isolated CABG when prasugrel-pretreatment was compared with clopidogrel. When the interval from last study drug intake (< 5, 6–7 or > 7 days) was compared, however, no difference in blood loss or transfusion requirements between prasugrel and clopidogrel-treated patients was demonstrated. Moreover, although a greater percentage of patients who received prasugrel underwent re-exploration for bleeding, 71% of these patients had a surgical bleeding site identified (16, 44).

In contrast, a subgroup analysis of the PLATO trial revealed a highly variable study drug intake (< 5, 6–7 or > 7 days) was compared, however, no difference in blood loss or transfusion requirements between prasugrel and clopidogrel-treated patients was demonstrated. Moreover, although a greater percentage of patients who received prasugrel underwent re-exploration for bleeding, 71% of these patients had a surgical bleeding site identified (16, 44).

To demonstrate the complexity of the issue of P2Y12 inhibitor withdrawal before surgery, both prasugrel and ticagrelor maintained their beneficial effects on 1-year mortality (6% and 5% reduction as compared to clopidogrel), despite, at least prasugrel, concomitantly increasing perioperative bleeding (16, 22, 44).

### American surgical guidelines

In patients pretreated with P2Y12 receptor inhibitors who need to undergo cardiovascular operations, current guidelines of the Society of Thoracic Surgeons (STS) recommend postponing surgery for a few days to reduce bleeding and transfusion (Table 1). The interval between discontinuation of antiplatelet drugs and operation is uncertain and depends on drug responsiveness and thrombotic risk (class I). For ACS patients needing urgent operations, delay of even one to two days is reasonable to decrease bleeding risk and minimize thrombotic risk (class IIa). Decisions about a surgical delay should rather be based on platelet function assays than on arbitrary use of a specified delay (class III) (14). The optimal platelet function assay and a bleeding cutoff are, however, not further specified in these guidelines. “Validated, absolute levels of "safe" residual platelet inhibition have not yet been established but may need to be as low as 20–40%” (14).

To address the issue of the optimal platelet function assay to identify clopidogrel non-responders after PCI, Cuisset et al. (10) recently performed a head-to-head comparison of different platelet function assays. ADP-induced light transmittance aggregometry (LTA), the VASP’ assay and the Verify Now assay poorly correlated in this trial. Therefore, when establishing bleeding cutoffs, the type of platelet function assay also has to be taken into consideration.

### Association between measured platelet inhibition and surgery-related bleeding?

Thrombelastography (TEG) is an established tool to assess the strength of the platelet-fibrin clot strength and TEG-based
transfusion algorithms reduce transfusion requirements in patients undergoing CABG and complex cardiac surgery (33, 41, 49).

An association between LTA-assessed platelet inhibition and on-pump CABG-related bleeding was initially demonstrated by Chen et al. (8). Unadjusted for potential confounders, an ADP-induced aggregation less than 40% predicted 92% of severe coagulopathies, requiring multiple transfusions. In 100 patients with recent clopidogrel exposure undergoing off-pump CABG, using the TEG Platelet Mapping® assay, Kwak et al. (26) demonstrated an association between clopidogrel responsiveness and bleeding, irrespective of discontinuation time. Patients in the highest tertile of platelet inhibitory response (>76.5% inhibition) had significantly higher chest tube output and transfusion requirements as compared to patients in the other tertiles. Importantly, the third tertile of platelet inhibitory response was associated with an adjusted 11.44-fold (95% CI: 2.77–47.30) relative increased risk of transfusion.

Using the Multiplate analyser, ADP-induced platelet aggregation was independently associated with major bleeding with a cutoff of 31 U (AUC [95% CI] = 0.71[0.59–0.83]) in patients on P2Y12 receptor inhibitors until at least one week before on-pump cardiac surgery, yielding a negative predictive value of 92% (37). As 10 of the 14 patients sustaining major bleeding were below the cutoff of 31 U, an impact of residual platelet inhibition on surgery-related bleeding was suggested. Due to the inherent different bleeding risks of CABG and combined procedures and a therapeutic algorithm treating microvascular bleeding based on preoperative aggregation values, these results, however, may be a matter of debate. For example, the predictive cutoff for surgery-related bleeding of 31 U (comparing to 310 AU × min) as suggested in the former study (37) was substantially higher than a suggested cutoff of 188 AU × min for procedure-related bleeding in patients undergoing PCI (42, 43).

The TARGET CABG study (Platelet Function Measurement Based Strategy to Reduce Bleeding and Waiting Time In Clopidogrel-Treated Patients Undergoing Coronary Artery Bypass Graft Surgery) (28) evaluated the feasibility and safety of an individualized, TEG Platelet Mapping® assay-based, preoperative waiting period in on-pump CABG patients. After adjustment for confounders, clopidogrel-treated patients had similar bleeding as compared to clopidogrel-naïve patients on background aspirin (24-hours chest tube drainage median: 703 ml vs. 753 ml, p = 0.496; total amount of red blood cell transfusions mean 1.80 vs. 2.08, p = 0.540). Surgery was scheduled within

- one day in patients with a MAADP > 50 mm,
- three to five days in those with a MAADP of 35–50 mm, and
- after five days in those with a MAADP < 35 mm.

In the absence of a validated bleeding cutoff this expert opinion-based cutoff was chosen based on prior evidence of an association between a MAADP >47 mm and occurrence of ischemic events in patients undergoing PCI (19). Moreover, this individualized TEG Platelet Mapping® assay-based approach reduced the preoperative waiting time by about 50% as compared to valid recommendations at that time (21) (Tab. 2).

While preliminary data suggest an association between measured platelet inhibition and bleeding, the bleeding cutoff remains elusive. Based on TARGET data, it is tempting to speculate that in patients requiring on-pump CABG during DAPT, “high on-treatment platelet reactivity” (Tab. 3) reduces bleeding. In patients undergoing off-pump CABG even lower platelet reactivity may guarantee adequate surgical hemostasis as suggested by Kwak et al. (26). However, large scale well controlled studies employing standardized bleeding definitions and perioperative management including strict transfusion triggers and are needed to establish a bleeding cutoff.

In patients undergoing non-cardiac surgery during DAPT the “Platelet Inhibition and Bleeding in Patients undergoing Non-Cardiac Surgery (The BIANCA trial) is currently evaluating the association between measured platelet inhibition and surgery-related bleeding using different platelet function assays (ClinicalTrials. Gov Identifier: NCT01606865).

**Tab. 3** Consensus cutoffs for “high on-treatment platelet reactivity”; adapted from (7)

<table>
<thead>
<tr>
<th>platelet function assay</th>
<th>consensus-cutoff for HPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light transmittance aggregometry (5 µm ADP)</td>
<td>&gt;46% aggregation</td>
</tr>
<tr>
<td>Multiplate analyzer</td>
<td>≥ 468 AU × min</td>
</tr>
<tr>
<td>Verify Now assay</td>
<td>235 PRU</td>
</tr>
<tr>
<td>VASP assay</td>
<td>&gt;50% PRI</td>
</tr>
</tbody>
</table>

HPR: high on-treatment platelet reactivity; ADP: adenosine-diphosphate; AU: aggregation units; PRU: platelet reactivity units; VASP: vasodilator stimulated phosphorylation; PRI: platelet reactivity index

**Association between perioperative DAPT-withdrawal and major adverse cardiac events?**

While a relation between platelet inhibition and bleeding is obvious, the ischaemic risk associated with preoperative P2Y12 drug withdrawal is uncertain. Two recent meta-analyses, including mostly non-randomized studies in patients undergoing cardiac surgery demonstrated similar rates of postoperative myocardial infarction in patients exposed to a P2Y12 receptor inhibitor within 2–7 days preoperatively as compared to patients not exposed to a P2Y12 receptor inhibitor (2, 31).

Current ACC/AHA guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery recommend postponing elective surgery in patients after PCI until completion of the full course of DAPT and to perform surgery without interrupting aspirin therapy, whenever feasible (15). The incidence of MACEs after early discontinuation of the P2Y12 inhibitor is 5–20%, and mainly depends on time interval between PCI and surgery, the type of stent used (bare metal stent [BMS] vs. drug eluting stent [DES]) and on whether PCI was performed because of ACS or chronic coronary artery disease (4, 38, 50). A recent registry demonstrated a 2.5 to 12-fold relative increased risk of 30-day MACEs in 8116 patients undergoing non-cardiac surgery within 45 days.
days after BMS and DES implantation for PCI, respectively, as compared to patients who underwent PCI two years preoperatively (50). Although it is tempting to speculate that ischaemic events, early after PCI, are triggered by a high platelet reactivity due to discontinuation of DAPT, perioperative catecholamine surges and stress-induced hypercoagulability, an association between pre- or postoperative platelet function and MACEs has not yet been demonstrated (27). To deal with the issue of high ischemic risk in patients requiring urgent surgery during DAPT, perioperative bridging with tirofiban has been suggested as an option to reduce both bleeding and ischaemia (39).

**Short acting P_{2}Y_{12} receptor blocker inhibitors**

Cangrelor and elinogrel are reversible, short acting, potent, investigational P_{2}Y_{12} receptor inhibitors available as intravenous and intravenous and oral formulation, respectively (1, 17). The BRIDGE (Bridging antiplatelet therapy with cangrelor and patients undergoing cardiac surgery) was a randomized controlled multicenter study evaluating safety and efficacy of cangrelor for bridging in 210 patients pre-treated with a P_{2}Y_{12} receptor inhibitor before cardiac surgery (1). P_{2}Y_{12} receptor inhibitors were stopped at least 48 hours preoperatively. Compared to placebo, cangrelor treated patients consistently achieved and maintained substantial platelet inhibition, which rapidly recovered after discontinuation of cangrelor infusion. Although, there was no difference in excessive CABG related bleeding (11.8% vs 10.4%, p=0.763), or any other surgery-related bleeding between cangrelor and placebo the BRIDGE-study was not powered to detect a difference, if any (1).

**Potential covariates with effect on surgery-related bleeding**

In a recent randomized controlled multicenter trial, tranexamic acid significantly reduced mean total volume of chest tube drainage, volume of transfused red blood cells (RBC) and RBC exposure as compared to placebo by 278 ml, 2.58 units and 19%, respectively in patients undergoing isolated on-pump CABG within 7 days after last clopidogrel exposure (40). In addition, thrombelastometry-guided first-line administration of fibrinogen in patients undergoing major aortic surgery using cardiopulmonary bypass, but not exposed to antiplatelet drugs, reduced transfusion of allogenic blood components (units median 2 vs. 13 U, p < 0.001) and total donor exposure (55% vs. 0%; p < 0.001) as compared to placebo (36). Whether this benefit also is verifiable in patients with recent DAPT, however, remains elusive (12).

**Conclusion**

- Preoperative platelet function assessment may be helpful for timing surgery particularly in patients with high risk of myocardial ischaemia.
- In the absence of large scale trials defining the best assay and assay-specific bleeding cutoffs, a universal recommendation currently is not possible. Similarly, platelet function testing to reduce major adverse ischaemic events cannot be supported due to the lack of data.
- In patients at high risk for ischaemia, bridging with tirofiban might be an option to safely reduce bleeding and ischaemia.
- Short acting P2Y12 receptor inhibitors may be a future alternative for perioperative bridging.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**


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