Peri-operative platelet function testing: The potential for reducing ischaemic and bleeding risks

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Summary
The pivotal role of platelet activation and reactivity during atherothrombotic event occurrence associated with acute coronary syndromes (ACS) or percutaneous coronary interventions (PCI) is well established. Numerous translational research studies have established a threshold level of platelet reactivity during dual antiplatelet therapy above which a higher risk for ischaemic event occurrence has been observed. The clinical validity of these threshold values in reducing ischaemic event occurrence with modified P2Y₁₂ receptor therapy is currently under investigation in large-scale clinical trials. The association between on-treatment platelet reactivity measured by an ex vivo assay and the occurrence of bleeding events is less established. Currently, there is limited evidence of an association between platelet inhibition and coronary artery bypass grafting (CABG)-related bleeding in patients on clopidogrel therapy indicating that preoperative platelet function monitoring may guide both the timing of elective CABG and the administration of blood products in patients needing surgery. However, in the absence of a large-scale prospective clinical trial, routine platelet function monitoring and modification of timing of surgery based on platelet function monitoring are currently not recommended.

Keywords
Atherothrombosis, antiplatelet drugs, platelet pharmacology

Role of platelet function testing during dual antiplatelet therapy
The pivotal role of platelet activation and reactivity during normal haemostasis and atherothrombotic event occurrence associated with acute coronary syndromes (ACS) or percutaneous coronary interventions (PCI) is well established. Thromboxane A₂ and adenosine diphosphate (ADP), the two most important agonists released from activated platelets, are responsible for the amplified platelet activation and aggregation and generation of a stable thrombus at the site of vascular injury. Therefore, pharmacologic management of patients with atherothrombotic disease mainly consists of aspirin and clopidogrel to inhibit thromboxane A₂ generation and the ADP-P₂Y₁₂ interaction, respectively (1, 2). Despite its well established anti-ischaemic benefits, clopidogrel therapy is associated with numerous limitations – a) resistance and response variability, b) high on-treatment platelet reactivity associated with increased risk for ischaemic event occurrence, and c) influences of genotype and concomitant pharmacotherapy on pharmacodynamic effects (3, 4). These limitations provide a strong rationale for the personalised antiplatelet therapy concept based on objective measurement of platelet function in high-risk patients. Numerous translational research studies have established a threshold level of platelet reactivity above which a higher risk for ischaemic event occurrence has been observed. The clinical validity of these threshold values in reducing ischaemic event occurrence with modified P2Y₁₂ receptor therapy is currently under investigation in large-scale clinical trials. The association between on-treatment platelet reactivity measured by an ex vivo assay and the occurrence of bleeding events is less established (5, 6). In addition to the limitations mentioned, irreversible binding, and slow offset of pharmacodynamic effect associated with clopidogrel therapy are important concerns in patients requiring urgent surgery (3, 4).

Current management of patients undergoing surgery who are on dual antiplatelet therapy
Current practice guidelines for antiplatelet therapy advocate up to 12 months of uninterruptible dual antiplatelet therapy in patients treated with coronary artery stenting (1, 2). Currently, 10–15% of patients presenting with ACS have to undergo aorto-coronary artery bypass grafting (CABG) and 5% to 25% of patients have to undergo non-cardiac surgery during the first five years after PCI (7, 8). While preoperative discontinuation of antiplatelet therapy is associated with ~20% incidence of ischaemic events, continuation puts patients at ~35% incidence of bleeding (9–11). Likewise,
bleeding and transfusion of red blood cells have been associated with increased risk of infection, myocardial infarction and mortality (13–15). Notably, studies in patients undergoing cardiac surgery demonstrated a specific dose-response relationship, with each unit of transfused red blood cells increasing the relative risk of 30-day complications and mortality by 20% (14, 16). The treatment options recommended by current guidelines are primarily based on subgroup analysis of large-scale clinical trials demonstrating a link between bleeding and the duration of P2Y$_{12}$ receptor blocker therapy before cardiac surgery (17).

Based on the results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) and the Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) current guidelines for cardiac surgery recommend withholding clopidogrel for at least five days and prasugrel at least seven days before scheduled CABG in order to limit blood loss and transfusion (class I recommendation, level of evidence C) (17–19). In TRITON TIMI 38, prasugrel was associated with a significant four-fold increased relative risk (absolute difference: 10.2%) of CABG related bleeding as compared to clopidogrel (19). Furthermore, the observation that a short time interval between clopidogrel withdrawal and surgery precipitates the risk of bleeding, suggests the association between insufficient platelet function recovery and bleeding (9, 10, 21–23). Ticagrelor is a reversibly binding P2Y$_{12}$ receptor inhibitor associated with faster onset, superior platelet inhibition and comparatively faster offset of pharmacodynamic effects compared to clopidogrel therapy (24). In a subgroup analysis of patients who underwent CABG, ticagrelor therapy was associated with significantly reduced primary efficacy endpoint (p=0.029) and similar rate of CABG-related major bleeding (81.3%) vs. 80.1%, hazard ratio [HR]=1.01, 95% confidence interval [CI]=0.90–1.15, p=0.84) (25).

### Table 1: Relation of platelet function measurement and perioperative bleeding.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Platelet function assay</th>
<th>Bleeding outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibbing et al. (30)</td>
<td>PCI patients pretreated with 600 mg clopidogrel (n=2,533)</td>
<td>ADP-induced PA with MEA</td>
<td>&lt; 188 AU min is an independent predictor in-hospital of major bleeding (OR 3.5, 95% CI 1.6–7.3; P = 0.001)</td>
</tr>
<tr>
<td>Cuisset et al. (31)</td>
<td>NSTE-ACS (n=597)</td>
<td>ADP-induced PA</td>
<td>&lt;40% post-treatment PA (hyper-responders, first quartile) had higher risk of 30day TIMI major and minor bleeding</td>
</tr>
<tr>
<td>Gurbel et al. (32)</td>
<td>PCI patients treated with dual antiplatelet therapy (n=225)</td>
<td>MA-ADP platelet mapping assay</td>
<td>ROC curve and quartile analyses suggest MA (ADP) ≤31mm as a predictive value for post-PCI bleeding</td>
</tr>
<tr>
<td>Chen et al. (36)</td>
<td>Patients treated with clopidogrel within 6 days of CABG (n=45)</td>
<td>ADP-induced PA</td>
<td>&lt;40% pre-heparin ADP-induced platelet aggregation predicted 92% severe bleeding requiring multiple transfusions</td>
</tr>
<tr>
<td>Mahla et al. (37)</td>
<td>CABG patients treated with and without clopidogrel (n=192)</td>
<td>MA-ADP platelet mapping assay</td>
<td>Stratifying clopidogrel treated patients based on preoperative assessment of clopidogrel response results in similar peri-operative bleeding as compared to clopidogrel naïve patients</td>
</tr>
<tr>
<td>Reece et al. (39)</td>
<td>CABG patients (n=44)</td>
<td>ADP- and TRAP-induced PA by LTA and MEA</td>
<td>PA measured by MEA was reduced in transfused patients compared to patients not transfused</td>
</tr>
<tr>
<td>Kwak et al. (40)</td>
<td>CABG patients (n=100)</td>
<td>MA-ADP platelet mapping assay</td>
<td>70% platelet inhibition was associated with post-operative transfusion requirement in ROC analysis (AUC=0.77, 95%CI=0.67–0.87; p&lt;0.001)</td>
</tr>
<tr>
<td>Ranucci et al. (41)</td>
<td>On-pump CABG patients treated with clopidogrel (n=87)</td>
<td>ADP-and TRAP-induced PA MEA</td>
<td>ADP-induced PA &gt;31U was associated with postoperative bleeding in ROC curve analysis (AUC=0.71, 95%CI=0.59–0.83;p=0.013)</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary interventions; ADP, adenosine diphosphate; PA, platelet aggregation; MEA, multiple electrode analyser; AU, arbitrary units; CI, confidence interval; NSTE-ACS, non-ST segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; CABG, coronary artery bypass surgery; ROC, receiver operating characteristic curve; AUC, area under the curve.
Current guidelines for patients undergoing non-cardiac surgery recommend postponing surgery until six weeks to optimally three months after bare-metal stent (BMS) PCI and until one year after drug-eluting stent (DES) PCI and to perform surgery without discontinuing aspirin whenever possible (26, 27). These recommendations are based on the reported inverse relation between the interval from PCI and major adverse cardiac events (10, 11, 28, 29). The association between bleeding and time between clopidogrel withdrawal and non-cardiac surgery remains elusive.

Rationale for perioperative platelet function testing

The major rationale for discontinuation of thienopyridine treatment recommended by the guidelines was to allow platelet function recovery thereby avoiding excessive perioperative bleeding. The current guidelines are based on a “one size fits all strategy” of clopidogrel therapy and there is currently little evidence for a tailored approach to the patient at high perioperative risk for ischaemia and bleeding (3, 4). However, clopidogrel therapy is associated with substantial response variability and in a significant proportion of patients (~30%) a negligible or no antiplatelet effect has been demonstrated. Moreover, the offset of the antiplatelet effect of clopidogrel is also variable (3, 4). The above factors strongly suggest that objective measurement of the antiplatelet effect of clopidogrel before CABG may obviate the need for the recommended five days waiting period in a substantial percentage of patients.

Preliminary evidence suggesting an association of preoperative platelet function testing and bleeding

An increased responsiveness to clopidogrel measured by ADP-induced platelet aggregation using multiple electrode aggregometry (MEA) was associated with a 3.5 increased risk of procedure related major bleeding in patients (n=2,533) undergoing PCI (30). Clopidogrel hyper responsivity as indicated by the first quartile of low post-treatment ADP-induced platelet reactivity (<40%) was shown to be associated with higher risk of non-CABG-related bleeding (TIMI major and minor) in 597 patients presenting with non-St segment elevation myocardial infarction-ACS (31). In a recent study involving 225 patients who were treated with dual antiplatelet therapy over three years, ADP-induced platelet fibrin clot strength (MA) >47 mm had the best predictive value of long-term ischaemic events compared with light transmittance aggregometry (LTA) (p < 0.0001). Moreover, receiver operating characteristic curve and quartile analyses suggest MA (ADP) ≤31 mm as a predictive value for post-PCI bleeding (32).

Thrombelastography (TEG) is an established tool to assess the strength of the platelet fibrin clot strength. TEG-based transfusion algorithms have been demonstrated to reduce transfusion requirements in patients undergoing CABG (33, 34). Moreover, the addition of TEG measurements (maximum thrombin-induced platelet-fibrin clot strength) to an existing risk-prediction model significantly improved the risk stratification for excessive blood loss in patients undergoing on-pump cardiac surgery (35). Chen et al. were the first to demonstrate an association between platelet aggregation measured by LTA and CABG-related bleeding in patients on clopidogrel undergoing first time on-pump CABG. Unadjusted for potential pre- and intra-operative confounders, a pre-heparin ADP-induced aggregation less than 40% corresponding to a 60% platelet inhibition predicted 92% of severe coagulopathies, needing multiple transfusions (36).

Recently, the non-randomised prospective Time BAsed StReased Gy to REduce Clopidogrel AssociaTed Bleeding During CABG (TARGET CABG) study, demonstrated that stratifying clopidogrel-treated patients based on preoperative assessment of clopidogrel response results in similar peri-operative bleeding as compared to clopidogrel naïve patients undergoing elective first time on-pump CABG (37). In this study pre-operative clopidogrel response was measured by TEG with Platelet Mapping. Surgery was scheduled with no delay in those with a maximum amplitude (MA< ADP >50 mm, within 3–5 days in those with an MA ADP 35–50 mm, and after five days in those with an MA ADP <35 mm) (37). The rationale for scheduling surgery with no delay in patients with an MA ADP > 50 mm was based on the fact that an MA ADP > 47 mm has been associated with short- and long-term ischaemic events after PCI (32). The rationale for the delayed groups was based on the platelet turnover of 10 days. This study underlines previous findings and demonstrates that CABG induces a cyclic pattern of platelet reactivity with a post-pump decrease and a rebound at 24 hours post-CABG in the presence of thrombocytopenia (38). This may provide a potential mechanism for postoperative thrombotic events. Recently, Reece et al. investigated if the Multiplate analyser-based ADP-and thrombin receptor agonist peptide-induced platelet aggregation predicted bleeding during scheduled on-pump CABG (38). Notably, during chest closure patients being transfused exhibited significantly less platelet aggregation as compared to patients not transfused (ADP-induced aggregation 18 U vs. 29 U, p=0.01) (39).

Finally TARGET CABG suggested that delays in surgery may be obviated by preoperatively measuring platelet function and timing surgery appropriately thereby reducing hospital costs. These preliminary data are corroborated by Kwak et al. (40) who demonstrated an association between clopidogrel responsiveness and bleeding in patients with recent clopidogrel exposure undergoing off-pump CABG, irrespective of discontinuation date. Notably, patients in the highest tertile of platelet inhibitory response (> 76.5% inhibition) had a higher chest tube output and higher 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 relative increase risk of allogenic blood products (40).

Similarly, Rannucci et al. demonstrated that ADP-induced platelet aggregation measured by MEA in clopidogrel-treated patients

Thrombosis and Haemostasis 106.2/2011

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undergoing on-pump cardiac surgery was independently associated with excessive bleeding with a cut-off of 31 U yielding an area under the curve of 0.71 and a negative predictive value of 92% (41). Ten of the 14 patients sustaining excessive surgery-related bleeding were below this cut-off, substantiating the association between platelet inhibition and bleeding. However, data may be biased due to the inherent different bleeding risks of CABG and combined procedures and a therapeutic algorithm treating microvascular bleeding based on preoperative aggregation values. Interestingly, the predictive cut-off for surgery-related bleeding of 31 U (equal to 310 AU x min) was substantially higher than the recently reported cut-off by Sibbing et al. for procedure-related bleeding in patients undergoing PCI (188 AU x min) (30).

Conclusions

Currently, there is limited evidence of an association between platelet inhibition and CABG-related bleeding in patients on clopidogrel therapy indicating that preoperative platelet function monitoring may guide both the timing of elective CABG and the administration of blood products in patients needing surgery. However, a safe therapeutic window preventing both perioperative ischaemia and bleeding remains unclear. In the absence of a large-scale prospective clinical trial, routine platelet function monitoring and modification of timing of surgery based on platelet function monitoring are currently not recommended (4, 42). Identification of pre-existing bleeding disorders utilising laboratory analysis should also be considered before surgery in patients treated with dual antiplatelet therapy to minimise the risk of bleeding in patients on dual antiplatelet therapy undergoing surgery.

Conflict of interest

Dr. Gurbel has received honoraria from Accumenetics and Haemonetics.

References


37. Mahla E, et al. Time-based strategy to reduce clopidogrel associated bleeding during CABG. Results from the TARGET CABG study. Presented at Clinical Science: Special reports, American College of Cardiology Meeting 2010.


