Why have studies of tailored anti-platelet therapy failed so far?

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**Summary**

Published data linking clopidogrel non-responsiveness to adverse ischaemic events lead to the suggestion that the magnitude of platelet inhibition by clopidogrel can be monitored and individually adjusted. This has been tested in randomised clinical trials (ARCTIC, GRAVITAS and TRIGGER-PCI), but despite reducing platelet reactivity, a strategy of therapy adjustment based on platelet function monitoring did not reduce the incidence of cardiac ischaemic events. Several critical issues regarding the design of these trials, which might in part have led to negative results, are discussed in this article.

**Introduction**

A growing body of evidence underlines a considerable concern surrounding the one-size-fits-all strategy with use of clopidogrel. The majority of published data linked high on treatment platelet reactivity (HTPR) to adverse ischaemic events (1-3), which led to the suggestion that the magnitude of platelet inhibition by clopidogrel can be monitored and individually adjusted. Some studies have demonstrated that the HTPR in patients on 75 mg clopidogrel can be overcome with higher loading or maintenance doses of clopidogrel, or by switching to prasugrel or ticagrelor (4-8). Whether clinical outcome can be improved with individualised antiplatelet therapy has been tested in clinical trials (Table 1).

Although tailored therapy based on platelet function monitoring reduced platelet reactivity in the three largest randomised trials (ARCTIC, GRAVITAS and TRIGGER-PCI), no improvement in clinical outcome was achieved by this strategy (9-11). Considering the potential clinical implications of these attractive studies, we address issues related to the study design.

**Treatment strategy**

In the open-label ARCTIC trial 2,440 patients were randomised to bedside platelet function monitoring versus no monitoring during 12 months follow-up (9). In the monitoring arm, antiplatelet therapy was intensified in poor responders by either an additional bolus plus increasing the maintenance dose of clopidogrel, by switching to prasugrel, by increasing the dose of aspirin, or by additional treatment with glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention (PCI) (9). However, only 3.3% of patients were switched to prasugrel whereas 80.2% received increased doses of clopidogrel during the procedure in the ARCTIC trial. A similar treatment strategy of single re-loading and doubling the maintenance dose of clopidogrel (600 mg initial dose, 150 mg daily thereafter) versus standard-dose clopidogrel (no additional loading dose, 75 mg daily) was also not efficacious in 2,200 patients with HTPR in the double-blind GRAVITAS trial during six months (10). A possible explanation for this negative finding of the GRAVITAS trial might be the fact that 40% of patients in the guided group remained low- or non-responders despite high dose of clopidogrel. Therefore, it is not surprising that this inadequate personalised therapy failed to show a significant benefit. These non-responders are often characterised by their inadequate metabolism of the prodrug clopidogrel into the active metabolite (2, 12): whereas clopidogrel maintenance doses of ≥225 mg in CYP2C19*2 heterozygotes (20–25% of patients) are necessary to achieve a sufficient level of platelet inhibition, doses of ≥300 mg daily are insufficient in CYP2C19*2 homozygotes (2–5% of patients) (13). Noteworthy, a switch from clopidogrel to prasugrel drastically reduced HTPR (14) and improved clinical outcome in clopidogrel non-responders in the MADONNA study (15). The TRIGGER-PCI trial, which compared prasugrel versus clopidogrel in patients with HTPR during six month follow-up, has been stopped by the steering committee prematurely after randomisation of 423 patients (of the planned 2,150) because an interim analysis indicated a lower than expected incidence of the primary endpoint consisting of the composite of ischaemic events (11).
Study endpoints

Whereas the primary endpoint in the TRIGGER-PCI trial consisted of myocardial infarction (MI) and cardiovascular death, in the GRAVITAS trial the primary endpoint was a composite of MI, cardiovascular death or stent thrombosis. Interestingly, in the ARCTIC trial the primary efficacy endpoint was even broader and consisted of the composite of death from cardiovascular causes, MI, stent thrombosis, stroke, or urgent revascularisation (9-11). Noteworthy, the primary endpoint in the ARTIC trial was mainly based on the incidence of peri-procedural MI. Authors defined periprocedural MI as a documented rise in cardiac biomarkers (cardiac troponins or CK-MB) measured 6 hours (h) after PCI higher than three-fold the upper reference limit. Indeed, the primary endpoint (34.6%) was driven by the occurrence of MI (30.3%), and the visual inspection of the survival analyses confirms that the peri-procedural MI was the major driver of the primary endpoint (as suggested by the vast majority of events occurring immediately after inclusion). Nevertheless, it is a crucial point to note that peri-procedural myocardial injury (characterised by a rise of cardiac biomarkers without additional characteristics of MI) is mainly due to balloon inflation, coronary dissection, occlusion of artery, no-reflow or embolisation of intracoronary thrombus or atherosclerotic plaque (16). As peri-procedural myocardial injury is unlikely preventable by use of intensified antiplatelet therapy (16), use of such a broad definition of MI might not be appropriate to test the given hypothesis and might therefore in part explain the negative results. Furthermore, in contrast to the ARCTIC definition of peri-procedural MI, the universal definition of periprocedural MI (type 4a) suggests the following diagnostic criteria: in patients undergoing PCI with normal baseline troponin, elevations of troponin five-fold the upper reference limit occurring

Table 1: Studies investigating the impact of personalized antiplatelet treatment on clinical outcome.

<table>
<thead>
<tr>
<th>Study author / acronym</th>
<th>Population</th>
<th>n</th>
<th>Follow-up</th>
<th>Method</th>
<th>Study type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAVITAS (10)</td>
<td>PCI for CAD or NSTE-ACS</td>
<td>2,214</td>
<td>6 months</td>
<td>VerifyNow</td>
<td>CRT: 300/75 mg clopidogrel vs. 600/75 mg clopidogrel in non-responders</td>
<td>The use of high-dose clopidogrel compared with standard-dose clopidogrel did not reduce the incidence of ischaemic events and did not increase the incidence of bleeding.</td>
</tr>
<tr>
<td>TRIGGER-PCI (11)</td>
<td>Elective PCI</td>
<td>423</td>
<td>6 months</td>
<td>VerifyNow</td>
<td>CRT: prasugrel (loading of 60 mg and maintenance 10 mg) vs clopidogrel (maintenance 75 mg) in non-responders</td>
<td>Given the low rate of adverse ischaemic events after PCI in stable CAD, the clinical utility of this strategy could not be demonstrated.</td>
</tr>
<tr>
<td>Valgimigli et al. (20)</td>
<td>Elective PCI</td>
<td>263</td>
<td>in hospital</td>
<td>VerifyNow</td>
<td>CRT: tirofiban vs placebo in non-responders</td>
<td>Intensified platelet inhibition with tirofiban lowered the incidence of myocardial infarction after elective coronary intervention.</td>
</tr>
<tr>
<td>ARCTIC (9)</td>
<td>PCI with DES</td>
<td>2,440</td>
<td>1 year</td>
<td>VerifyNow</td>
<td>CRT: : guided: clopidogrel (600 mg reloading and 75 mg or 150 mg maintenance) or prasugrel (60 mg loading and 10 mg maintenance) or GP IIb/IIIa inhibitors vs non-guided: clopidogrel (maintenance 75 mg) in non-responders</td>
<td>No improvement in clinical outcomes was achieved with platelet function monitoring and treatment adjustment as compared with standard antiplatelet therapy without monitoring.</td>
</tr>
<tr>
<td>Bonello et al. (8)</td>
<td>PCI</td>
<td>162</td>
<td>1 month</td>
<td>VASP assay</td>
<td>CRT: guided (reloading with clopidogrel 600 mg) vs non-guided group</td>
<td>Adjusting clopidogrel loading dose according to platelet monitoring improved clinical outcome.</td>
</tr>
<tr>
<td>Bonello et al. (7)</td>
<td>PCI</td>
<td>429</td>
<td>1 month</td>
<td>VASP assay</td>
<td>CRT: guided (reloading with clopidogrel 600 mg) vs non-guided group</td>
<td>Tailored clopidogrel loading doses according to platelet reactivity monitoring decreased the rate of early stent thrombosis without increasing bleeding events.</td>
</tr>
<tr>
<td>Cuisset et al. (21)</td>
<td>Elective PCI</td>
<td>149</td>
<td>1 month</td>
<td>LTA</td>
<td>CRT: GP IIb/IIIa antagonists vs control in non-responders</td>
<td>Tailored antiplatelet therapy with GP IIb/IIIa antagonist for clopidogrel nonresponders during elective PCI improved outcome.</td>
</tr>
<tr>
<td>MADONNA (15)</td>
<td>PCI</td>
<td>798</td>
<td>1 month</td>
<td>MEA</td>
<td>Non-randomised, controlled: non-guided vs guided group (up to 4 loadings with 600 mg clopidogrel or 1 loading with prasugrel in non-responders)</td>
<td>Personalized antiplatelet treatment according to the platelet function testing resulted in an improved efficacy with an equal safety compared to the standard treatment.</td>
</tr>
</tbody>
</table>

ACS=acute coronary syndrome, CRT=controlled randomised trial, DM=diabetes mellitus, LTA=light transmission aggregometry, MEA=multiple electrode aggregometry, NSTE-ACS=non ST elevation acute coronary syndrome, PCI=percutaneous coronary intervention, VASP=vasodilator stimulated phosphoprotein.
within 48 h of the procedure – plus either i) evidence of prolonged ischaemia (≥20 minutes) as demonstrated by prolonged chest pain, or ii) ischaemic ST changes or new pathological Q waves, or iii) angiographic evidence of a flow limiting complication, such as of loss of patency of a side branch, persistent slow-flow or no-reflow, embolisation, or iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (16).

Therefore, the inclusion of cardiac biomarker rise into the definition of MI in the ARCTIC study explains the difference in the incidence of MI between the trials: ARCTIC (30.2%), GRAVITAS (1.8%) and TRIGGER-PCI (0%) (9-11).

Sample size calculation

The sample size calculation in the ARCTIC, GRAVITAS and TRIGGER-PCI trials was based on an estimated event rate of 15%, 5% and 4.7%, respectively. Based on these assumptions, it has been calculated that for all three studies inclusion of only 2,000–2,500 patients would show a statistical difference. Interestingly, in the ARCTIC trial the primary efficacy endpoint occurred two-fold more frequently than expected (34.6%), whereas the incidence of events in the GRAVITAS (2.3%) and TRIGGER-PCI (0.5%) trials was lower than expected (9-11). It has been suggested that as for studies with novel platelet inhibitors prasugrel or ticagrelor much higher sample size (at least 17,000 patients) would be required to show statistical differences (17).

Patient selection

Accordingly, the ADAPT-DES registry indicates that intensified antiplatelet treatment might not be efficacious in low-risk patients (e.g. elective PCI representing approximately 70% of the ARCTIC population) but might improve outcome in patients at higher risk when stents are used (high-risk acute coronary syndrome [ACS] with drug-eluting stents or in those with a high risk for stent thrombosis [predisposing factors: diabetes, ACS, multiple stenting and multivessel disease]) (18). In the ARCTIC study, however, patients with ST elevation MI were excluded whereas patients with non ST elevation-ACS (NSTEMI) represented only 25% of the study population. In line with the latter, also the GRAVITAS trial included only stable patients undergoing elective PCI (60%) and NSTE-ACS (40%). For the TRIGGER-PCI trial only patients undergoing elective DES-PCI were eligible. Therefore, exclusion of high-risk patients may have accounted for the negative study results.

Time point of randomisation

Furthermore, it is a crucial point to note that randomisation was performed 12–24 h after PCI in the GRAVITAS trial and 2–7 h after the first clopidogrel maintenance dose intake the day after successful PCI in the TRIGGER-PCI trial. Therefore, patients experiencing peri-procedural events, early after PCI or those with unsuccessful or complicated PCI procedures were not eligible for GRAVITAS or TRIGGER-PCI.

Summarisation

In summary, it may well be that the chosen study design of the above discussed trials had an impact on the negative results. Therefore, it remains a fundamental issue to characterise patient populations, which might benefit from use of proper protocols of personalised antiplatelet treatment. Taken together we have learned that future studies investigating the personalised antiplatelet approach should be performed in patients with a high risk for stent thrombosis (predisposing factors: diabetes, ACS, multiple stenting and multivessel disease). Furthermore, when intensified antiplatelet treatment is applied to high-risk ACS patients, the more potent drugs prasugrel or ticagrelor are preferred over doubling the maintenance dose of clopidogrel or use of repeated loading doses of clopidogrel. Moreover, the timing of testing and switching should be set before or at least very early after stenting, as HTPR seems to play the most important role in the early phase. Until ongoing trials (e.g. ANTARTIC, MATTIS-D, TAILOR-PCI, RAPID-STEMI, GIANT) will show clinical benefit by use of personalised antiplatelet therapy, the consensus document on high on treatment platelet reactivity recommends testing only in patients with a history of stent thrombosis or in patients undergoing high-risk PCI (19).

Conflicts of interest

Jolanta M. Siller-Matula has received lecture and/or consultant fees from AstraZeneca, Daiichi Sankyo and Eli Lilly. Bernd Jilma has received lecture fees from AstraZeneca.

References


