Safety and efficacy of IIb/IIIa inhibitors in combination with highly active oral antiplatelet regimens in acute coronary syndromes: A meta-analysis of pivotal trials

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Safety and efficacy of IIb/IIIa inhibitors in combination with highly active oral antiplatelet regimens in acute coronary syndromes: A meta-analysis of pivotal trials

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Abstract
The risk and benefit of GP-IIb/IIIa Inhibition (GPI) in combination with recent antiplatelet regimens in acute coronary syndromes (ACS) remain unassessed. The advent of fast-acting highly active oral P2Y12 inhibitors questions the additional value and risk of their association with GPI. We studied the effect of GPI in combination with prasugrel and ticagrelor, compared to clopidogrel on major bleeding in pivotal randomized controlled trials in the setting of ACS, using a meta-analytic approach. A similar analysis, further including the comparison of a double versus standard dose clopidogrel regimen, was performed for the risk of the primary efficacy endpoint. The combination of GPI and recent P2Y12 inhibitors was associated with a similar risk of bleeding as compared with GPI and the standard clopidogrel regimen (RR 0.92 [0.74; 1.13]). The benefit of recent regimens, including double dose clopidogrel, in reducing the primary ischemic endpoint (RR 0.86 [0.78; 0.94]) persisted in those treated with GPI. Although GPI use was associated with a consistent increase in the risk of bleeding in both recent (RR 1.27 [1.05–1.55]) and standard regimens (RR 2.01 [1.64–2.47]), the relative magnitude of such an increase was lower in association with prasugrel or ticagrelor as compared with clopidogrel. The risk of bleeding using a combination of GPI and oral antiplatelet regimens is mainly related to the use of GPI and not the oral antiplatelet regimen. Considering the absence of increased risk of bleeding and the persistence of the benefit of recent P2Y12 regimens in combination with GPI as compared with the standard clopidogrel regimen, the use of such a combination within the guidelines is supported by our findings.

Introduction
Antithrombotic therapy plays a pivotal role in the management of patients with acute coronary syndrome (ACS). The combination of aspirin and clopidogrel (300 mg loading dose followed by 75 mg daily) has been the standard oral antiplatelet regimen in the past [1], but this monopoly has been challenged. Slow onset of action, irreversibility of platelet inhibition, and variability of platelet response [2] partially due to genetic polymorphisms of the hepatic cytochrome CYP2C19 [3] in converting clopidogrel to its active metabolite, has been the impetus for the development of new antiplatelet options. The increase in clopidogrel dosage [4] and more recent antiplatelet agents, prasugrel and ticagrelor, showed reduced rates of ischemic events compared to standard-dose clopidogrel [5,6]. However, prasugrel and ticagrelor were also associated with an increased risk of major bleeding [6] and non-coronary artery bypass grafting (CABG) bleeding [5], respectively.

Glycoprotein IIb/IIIa inhibitors (GPI) providing a fast platelet inhibition are recommended in addition to oral antiplatelet therapy in the setting of high risk ACS with subsequent benefits in terms of death and MI [7–9], mainly attributable to the delay between clopidogrel loading dose and effective platelet inhibition. However, their use is also associated with an increased risk of major bleeding [10,11]. Hence, the recent advent of fast-acting oral P2Y12 inhibitors questions the additional value of GPI in such settings.

The aim of this study was to assess the risks and benefits of the combination of GPI and recent oral P2Y12-inhibitor regimens using a meta-analytic approach of the data published in major pivotal trials in the setting of ACS.

Methods
Selected studies
We performed a search of MEDLINE (source PubMed) and the Cochrane Controlled Clinical Trials Register Database for randomized controlled trials as well as European Society of Cardiology, American Heart Association and American College of Cardiology annual meetings since 2007 on the three randomized trials that compare standard-dose clopidogrel with more recent antiplatelet regimens in patients with ACS namely: CURRENT-OASIS 7 [4], PLATO [5], and the TRITON-TIMI 38 study [6]. The search
terms limited to randomized controlled trials were “TRITON” & “Prasugrel” (n = 17 publications), “PLATO” & “Ticagrelor” (n = 39 publications) and “CURRENT” & “Clopidogrel” (n = 33 publications). The results were independently reviewed by two investigators, identifying adequate publications providing data on GPI use.

Finally, data from 10 publications including the main publications (n = 3) [4–6], subgroup publications of STEMI patients (n = 2) [12,13], invasively managed or PCI patients (n = 3) [14–16] as well as specific publications on GPI use (n = 1) [17] and bleeding complications (n = 1) [18] were integrated in the analyses. The subgroup analysis of patients who underwent PCI in the PLATO trial was derived from an abstract [14] reporting a 30-day outcome only.

In CURRENT-OASIS 7 [4] and CURRENT-PCI [15] studies, the analysis was restricted to patients who had received GPI after randomization (23.4% and 28.6% of the patients, respectively) since the primary endpoint according to the use of the GPI was only reported for such patients.

Outcome definition
Non-CABG-related major bleeding defined the safety endpoint when available. Major bleeding complications were defined according to the TIMI hemorrhage classification [19] in TRITON and CURRENT-OASIS 7 trials. Major bleeding complications’ definition was study-specific in PLATO trial [20]. Outcomes were based on the longest follow-up available.

The primary efficacy endpoint was the composite endpoint of cardiovascular death, MI and stroke as defined in all studies. Follow-up data were collected in the CURRENT, PLATO, and TRITON-TIMI 38 trials at 30 days, 12, and 15 months, respectively.

Statistical analysis
The absolute number of patients with or without events in each arm was extracted directly from the publications, when provided, or calculated, when needed. We performed a primary analysis comparing the general effect of the combination of GPI with recent regimens in comparison with its combination with standard-regimen clopidogrel. A supplementary analysis presenting the effect of GPI in combination with each oral antiplatelet regimen compared to the oral antiplatelet regimen alone was also performed to assess the risk, specifically attributable to GPI use. Results are presented as relative risks with 95% confidence intervals (CI). Outcomes from individual studies were combined using both Mantel–Haenzel fixed- and random-effect models. Heterogeneity across studies was studied by the Cochran’s Q statistic with a p value set at 0.1. The fixed-effect model was considered for the primary analysis and reported in the text. The random effect-model is also reported in figures, considered for a sensitivity analysis purpose in case of significant heterogeneity. Tests were two-tailed and a p-value of <0.05 was considered statistically significant. R software version 3.0.0 (2013-04-03) for MacOS (R Foundation for Statistical Computing) with the Meta package was used for statistical analysis.

Results
The major characteristics of the patients of each study and the rates of the clinical endpoints are detailed in Tables I and II, respectively.

Safety endpoint
The rate of major bleeding according to the use of the GPI was not available for the CURRENT-OASIS 7 trial. It was collected, respectively, at 30 days and 12 months in TRITON and PLATO trials, respectively [17,18].

The risk of bleeding in case of GPI use was consistently similar between patients receiving more recent drugs (e.g. prasugrel or ticagrelor) and those receiving clopidogrel both in the general population (RR 0.92 [0.74; 1.13]; Figure 1A) and the PCI subgroup (RR 1.02 [0.70; 1.13]; Figure 1B).

As reported in supplementary Figure S1A and S1B GPI use in both recent (RR 1.27 [1.05; 1.55]) and standard regimen arms (RR 2.01 [1.64; 2.47]) was significantly and consistently associated with a higher risk of major bleeding with no heterogeneity among studies.

When the analysis was restricted to patients who underwent PCI, the association between the risk of major bleeding and GPI use was significant in the standard regimen arm only (RR 1.69 [1.29; 2.23]) with no significant heterogeneity among studies (Supplementary Figure S1C and S1D).

Primary ischemic endpoint
In patients receiving GPI, recent regimens were associated with lower rates of primary ischemic outcome both in the general population (RR 0.86 [0.78; 0.94]) and PCI subgroups (RR 0.83 [0.75; 0.92]) as shown in Figure 2A and 2B, respectively. Such a finding was consistent between studies.

Considering the analysis in individual study arms, the use of GPI was associated with higher risk of the primary endpoint both in the recent (RR 1.14 [1.04; 1.24]) and standard regimen arms (RR 1.12 [1.03; 1.21]), however, with significant heterogeneity between studies (p = 0.035 and p = 0.0003, respectively; Supplementary Figure S2A and S2B). There was no effect on the primary endpoint in the PLATO trial in either treatment arm. When CURRENT-OASIS 7 trial was excluded from the analysis, the heterogeneity remained significant only in the standard regimen arms (p = 0.0138) and the association with the risk of the primary endpoint was not significant anymore (Supplementary Figure S2C and S2D). The analyses restricted to subgroups are detailed in the supplementary appendix.

Discussion
The main findings of our meta-analysis are that compared to the combination of GPI with standard clopidogrel regimens, the combination of GPI with recent oral antiplatelet regimens is not associated with a higher risk of bleeding complications. On the other hand, the benefit of recent P2Y12 inhibitors in reducing the risk of thrombotic events is independent of GPI use. The combination of GPI and all oral antiplatelet regimens is consistently associated with a higher risk of major bleeding regardless of which P2Y12 inhibitor is used. However, the magnitude of the bleeding risk is more pronounced when GPI is combined with the standard clopidogrel regimen leading to similar absolute bleeding rates between recent and standard arms when GPI is used. This finding supports the relative safety of GPI combination with recent regimens.

The short delay in action of prasugrel and ticagrelor is derived from data on healthy volunteers [21]. However, in the setting of STEMI, recent studies [22,23] have shown that these two drugs provide an effective platelet inhibition 2 h after the loading dose in only half of patients and at least 4 h were required to achieve an effective platelet inhibition in a majority of patients. The concomitant administration of GPI could be used as a bridge to overcome this period of insufficient platelet inhibition [23]. Several studies have assessed the role and the optimal timing of the GPI administration in the setting of ACS supporting their use only in high-risk patients [7,10] with short symptom-to-administration...
Table I. Demographic characteristics of the patients in selected studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>C</th>
<th>n</th>
<th>T</th>
<th>C</th>
<th>n</th>
<th>T</th>
<th>C</th>
<th>n</th>
<th>T</th>
<th>C</th>
<th>n</th>
<th>T</th>
</tr>
</thead>
<tbody>
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<td>18 624</td>
<td>9291</td>
<td>9333</td>
<td>7544</td>
<td>3792</td>
<td>3752</td>
<td>13 408</td>
<td>6795</td>
<td>6813</td>
<td>25 086</td>
<td>12 566</td>
<td>2C</td>
<td>8703</td>
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<td>Median age (year)</td>
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<td>Age &gt; 75 (%)</td>
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<td>15</td>
<td>13.9</td>
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<td>12.5</td>
<td>12.5</td>
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<td>13</td>
<td>13</td>
<td>13.3</td>
</tr>
<tr>
<td>Female sex (%)</td>
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<td>28.3</td>
<td>28.4</td>
<td>23.4</td>
<td>24.2</td>
<td>25.3</td>
<td>25.2</td>
<td>27</td>
<td>25</td>
<td>24</td>
<td>21</td>
<td>27.5</td>
<td>27.3</td>
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<tr>
<td>Tobacco use (%)</td>
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<td>35.7</td>
<td>36</td>
<td>44.3</td>
<td>45.9</td>
<td>38</td>
<td>38</td>
<td>44</td>
<td>47</td>
<td>33.2</td>
<td>33.6</td>
<td>36.6</td>
<td>37.5</td>
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<tr>
<td>Hypertension (%)</td>
<td></td>
<td>65.1</td>
<td>65.8</td>
<td>58.3</td>
<td>59.3</td>
<td>64</td>
<td>64</td>
<td>50</td>
<td>49</td>
<td>60.2</td>
<td>60.5</td>
<td>58.8</td>
<td>59.4</td>
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<td>Dyslipidemia (%)</td>
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<td>46.7</td>
<td>46.6</td>
<td>39.3</td>
<td>39</td>
<td>56</td>
<td>56</td>
<td>41</td>
<td>41</td>
<td>41.1</td>
<td>41.2</td>
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<td>Diabetes</td>
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<td>mellitus (%)</td>
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<tr>
<td>History of MI</td>
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<td>20.7</td>
<td>20.4</td>
<td>13.6</td>
<td>13.3</td>
<td>16.9</td>
<td>17.1</td>
<td>18</td>
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<td>17.7</td>
<td>18</td>
<td>16.8</td>
<td>17.2</td>
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<tr>
<td>History of PCI</td>
<td></td>
<td>13.1</td>
<td>13.6</td>
<td>8</td>
<td>8.7</td>
<td>13.3</td>
<td>14.1</td>
<td>18</td>
<td>18</td>
<td>14.8</td>
<td>14.9</td>
<td>14.5</td>
<td>14.6</td>
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<tr>
<td>History of CABG</td>
<td></td>
<td>6.2</td>
<td>5.7</td>
<td>2.6</td>
<td>2.6</td>
<td>5.7</td>
<td>5.3</td>
<td>7</td>
<td>8</td>
<td>6.7</td>
<td>6.2</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Chronic disease*</td>
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<td>4.4</td>
<td>4.1</td>
<td>3.3</td>
<td>2.8</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa use</td>
<td></td>
<td>26.8</td>
<td>26.4</td>
<td>35.7</td>
<td>34.6</td>
<td>35.4</td>
<td>35.2</td>
<td>55</td>
<td>54</td>
<td>64</td>
<td>62</td>
<td>31.7</td>
<td>31.8</td>
</tr>
</tbody>
</table>

C, clopidogrel; P, prasugrel; T, ticagrelor; 2C, clopidogrel double dose; CABG, coronary-artery bypass grafting; PCI, percutaneous coronary intervention.

*Creatinine clearance <60 ml/min.
†For OASIS 7 and OASIS 7 PCI, the rate of GPI use is the rate before randomization.
Table II. Rates of primary endpoint and major bleeding in selected studies and their subgroups.

<table>
<thead>
<tr>
<th>Study</th>
<th>C n</th>
<th>GPI n</th>
<th>Primary End Point</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRITON</strong></td>
<td>6795</td>
<td>3738</td>
<td>482 (12.9%)</td>
<td>41 (1.1%)</td>
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<tr>
<td></td>
<td>3057</td>
<td></td>
<td>336 (11%)</td>
<td>18 (0.6%)</td>
</tr>
<tr>
<td></td>
<td>3137</td>
<td></td>
<td>291 (9.3%)</td>
<td>28 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>6813</td>
<td>3676</td>
<td>383 (10.4%)</td>
<td>44 (1.2%)</td>
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<td></td>
<td>3057</td>
<td></td>
<td>336 (11%)</td>
<td>18 (0.6%)</td>
</tr>
<tr>
<td><strong>PLATO</strong></td>
<td>9291</td>
<td>2487</td>
<td>276 (11.1%)</td>
<td>131 (5.3%)</td>
</tr>
<tr>
<td></td>
<td>6804</td>
<td></td>
<td>810 (11.9%)</td>
<td>175 (2.6%)</td>
</tr>
<tr>
<td></td>
<td>9333</td>
<td>2468</td>
<td>247 (10%)</td>
<td>112 (4.5%)</td>
</tr>
<tr>
<td></td>
<td>6865</td>
<td></td>
<td>666 (9.7%)</td>
<td>248 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>3792</td>
<td>1407</td>
<td>138 (9.8%)</td>
<td>226 (9.4%)</td>
</tr>
<tr>
<td></td>
<td>2385</td>
<td></td>
<td>272 (11.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>PLATO PCI</strong></td>
<td>5214</td>
<td>1929</td>
<td>98 (5.1%)</td>
<td>73 (3.8%)</td>
</tr>
<tr>
<td></td>
<td>3285</td>
<td></td>
<td>154 (4.7%)</td>
<td>76 (2.3%)</td>
</tr>
<tr>
<td></td>
<td>5215</td>
<td>1929</td>
<td>98 (5.1%)</td>
<td>71 (3.7%)</td>
</tr>
<tr>
<td></td>
<td>3286</td>
<td></td>
<td>131 (4%)</td>
<td>105 (3.2%)</td>
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<tr>
<td><strong>PLATO invasive</strong></td>
<td>2259</td>
<td>2245</td>
<td>244 (10.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4019</td>
<td></td>
<td>422 (10.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4106</td>
<td></td>
<td>349 (8.5%)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Recent ESC and ACCF/AHA guidelines [25–28], based only on studies with the standard clopidogrel regimen, recommend the selected use of GPI in high-risk PCI, or in the presence of angiographic evidence of large thrombus burden or no-reflow phenomenon. However, GPI is associated with higher risk of bleeding [10,11] and its combination with more recent potent platelet inhibitors may be of no benefit or even deleterious. Consistent with previous studies on GPI use [10,11], our analysis showed that the association of GPI with antiplatelet regimens leads to a homogeneous increase in the risk of major bleeding. The relative
The magnitude of the risk increase seems, however, to be lower in association with prasugrel or ticagrelor (RR: 1.27) as compared with clopidogrel (RR: 2). Interestingly, the absolute level of risk in association with GPI use was comparable between active and control arms of the TRITON trial (1.2 and 1.1%) and even lower in the active versus control arm of the PLATO trial (4.5 versus 5.3%). Similar results were observed in the PCI subgroups, with an increase in the risk of major bleeding associated with GPI use, statistically significant in combination with clopidogrel but non-significant in combination with recent drugs. In the PLATO trial, GPI use was associated with lower rates of major bleeding in the PCI subgroup compared to the general population of the study. This may be related to the results of GPI use in some 539 with no invasive approach and/or 1097 patients with or without invasive approach but no PCI in the PLATO trial. Based on the international guidelines, GPI is mainly an adjunctive therapy to PCI and it is difficult to speculate on the unreported reasons of GPI use in medically managed patients. Moreover, conservatively treated patients represented higher-risk patients for bleeding as they were older, more often of female gender, diabetic and more likely to have a history of prior MI or stroke. Hence, the “off label” use of GPI may be an explanation to this finding. On the other hand our analysis underscores the relative safety of more recent P2Y12 inhibitors in combination with GPI when used in the recommended setting of PCI for ACS. It also supports the hypothesis that the risk of major bleeding is driven by the GPI use and not the P2Y12 inhibitor regimen in patients receiving the combination of the two.

The benefit of more recent P2Y12 inhibitor regimens over the standard clopidogrel regimen among patients receiving GPI is also confirmed by our analysis. The association of GPI use and the higher risk for the ischemic endpoint is very likely a consequence of the guideline-based targeted use of GPI in patients with baseline high-risk feature.

The benefit of GPI in addition to recent P2Y12 inhibitors on ischemic events could not be assessed by our analysis that mainly shows a significant heterogeneity between the studies. Such heterogeneity may be explained by several factors. First, it may be related to the results of GPI use in patients with or without invasive approach but no PCI in the PLATO trial. The use of GPI in these non-PCI patients in the acute phase remains questionable as no reduction in death or MI has previously been observed with GPI among medically managed patients. Another source of heterogeneity may be a specific drug effect, as the exclusion of the CURRENT trial from the analysis led to homogenous results between the active arms of PLATO and TRITON trials. The timing of administration of drugs could also explain some differences. Unlike PLATO trial, where ticagrelor could have been administered prior to angiography, in TRITON trial, prasugrel was administered after coronary angiography in all patients with the exception of those undergoing primary PCI for STEMI. The later administration of prasugrel may also explain the higher rates of GPI use in the trial. Finally, differences between studies’ designs with patients managed medically or surgically in PLATO but not in TRITON, may also participate to the heterogeneity. Among STEMI patients, 97% underwent PCI in TRITON trial while in PLATO trial, only 72.1% underwent PCI although all were initially planned for primary PCI. However, the global and sub-group analyses of PLATO and TRITON active arms showed a consistent GPI-use effect, suggesting the comparable efficacy of prasugrel and ticagrelor despite population- and study-based variability.

**Study limitations**

Our meta-analysis was not performed on individual patients’ data. Hence analyses could not take in to account the individual levels of risk.

Our meta-analysis was not based on a systematic review. It aimed to explore the potential role of GPI in association with “recent” P2Y12 inhibitors.
P2Y$_{12}$ inhibitor in the setting of ACS as assessed in major pivotal trials referenced in international guidelines. Several studies comparing different clopidogrel loading and/or maintenance doses, mainly in the setting of PCI or with biological endpoints, have not been included in our analysis. Hence, our findings only apply to the specific ACS population assessed in the included studies.

Another limitation is the non-randomized use of GPI with a risk of un-assessed confounding factors. However, the guideline-based use of GPI is likely in most cases and the similar rates of GPI use in different study arms in different trials suggest a relatively low risk of major bias.

Major limitations of our analysis are those of the included trials:

1. The type and the duration of administration of the GPI were not documented in any study.
2. Recent regimens were mainly compared to 300 mg loading/75 mg maintenance dose clopidogrel regimens, while a double loading dose is recommended in high-risk ACS patients. Hence, the benefit of recent drugs over higher dose clopidogrel regimens still remains uncertain.
3. In the PLATO trial [5], some patients received an additional dose of their study drug at the time of the PCI. Hence, the control arm includes patients who finally received 300 or 600 mg of clopidogrel. The individual rate of GPI use in these groups is not reported.
4. Rates of major bleeding are not reported in the CURRENT-OASIS 7 trial according to the use of GPI.
5. In the CURRENT-OASIS 7 [4] and CURRENT-PCI [15] there is a discrepancy between total GPI use and reported GPI use after randomization [4]. This might generate some uncontrolled bias.

With respect to the above-mentioned limitations and the possibility of un-assessed confounders, our conclusions require adequately designed studies to be confirmed and should be considered as suggestive.

**Conclusion**

Our analysis shows that the combination of GPI and oral P2Y$_{12}$ inhibitors is consistently associated with a higher risk of major bleeding, which is mainly related to the GPI use and not the oral antiplatelet regimen. Such a finding underscores the relative safety of GPI association with more recent highly active P2Y$_{12}$ inhibitors. On the other hand, the benefit of recent P2Y$_{12}$ regimens in preventing thrombotic events appears to be independent of the GPI use.

In the absence of randomized trials, which are warranted to assess the direct benefit of GPI in addition with more recent P2Y$_{12}$ inhibitors, our analysis suggests the safety of such strategy and supports the unchanged use of GPI in association with such regimens with respect to indications recommended by guidelines.

**Acknowledgments**

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**Declaration of interest**

The authors report no declarations of interest with respect to the present manuscript.

**Supplemental material**

Supplemental data for this article can be accessed on the publisher’s website at www.tandfonline.com/iplt

**References**


