Implications of variability in definition and reporting of major bleeding in randomized trials of oral P2Y₁₂ inhibitors for acute coronary syndromes

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Aims

Various definitions of major bleeding have been used to evaluate safety in randomized controlled trials of antiplatelet therapy. We compared the definitions and rates of major bleeding in phase III randomized controlled trials of oral P2Y₁₂ inhibitors in the management of patients with acute coronary syndromes (ACS).

Methods and results

Electronic searches identified six phase III randomized controlled oral P2Y₁₂ inhibitor trials published between 2001 and 2010 involving 119,020 patients with ACS. The trials compared clopidogrel standard-dose (300-mg loading dose, 75-mg daily thereafter) vs. placebo (CURE, CLARITY-TIMI 28, COMMIT), clopidogrel standard-dose vs. prasugrel (TRITON-TIMI 38) or ticagrelor (PLATO) and clopidogrel standard-dose vs. clopidogrel double-dose (600-mg loading dose, 150-mg daily for 6-days, 75-mg daily thereafter) (CURRENT-OASIS 7). Using the trial definition, major bleeding rates in patients treated with standard-dose clopidogrel ranged from 0.6% in COMMIT to 11.2% in PLATO. The contrast in bleeding rates of standard-dose clopidogrel among the trials was attenuated when using the thrombolysis in myocardial infarction (TIMI) definition for major bleeding (range 1.1–7.7%) and bleeding rates in all the trials were less than 2% when comparing 30 day rates of non-coronary artery bypass graft surgery-related TIMI major bleeding (range 0.3–1.9%).

Conclusion

Differences in major bleeding rates between trials of P2Y₁₂ inhibitors in patients with ACS are minimized after standardization of bleeding definitions, timing of reporting of bleeding outcomes, and procedure rates. Interpretation of the risk of bleeding associated with different P2Y₁₂ inhibitors would be facilitated by a consistent approach to the definition and reporting of bleeding.

Keywords

Bleeding • P2Y₁₂ inhibitors • Acute coronary syndrome • Definition

Introduction

The combination of aspirin and clopidogrel has been the standard of antiplatelet therapy across the spectrum of patients with acute coronary syndromes (ACS) and in those undergoing percutaneous coronary intervention (PCI).¹,² Concern about clopidogrel’s delayed onset and offset of action, incomplete inhibition of the platelet P2Y₁₂ receptor and variability in patient response to the drug³ has prompted evaluation, in large randomized controlled trials, of the efficacy and safety of new more potent and rapidly acting oral P2Y₁₂ inhibitors and of double-dose clopidogrel (600 mg loading dose, 150 mg daily for 6-days, 75 mg daily thereafter) compared with standard-dose clopidogrel (300 mg loading dose, 75 mg daily thereafter).⁴–⁶ The new oral P2Y₁₂ inhibitors...
and double-dose clopidogrel were associated with improved efficacy compared with standard doses of clopidogrel, but in some trials these new treatment strategies also increased major bleeding.6,6

Randomized controlled trials provide the most valid comparisons of the efficacy and safety of two treatments but the new oral P2Y12 inhibitors have not been directly compared with double-dose clopidogrel or with one another. Although indirect comparisons across trials are subject to confounding because of differences in patients characteristics, cointerventions, and outcome definitions, they are important for clinicians faced with having to choose the best treatment for their patients. Indirect comparisons of rates of bleeding outcomes across trials provide particular challenges because of variability in the definitions and reporting of major bleeding, but are important because bleeding is at least as frequent as ischaemic events and is associated with a substantial risk of morbidity and mortality.7–10 The objective of this review was to examine the potential impact of differences in major bleeding definitions on the interpretation of safety outcomes in trials of oral P2Y12 inhibitors in patients with ACS. To achieve this objective, we compared the rates and relative risks of major bleeding as reported according to the primary trial definition with those obtained using a standardized definition of bleeding ascertained at a common time point.

Methods
Before commencing this study, we developed a protocol detailing the objectives, criteria for study selection, data retrieval, primary and secondary major bleeding outcomes, and planned statistical analyses.

Study selection and data retrieval
MEDLINE and EMBASE electronic databases were searched from 2001 to 2010 to identify published unconfounded randomized phase III trials in patients with ACS comparing standard doses of clopidogrel (75 mg daily with or without a preceding 300 mg loading dose) with placebo, a new oral P2Y12 inhibitor (prasugrel, ticagrelor) or double-dose clopidogrel, and that reported major bleeding outcomes.

Two investigators (DJQ, JWE) independently reviewed the trial reports and any disagreements regarding their eligibility for inclusion were resolved by discussion. Data were extracted regarding study design and the definitions and rates of major bleeding. Missing data from individual trials were requested from the first or corresponding author or sponsoring pharmaceutical company.

Major bleeding outcomes
The primary outcomes of interest were the rate of major bleeding as defined by the trial investigators and as defined by Thrombolysis in Myocardial Infarction (TIMI) major bleeding criteria. We accepted the reported definitions of major bleeding and did not attempt to retrospectively re-classify events. Thrombolysis in myocardial infarction major bleeding was further subdivided as coronary artery bypass graft (CABG)-related and non-CABG-related bleeding. If data on rates of major bleeding were not reported, we contacted the authors to obtain the missing information. We were unable to obtain information on non-CABG major bleeding at 30 days from the PLATO trial and therefore estimated the rates by extrapolation from Kaplan–Meier curves. We also examined the rates of life-threatening bleeding where available.

We assessed the potential impact of differences in the method of reporting of bleeding on the interpretation of the trials by comparing the reported rates and relative risks of major bleeding in each trial with the rates and relative risks that were calculated (i) using the same definition of bleeding (TIMI major bleeding where possible), (ii) after excluding CABG-related major bleeding, and (iii) at the same time point in each trial (30 days). We focused on TIMI major bleeding because it is the most commonly used definition of major bleeding and is reported in all of the trials.

Statistical analysis
We compared the rates and relative risks of major bleeding in each trial. For those trials that did not report hazard ratios or relative risks, we calculated the relative risks and tested for heterogeneity using Review Manager (RevMan, version 5.024. Copenhagen, The Cochrane Collaboration 2008). All of our calculations were performed using the Mantel–Haenszel method and the results that we obtained using a fixed effects model were compared with those obtained using a random-effects model. A P value of <0.10 was considered to denote statistically significant heterogeneity.

Results
Description of trials
Six studies involving 119,020 patients with ACS were included in this review: three trials compared clopidogrel with placebo (CURE [Clopidogrel in Unstable angina to prevent Recurrent ischemic Events]),1 CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28)11 and COMMIT (ClOpidogrel Metoprolol in Myocardial Infarction Trial)),12 two trials compared clopidogrel with new P2Y12 inhibitors, prasugrel (TRITON-TIMI 38)13 or ticagrelor (PLATELET inhibition and patient Outcomes).14 respectively, and one trial compared standard-dose with double-dose clopidogrel (CURRENT–OASIS 7 [Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs]).15 Treatment duration ranged from 48 h (median of four doses) in CLARITY-TIMI 28 to 15 months (median 14.5 months) in TRITON-TIMI 38 (Table 1).

Patient characteristics
The baseline characteristics of patients included in the trials are summarized in Supplementary material online, Table A. The mean age ranged from 57.5 to 64.2 years and the majority of patients in each trial were male (range 61.5–80.3%). The CLARITY-TIMI 28 trial only included patients with ST-elevation myocardial infarction (STEMI), COMMIT included patients with suspected STEMI, CURE only included patients with non-ST elevation ACS and the remaining trials included about two-thirds of patients with non-ST elevation ACS and one-third with STEMI. Renal function, TIMI risk scores, and the percentage of patients with positive cardiac biomarkers were not consistently reported.

Co-interventions
The COMMIT trial did not report the proportion of patients undergoing CABG surgery or PCI during the study. In the remaining trials, the proportion of patients undergoing CABG surgery ranged from 2.7% in TRITON-TIMI 38 to 16.5% in CURE. The
The proportion of patients undergoing PCI was 21.2% in CURE compared with 57–99% in the remaining studies. Fibrinolysis use was reported in the COMMIT and CLARITY-TIMI 28 trials but was not consistently reported in other trials. In PLATO, a dose of clopidogrel (study drug or not) was given to 47.1% of patients in the ticagrelor group within 24 h before or after randomization; 300–375 mg and 600–675 mg was given to 20.6% and 13.7% of patients, respectively. In the CURE, CLARITY, TRITON-TIMI 38, and CURRENT-OASIS 7 trials, prior use of clopidogrel 24 h up to 7 days before randomization was an exclusion criterion.

### Bleeding definitions and timing of reporting of bleeding

Major bleeding definitions used in the trials are summarized in Table 2. The six trials included in our review each used a different definition for the primary major bleeding outcome. The primary major bleeding definition included any red cell transfusion in COMMIT, a ≥ 2 unit red cell transfusion in CURE, ≥ 2 unit red cell transfusion in CURRENT-OASIS 7, and a ≥ 4 units transfusion over 48 h in TRITON-TIMI 38. The CURE, COMMIT, TRITON-TIMI 38, and PLATO trials further categorized major bleeding according to whether it was life-threatening or not.

The CURE, CLARITY-TIMI 28, and TRITON-TIMI 38 reported adjudicated TIMI major bleeding although the TIMI definitions differed among the trials. The PLATO and CURRENT-OASIS 7 trials reported non-adjudicated TIMI major bleeding rates. COMMIT did not report TIMI major bleeding.

The timing of reporting of the major bleeding outcome ranged from 15 days in COMMIT to 15 months in TRITON-TIMI 38.

### Major bleeding rates according to primary trial definition

#### Rate of bleeding

The rates of major bleeding among patients receiving standard-dose clopidogrel ranged from 0.6% in COMMIT to 11.2% in PLATO (Figure 1A). The TRITON-TIMI 38 trial reported a 1.8% rate of major bleeding at 15 months among patients receiving standard-dose clopidogrel, which is more than 5-fold lower than the 11.2% rate reported in PLATO at 12 months.

#### Relative risk of bleeding

Despite the differences in the reported rates of major bleeding in patients treated with standard-dose clopidogrel, estimates of risk ratios for major bleeding were not statistically heterogeneous among the three placebo-controlled trials (heterogeneity $P = 0.25$). In contrast, there was significant heterogeneity in the risk ratios of major bleeding among the three active-controlled trials ($P = 0.05$). In the PLATO trial, ticagrelor compared with clopidogrel did not increase major bleeding whereas in the TRITON-TIMI 38 trial and the CURRENT-OASIS 7 trial, both prasugrel and double-dose clopidogrel, respectively, increased major bleeding compared with standard-dose clopidogrel (Figure 2).
Table 2  Criteria for the primary definitions of major bleeding used in randomized controlled trials evaluating P2Y12 receptor inhibitors in acute coronary syndromes patients

<table>
<thead>
<tr>
<th>Trial definition, year definition published</th>
<th>Site of bleeding</th>
<th>Haemoglobin decrease (g/dL)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Transfusion requirements for bleeding</th>
<th>Death</th>
<th>Other criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE, 2001&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Substantial disabling bleeding</td>
</tr>
<tr>
<td>Primary endpoint: CURE major, comprising life-threatening bleeding as a subset</td>
<td></td>
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<tr>
<td>CURE major</td>
<td>Intraocular (not conjunctival) bleeding leading to significant loss of vision</td>
<td>–</td>
<td>≥ 2 units of blood</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>CURE life-threatening</td>
<td>Symptomatic intracranial haemorrhage</td>
<td>≥ 5.0</td>
<td>≥ 4 units of blood</td>
<td>Fatal bleeding</td>
<td>Bleeding requiring surgical intervention, significant hypotension requiring inotropes</td>
</tr>
<tr>
<td>Secondary endpoint:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI major 1988 version&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Intracranial, overt&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≥ 5.0 (or &gt;15% drop in haematocrit)</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>CLARITY-TIMI 28, 2005</td>
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<tr>
<td>Primary endpoint: TIMI major</td>
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<tr>
<td>TIMI major 1991 version&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Intracranial&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≥ 5.0 regardless of whether bleeding site identified</td>
<td>Haemoglobin decrease adjusted for transfusions&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Fatal bleeding</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Secondary endpoints:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding&lt;sup&gt;1,24&lt;/sup&gt;</td>
<td>Intracranial</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>COMMIT, 2006</td>
<td></td>
<td></td>
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<tr>
<td>Primary endpoint: COMMIT life-threatening</td>
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<tr>
<td>COMMIT life-threatening&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Cerebral</td>
<td>–</td>
<td>Any transfusion</td>
<td>Fatal bleeding</td>
<td>–</td>
</tr>
<tr>
<td>Secondary endpoints:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Not defined</td>
<td></td>
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<tr>
<td>TRITON-TIMI 38, 2007&lt;sup&gt;25&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Primary endpoint: Non-CABG related TIMI major, comprising TIMI life-threatening as a subset</td>
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</tr>
<tr>
<td>Non-CABG related TIMI major</td>
<td>Any intracranial haemorrhage, clinically overt (including imaging)</td>
<td>≥ 5.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Trial definition, year definition published</th>
<th>Site of bleeding</th>
<th>Haemoglobin decrease (g/dL)a</th>
<th>Transfusion requirements for bleeding</th>
<th>Death</th>
<th>Other criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG TIMI life-threatening</td>
<td>Symptomatic intracranial haemorrhage</td>
<td>–</td>
<td>≥4 units of blood over a 48 h period</td>
<td>Fatal bleeding</td>
<td>Bleeding requiring surgical intervention, hypotension requiring intravenous inotropes</td>
</tr>
<tr>
<td>PLATO, 2009</td>
<td>PLATO-defined major-other</td>
<td>≥3 and &lt; 5</td>
<td>2–3 units</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>PLATO-defined major life-threatening</td>
<td>≥5.0</td>
<td>≥4 units of blood</td>
<td>Fatal bleeding</td>
<td>Bleeding with hypovolemic shock or severe hypotension requiring inotropes or surgery, intrapericardial with tamponade</td>
</tr>
<tr>
<td>Secondary endpoints:</td>
<td>TIMI majord</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Non-CABG related TIMI majord</td>
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<td></td>
</tr>
<tr>
<td>CURRENT-OASIS 7, 2010</td>
<td>Other major</td>
<td>Intraocular bleeding leading to significant loss of vision</td>
<td>2–3 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Symptomatic intracranial haemorrhage</td>
<td>≥5.0</td>
<td>≥4 units of blood</td>
<td>Fatal bleeding</td>
</tr>
<tr>
<td>Secondary endpoints:</td>
<td>TIMI major</td>
<td>Intracranial haemorrhage, any clinically overt bleeding (including bleeding on imaging studies)</td>
<td>&gt;5.0 from baseline</td>
<td>Haemoglobin decrease adjusted for transfusionsb</td>
<td>Fatal bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac tamponade</td>
</tr>
</tbody>
</table>

aHaemoglobin decrease was adjusted for blood transfusions, and so each unit of blood transfused resulted in a 1 g/dL increase in haemoglobin or 3% increase in haematocrit. Therefore, the true change in haemoglobin or haematocrit if there has been an intervening transfusion between two blood measurements is calculated as follows: \( \Delta \text{Haemoglobin} = [\text{baseline haemoglobin} - \text{post-transfusion haemoglobin}] + [\text{number of transfused units}] \). \( \Delta \text{haematocrit} = [\text{baseline haematocrit} - \text{post-transfusion haematocrit}] + [\text{number of transfused units} \times 3] \).
bIf the bleeding event fulfilled criteria in >1 category, the event was assigned to the most severe category.
cBlood loss attributable to revascularization or other surgical procedures was not classified as a Thrombolysis in myocardial infarction haemorrhagic event.
dThrombolysis in myocardial infarction major bleeding events in PLATO were non-adjudicated and analysed with the use of a statistical programme in accordance with definition used in TRITON-TIMI 38.
Major bleeding rates according to the thrombolysis in myocardial infarction major bleeding definition

Rate of bleeding

Major bleeding rates using the TIMI criteria were substantially lower in the CURE, PLATO, and CURRENT-OASIS 7 trials than the rates that were reported using the primary trial definition for major bleeding but still ranged from 1.1% in CURE to 7.7% in PLATO in patients treated with standard-dose clopidogrel (Figure 1B).

The high rate of TIMI major bleeding (non-CABG related plus CABG-related) in PLATO appeared to be related to the higher proportion of CABG-related bleeding events observed in this trial compared with TRITON-TIMI 38 and CURRENT-OASIS 7 (Figure 3).

Relative risk of bleeding

The risk ratios for TIMI major bleeding were similar in the two placebo-controlled trials that reported this outcome (0.94, 95% CI: 0.68–1.30 for CURE, 1.09, 95% CI: 0.67–1.78 for CLARITY-TIMI 28), without statistical evidence for heterogeneity ($P = 0.62$). In contrast, there was significant heterogeneity among the three active-controlled trials in the risk ratios of TIMI major bleeding ($P = 0.01$). In the PLATO trial, ticagrelor compared with clopidogrel did not increase TIMI major bleeding whereas in the TRITON-TIMI 38 trial and the CURRENT-OASIS 7 trial both prasugrel and double-dose clopidogrel, respectively, increased TIMI major bleeding compared with standard-dose clopidogrel (Figure 2).
Figure 2  Impact of bleeding definition on estimates of the relative risk of bleeding in P2Y₁² inhibitor trials in patients with acute coronary syndromes.

Figure 3  Proportion of Thrombolysis in myocardial infarction major bleeding events reported as coronary artery bypass graft related and non-coronary artery bypass graft related in standard-dose clopidogrel treatment arms. Non-coronary artery bypass graft-related major bleeds and coronary artery bypass graft-related major bleeds are not mutually exclusive; therefore, the actual major bleeding rate may not equal the sum of the non-coronary artery bypass graft- and coronary artery bypass graft-related major bleeds. Coronary artery bypass graft.
Implications of variability in definition and reporting of major bleeding

Major bleeding rates according to the non-coronary artery bypass graft thrombolysis in myocardial infarction major bleeding definition

Rate of bleeding
Non-CABG TIMI major bleeding rates were reported separately in the CURE, TRITON-TIMI 38, PLATO, and CURRENT-OASIS 7 trials. The rates of non-CABG-related TIMI major bleeding rates were substantially lower than the rates of TIMI major bleeding, ranging from 0.6% in CURRENT-OASIS 7–2.2% in PLATO among patients receiving standard-dose clopidogrel (Data not shown). In PLATO, major bleeding rate according to the loading dose of clopidogrel (none, 300 or 600 mg) was not reported.

Relative risk of bleeding
In the CURE trial, standard-dose clopidogrel compared with placebo did not significantly increase non-CABG-related TIMI major bleeding. In PLATO and CURRENT-OASIS 7 there was a significant increase in the risk of non-CABG-related TIMI major bleeding with ticagrelor, and double-dose clopidogrel vs. standard-dose clopidogrel, with the hazard ratio point estimates ranging from 1.25 to 1.40 (heterogeneity \( P = 0.80 \)).

Major bleeding rates at 30 days

Rate of bleeding
In the CLARITY-TIMI 28 trial, major bleeding rates at 30 days were reported using the TIMI major bleeding definition, whereas the CURE, TRITON-TIMI 38, and CURRENT-OASIS 7 trials reported non-CABG-related TIMI major bleeding. In PLATO, non-procedure-related PLATO major bleeding rates at 30 days were estimated from the Kaplan–Meier curve. The 30-day rates of major bleeding among patients receiving standard-dose clopidogrel ranged from 0.3% to 1.9% (Figure 1C).

Day 30 non-CABG (or non-procedure) major bleeding rates for standard-dose clopidogrel were similar in the TRITON-TIMI 38, PLATO, and CURRENT-OASIS 7 trials (0.9%, 1.0%, and 0.6%, respectively).

Relative risk of bleeding
The risk ratios of non-CABG (or non-procedure) major bleeding in PLATO and CURRENT-OASIS 7 was significantly higher with ticagrelor and double-dose clopidogrel vs. standard-dose clopidogrel (risk ratios 1.39 and 1.40, respectively) with no significant differences observed for the two treatments in any of the other trials (Figure 2).

Life-threatening (severe) bleeding
All trials reported severe or life-threatening bleeding although the definitions varied (Table 2). The absolute rates of severe or life-threatening bleeding in patients receiving standard-dose clopidogrel were highest in PLATO (5.8% vs. 0.9–2.2% for the other trials) (data not shown). The risk ratios of life-threatening bleeding were similar in the two placebo-controlled trials that reported this outcome (1.21, 95% CI: 0.95–1.56 for CURE; 1.07, 95% CI: 0.84–1.36 for COMMIT), without statistical evidence for heterogeneity (\( P = 0.47 \)). In contrast, there was significant heterogeneity among the three active-controlled trials (\( P = 0.05 \)). In the PLATO trial, ticagrelor compared with clopidogrel did not increase life-threatening bleeding whereas in the TRITON-TIMI 38 trial and the CURRENT-OASIS 7 trial both prasugrel and double-dose clopidogrel, respectively, increased life-threatening (severe) bleeding compared with standard-dose clopidogrel (Figure 2).

Discussion
Our results demonstrate substantial differences in the reported rates of major bleeding associated with standard-dose clopidogrel plus aspirin (75–325 mg) among P2Y<sub>12</sub> inhibitor trials in patients with ACS. Application of a standardized approach to the reporting of major bleeding by using the same definition of bleeding at a consistent time point virtually eliminated these differences and also altered the interpretation of the relative safety of new P2Y<sub>12</sub> inhibitors compared with standard-dose clopidogrel. For example, the primary trial reports, prasugrel but not ticagrelor increased major bleeding compared with standard-dose clopidogrel whereas our re-assessment using a standardized bleeding definition and excluding procedure-related events indicates that ticagrelor, but not prasugrel, increases non-CABG TIMI major bleeding.

Factors that appear to explain most of the variability in reported rates of major bleeding among the P2Y<sub>12</sub> inhibitor trials include: (i) the definition of major bleeding, (ii) the timing of reporting of the primary outcome of major bleeding, and (iii) rates of CABG surgery. The highest rate of major bleeding in ACS patients receiving standard-dose clopidogrel was reported in the PLATO trial, but differences in bleeding rates among the trials were markedly reduced when we applied the same definition of major bleeding (TIMI major bleeding) in all the trials, excluded CABG-related bleeding and examined 30-day bleeding rates. We were unable to fully explore the impact of differences in the timing of reporting of major bleeding because data for non-CABG TIMI major bleeding were not reported at the same time point in all of the trials.

Additional factors that might also contribute to the variability in the rates of major bleeding reported in ACS trials include differences in patient characteristics (e.g. age, female sex, and renal function), clinical presentation (non-ST elevation ACS vs. STEMI) pharmacological co-interventions (e.g. aspirin dose, intravenous glycoprotein IIb/IIIa inhibitors, and thrombolytic therapy), timing of the trials (late 1990s to late 2000s), and treatments for bleeding (e.g. rates of red cell transfusion). However, these factors appeared to be much less important than the definition and timing of reporting of bleeding and the proportion of patients undergoing revascularization procedures because the variability in the risk of major bleeding disappeared when we used the same definition and timing of reporting of bleeding.

Increasing awareness of the adverse consequences of bleeding in patients with ACS has focused attention on the safety of new antithrombotic treatments. The results of our critical review of bleeding rates in P2Y<sub>12</sub> inhibitor trials highlight the challenges of comparing bleeding rates across trials when different definitions and methods of reporting of bleeding are used. We attempted to adjust for these differences by focusing on non-CABG-related bleeding.
Rao and colleagues have proposed standardization of the reporting of key bleeding data elements in ACS trials, including the timing, site, severity, consequences and treatment of bleeding, and the relationship of bleeding to procedures.11 If adopted, this approach has the potential to simplify comparison of bleeding rates across trials although it does not preclude reporting of bleeding using the definition favoured by the investigators. An ideal bleeding definition will be sensitive to clinically important bleeding that occurs in this patient population and sufficiently specific to distinguish bleeding associated with the intervention under evaluation from background bleeding rates.

In conclusion, the results of our review suggest that uncritical comparison of the absolute rates and relative risks of major bleeding across ACS trials can bias interpretation of the safety of new P2Y12 inhibitors and of double-dose clopidogrel compared with standard-dose clopidogrel. Use of a standardized approach to the evaluation of bleeding outcomes virtually eliminates the differences in bleeding rates between P2Y12 inhibitor trials and facilitates more reliable comparisons of bleeding rates across trials.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References


Implications of variability in definition and reporting of major bleeding

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A 91-year-old immunocompetent man with severe aortic stenosis due to senile dystrophic calcification underwent transapical aortic valve implantation (TAVI-Edwards Sapien 23 mm). Major risk factors contraindicating surgical intervention were chronic kidney disease and pulmonary hypertension.

Immediate post-TAVI transoesophageal echocardiography showed no insufficiency and normal flow profile across the prosthesis. Postoperatively, the patient presented intermittent fever up to 38°C, and he required endotracheal intubation due to respiratory failure and septic shock and died during hospitalization 54 days after TAVI. White blood cell count was abnormal starting on the second post-operative day, with a peak of 3.7 × 10^9/L 3 days before death. C-reactive protein was constantly increased as well as erythrocyte sedimentation rate with a peak of 280 mg/L and of 102 mm/h, respectively. Microbiological investigation on bronchoalveolar lavage and blood cultures was positive for Candida albicans and the patient was treated intravenously with an anti-fungal drug, with blood culture negativization.

During the follow-up, transthoracic echocardiography documented a transvalvular aortic gradient of 20/10 mmHg (max/mean) with early mild paravalvular leak that disappeared thereafter.

At gross examination, a prosthetic valve stenosis was detected with large, polyposus friable vegetations that completely occupied and blocked a pericardial cusp (Panel A) and extended along the mitroaortic fibrous continuity (Panel B).

Histological study using several stains (Panels C, HE, and D, PAS; inset, Grocott) showed clusters of Candida type yeasts, hyphae, and pseudohyphae entrapped within a fibrin network with platelets, red cells, and leukocytes.

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