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CLINICAL RESEARCH

Bleeding complications with the P_2Y_{12} receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial

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Aims More intense platelet-directed therapy for acute coronary syndrome (ACS) may increase bleeding risk. The aim of the current analysis was to determine the rate, clinical impact, and predictors of major and fatal bleeding complications in the PLATO study.

Methods and results PLATO was a randomized, double-blind, active control international, phase 3 clinical trial in patients with acute ST elevation and non-ST-segment elevation ACS. A total of 18 624 patients were randomized to either ticagrelor, a non-thienopyridine, reversibly binding platelet $P2Y_{12}$ receptor antagonist, or clopidogrel in addition to aspirin. Patients randomized to ticagrelor and clopidogrel had similar rates of PLATO major bleeding (11.6 vs. 11.2%; $P = 0.43$), TIMI major bleeding (7.9 vs. 7.7%, $P = 0.56$) and GUSTO severe bleeding (2.9 vs. 3.1%, $P = 0.22$). Procedure-related bleeding rates were also similar. Non-CABG major bleeding (4.5 vs. 3.8%, $P = 0.02$) and non-procedure-related major bleeding (3.1 vs. 2.3%, $P = 0.05$) were more common in ticagrelor-treated patients, primarily after 30 days on treatment. Fatal bleeding and transfusion rates did not differ between groups. There were no significant interactions for major bleeding or combined minor plus major bleeding between treatment groups and age $\geq$75 years, weight $<$60 kg, region, chronic kidney disease, creatinine clearance $<$60 mL/min, aspirin dose $>$325 mg on the day of randomization, pre-randomization clopidogrel administration, or clopidogrel loading dose.

Conclusion Ticagrelor compared with clopidogrel was associated with similar total major bleeding but increased non-CABG and non-procedure-related major bleeding, primarily after 30 days on study drug treatment. Fatal bleeding was low and did not differ between groups.

Trial registration information: Clinicaltrials.gov identifier number: NCT00391872.

Keywords Acute coronary syndrome • Platelet inhibition • Platelet $P2Y_{12}$ receptor antagonist

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Introduction

Dual antiplatelet therapy is strongly recommended in the early management of patients experiencing an acute coronary syndrome (ACS) either with or without ST-segment elevation, but may also increase the risk of bleeding.[1–4] In the PLATelet inhibition and Outcomes (PLATO) trial, ticagrelor, a reversibly binding direct-acting and non-thienopyridine platelet $P2Y_{12}$-receptor antagonist, reduced the composite endpoint of death from vascular causes, myocardial infarction, or stroke compared with clopidogrel [hazard ratio, 0.84; 95% confidence interval (95% CI), 0.77–0.92; $P < 0.001$]. Pre-defined hierarchical testing of secondary endpoints, including death from vascular causes, was also lower with ticagrelor.[5] While no significant difference in the rate of PLATO, total major bleeding was observed between ticagrelor and clopidogrel treatment groups, patients receiving ticagrelor did experience a higher rate of bleeding not related to coronary artery bypass grafting (CABG).

Because clinicians caring for patients with ACS must fully understand the benefits and potential risks of treatments they prescribe, we conducted a comprehensive analysis of bleeding complications reported in the PLATO trial, with a specific emphasis on non-CABG-related bleeding and its overall incidence, severity, timing from initiation of study drug treatment, independent predictors, site(s) of involvement, and associated clinical outcomes, including death.

Methods

Design overview

PLATO was a multicentre, randomized, double-blind, double-dummy, event-driven trial of 18 624 patients admitted to the hospital with either ST-segment elevation or non-ST-segment elevation ACS.[5] The trial was approved by ethical review boards and followed the principles of the Declaration of Helsinki. All patients gave a written informed consent to participate in the study. The details of the study design have been published previously.[6]

Randomization and interventions

Patients were randomly assigned to receive either ticagrelor or clopidogrel. Ticagrelor was administered as an oral loading dose of 180 mg, followed by 90 mg twice daily. Patients randomized to clopidogrel received a 300 mg oral loading dose, followed by a maintenance dose of 75 mg daily. Those in whom an open-label loading dose of clopidogrel had been given, or who had been taking clopidogrel up to 5 days before study randomization, were continued on a 75 mg daily dose as study treatment and did not receive an additional loading dose.

Patients undergoing percutaneous coronary intervention (PCI) after randomization received, in a blinded fashion, in the clopidogrel arm an additional 300 mg of clopidogrel at the investigator's discretion or, in the ticagrelor arm, an additional 90 mg ticagrelor if more than 24 h after the initial loading dose had elapsed. All patients received aspirin at a dose of 75–100 mg daily. For those who had not previously taken aspirin, 160–325 mg was recommended as an initial loading dose (although up to 500 mg was permitted). After stent placement, aspirin up to 325 mg daily was allowed for up to 6 months. Glycoprotein IIb/IIIa receptor inhibitors and approved parenteral anticoagulants were allowed, but oral anticoagulants were not.

For secondary analyses, clopidogrel loading dose was computed as open-label clopidogrel received before randomization plus clopidogrel (or placebo) during the first 24 h after the first dose of the investigational product.[7]

Patients were analysed according to the treatment to which they were randomized but only patients receiving the study drug were included (safety population).

Main outcome measures

The primary safety endpoint was PLATO total major bleeding. Secondary safety endpoints were the categories of major bleeding and minor bleeding combined, as well as TIMI (Thrombolysis In Myocardial Infarction) and GUSTO (Global Use of Streptokinase and Tissue plasminogen activator to Open occluded coronary arteries) bleeding scales and transfusion of blood products (packed red blood cells or whole blood). Bleeding events were mapped onto the TIMI and GUSTO bleeding scales by applying an algorithm. The PLATO definitions were chosen as an inclusive and clinically relevant measure suitable for assessing bleeding events in the context of surgical (or other procedures) and medical treatment. They also characterize bleeding in both the acute and chronic settings.

PLATO major fatal/life-threatening bleeding was defined as fatal bleeding, intrapericardial bleeding with cardiac tamponade, intracranial bleeding, severe hypotension, or hypovolemic shock due to bleeding and requiring either vasopressors or surgical intervention, a decline in haemoglobin of 5.0 g/dL or more after adjusting for red blood cell transfusions, or the need for transfusion of four or more units of packed red blood cells. Other major bleeding included an event that led to clinically significant disability or bleeding with an associated drop in haemoglobin of at least 3.0 g/dL but <5.0 g/dL or requiring a 2–3 unit red blood cell transfusion. We defined minor bleeding as any bleeding event requiring medical intervention but not meeting the criteria for major bleeding. Bleeding not associated with a procedure was categorized as 'spontaneous'.

TIMI major bleeding was defined as intracranial bleed or intrapericardial bleed with cardiac tamponade or a decline of 5.0 g/dL or more in haemoglobin after adjusting for red blood cell transfusions. Significant disabling was defined as any of the following conditions: the event increases the subject's length of hospital stay; the event necessitates a transfer into an ICU (intensive care unit); or the event causes a change in the subject's ability to perform their activities of daily living for more than a week. GUSTO Severe Bleeding definition included fatal and intracranial bleeds, intrapericardial bleeds with cardiac tamponade, hypovolemic shock, or severe hypotension due to bleeding and requiring vasopressors or surgery and bleeding that caused haemodynamic compromise or required a surgical intervention.

All bleeding events were analysed if they occurred after the study drug was started and up to 7 days after stopping the study drug.

An independent Clinical Events Committee (ICAC) adjudicated all PLATO major and minor bleeding events. Minimal bleeding events were not adjudicated nor were they included in the present analysis.

Statistical analysis

Baseline characteristics including demographics, medical history, clinical features, medications at randomization, and procedures during the index hospitalization were summarized with frequencies and percentages for categorical variables and medians and quartiles for continuous variables. No formal statistical tests were performed for baseline characteristics since no inference is being made.

ICAC-adjudicated bleeds were presented as the number of events and Kaplan–Meier rates from baseline to 360 days. All bleeding

events were tabulated separately for each study treatment by adjudicated category and by associated procedure.

Hazard ratios and 95% CI were derived from Cox proportional hazards models. The proportional hazard assumption was assessed by extending the Cox model with a time-dependent variable formed as the product of the time to the event and the treatment variable and testing the statistical significance of its associated coefficient. Since a departure from proportionality was only observed in non-CABG-related procedural major or minor bleeding and was not serious, no additional analyses to account for non-proportional hazards were performed.

Treatment differences for subgroup analyses were performed with a test of the interaction of that subgroup with treatment in a Cox proportional hazards model which included treatment, the subgroup, and the interaction of the two. Landmark analyses were used to examine the treatment differences during the more acute (0–30 days after randomization) vs. the later period (30–360 days) of the study. For the first period, only bleeds within the first 30 days were included. For the latter period, all patients who survived to 30 days were included in the analysis and the treatment effect was estimated unadjusted and adjusting for bleeding within 30 days of randomization, and for PCI within 30 days of randomization. Because a patient may have more than one bleeding event, the analysis after 30 days also included patients who experienced bleeding during the first 30 days.

Multivariate models for non-procedure-related major bleeding events, PCI-related major bleeding, non-CABG-related major bleeding, and major or minor bleeding were fitted using Cox proportional hazards models. For PCI-related major bleeding, only patients with a PCI performed in the first 48 h were included in the analysis. All baseline characteristics listed in *Table 1* were considered for inclusion in the models. The *P*-value threshold was set to 0.05.

Models were selected using a backward selection method with two-sided significance level to stay in the model set to 0.05. Candidate variables included all variables listed in *Table 1*, except randomized treatment. After the model was selected, randomized treatment was added to the model. Forward and stepwise selection methods produced the same models. Asimilar strategy was used for major bleeding and major or minor bleeding for the first 30 days after the start of study drug and after the first 30 days since the start of study drug. Confidence intervals for proportions were derived using Wilson's method.[8]

All analyses were performed using SAS® (version 9.2, Cary, NC, USA).

The role of the funding source

This work was supported by AstraZeneca who funded the PLATO trial. The academic members of the executive committee designed the PLATO trial in collaboration with representatives from the sponsor. AstraZeneca R&D coordinated data management. The statistical analyses for this manuscript were performed by the Duke Clinical Research Institute (DCRI) and all co-authors had full access to the data. Support for the analysis and interpretation of results and preparation of the manuscript was provided through funds from the sponsor to Uppsala Clinical Research Center and DCRI as part of the Clinical Study Agreement. The decision to submit the final version of the manuscript was the responsibility of the Executive Committee and all authors have read and approved the final version of the manuscript. The complete list of PLATO investigators and main study committees has been published previously.[6]

Results

Study participants

A total of 18 624 patients from 43 countries were randomized from October 2006 through July 2008. The study period ended in February 2009. The safety population included 18 421 patients—9235 and 9186 patients received ticagrelor and clopidogrel study drug, respectively (*Figure 1*). The two treatment groups were well balanced for all baseline characteristics, non-study antithrombotic agents, prior procedures, and procedures during the index hospitalization. A total of 8988 patients (32.5%) had received aspirin before the index event and randomization. Aspirin doses on the day of randomization ranged from 75 to >325 mg and were similar between the treatment groups. Open-label clopidogrel was given within 24 h of randomization to 47% of patients in both treatment groups. In addition, ~21% of patients in both treatments arms received a clopidogrel loading dose of ≥600 mg. The median duration of study drug exposure was 277 days (interquartile range, 179–365).

Bleeding complications

Study drug discontinuation

Patients who discontinued study medication because of non-procedural bleeding (2.3% ticagrelor; 1.0% clopidogrel) had gastrointestinal (GI) bleeding (0.7% ticagrelor; 0.3% clopidogrel), epistaxis (0.4% ticagrelor; 0.1% clopidogrel), contusions and cutaneous bleeds (each 0.2% ticagrelor; each 0.1% clopidogrel), and haematuria (0.1% ticagrelor and 0.1% clopidogrel). A total of 224 (2.4%) patients in the ticagrelor group permanently discontinued study medication because of bleeding, whereas 95 (1.0%) patients in the clopidogrel group permanently discontinued treatment for this specific reason ($P < 0.001$).

Incidence and severity

Baseline characteristics according to the presence or the absence of non-CABG-related major bleeding are summarized in *Table 1*. Patients treated with ticagrelor and those receiving clopidogrel had similar rates of PLATO major bleeding (11.6 and 11.2%, respectively; $P = 0.43$) (*Table 2*). Procedure-related, coronary procedure-related, and non-coronary procedure-related major bleeding were similar between the groups ($P = 0.62$, 0.73, and 0.22, respectively). Non-CABG-related major bleeding according to the study criteria occurred with greater frequency in ticagrelor-treated patients ($P = 0.03$), as did non-procedure-related major bleeding ($P = 0.01$), PLATO major or minor bleeding ($P = 0.01$), and GUSTO mild bleeding ($P = 0.008$). An excess of 21 ticagrelor patients (610 ticagrelor and 589 clopidogrel) received non-CABG-related transfusions, whereas an excess of 18 clopidogrel patients (209 ticagrelor and 227 clopidogrel) received transfusion within 7 days of undergoing CABG.

The primary causes and requirements met for being classified as a non-CABG-related major bleeding among patients randomized to ticagrelor or clopidogrel included: intracranial (26 vs. 15), intrapericardial with cardiac tamponade (11 vs. 13), hypovolemic shock, or severe hypotension due to bleeding and requiring vasopressors or surgery (23 vs. 19), clinically overt or apparent bleeding

Table 1 Baseline characteristics of the patients according to non-CABG-related major bleeding

	Non-CABG-related major bleeding	
	No (*n* = 17 753), *n* (%)	**Yes (*n* = 668), *n* (%)**
Demographics		
Age[a]	62 (54–70)	69 (60–76)
Age (>75 years)	2663 (15.0)	183 (27.4)
Gender: female	4971 (28.0)	266 (39.8)
Body weight[a]	80 (70–90)	75 (65–87)
Medical history		
Diabetes	4414 (24.9)	207 (31.0)
Prior myocardial infarction	3638 (20.5)	146 (21.9)
Prior non-haemorrhagic stroke	668 (3.8)	42 (6.3)
Prior PCI	2359 (13.3)	97 (14.5)
Prior CABG	1044 (5.9)	48 (7.2)
Congestive heart failure	983 (5.5)	58 (8.7)
Clinical features		
Heart rate (b.p.m.)[a]	73 (64–84)	75 (65–88)
Systolic blood pressure (mmHg)[a]	133 (120–150)	133 (120–150)
Diastolic blood pressure (mmHg)[a]	80 (70–90)	80 (70–87)
Creatinine (μmol/L)[a]	80 (71–97)	88 (71–106)
Creatinine clearance (mL/min)[a]	82.3 (66.6–97.7)	73.6 (56.0–90.0)
Type of ACS: STEMI (final diagnosis)	6748 (38.1)	238 (35.6)
Intended invasive strategy	12 729 (71.7)	507 (75.9)
Medications at randomization		
ASA on randomization day		
No	1101 (6.2)	55 (8.2)
75–162 mg/day	8444 (47.6)	306 (45.8)
163–325 mg/day	5667 (31.9)	208 (31.1)
>325 mg/day	2531 (14.3)	99 (14.8)
Open label clopidogrel pre-Rand		
No clopidogrel	10 432 (58.8)	374 (56.0)
1–600 mg	5154 (29.0)	214 (32.0)
≥600 mg	2165 (12.2)	80 (12.0)
Clopidogrel loading dose		
<600 mg	14 067 (79.3)	529 (79.2)
600 mg	3684 (20.7)	139 (20.8)
Co-interventions[b]		
Aspirin	17 262 (97.3)	644 (96.4)
Aspirin ≥300 mg/day[c]	8585 (48.4)	327 (49.0)
GPIIb/IIIa inhibitor	4783 (26.9)	220 (32.9)
Unfractionated heparin	10 247 (57.7)	414 (62.0)
Low-molecular-weight heparin	9211 (51.9)	370 (55.4)
Bivalirudin	354 (2.0)	17 (2.5)
Fondaparinux	484 (2.7)	21 (3.1)
Fibrinolytic therapy[d]	43 (0.2)	5 (0.8)
Procedures during index hospitalization		
Angiography	14 439 (81.3)	590 (88.3)
PCI	10 893 (61.4)	439 (65.7)
CABG	879 (5.0)	46 (6.9)

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome.
[a]Median (1st–3rd quartile).
[b]From index event to end of index hospitalization.
[c]Patient reported 300 mg/day at least once since index event to end of index hospitalization.
[d]Fibrinolytic therapy was one of the exclusion criteria for PLATO.

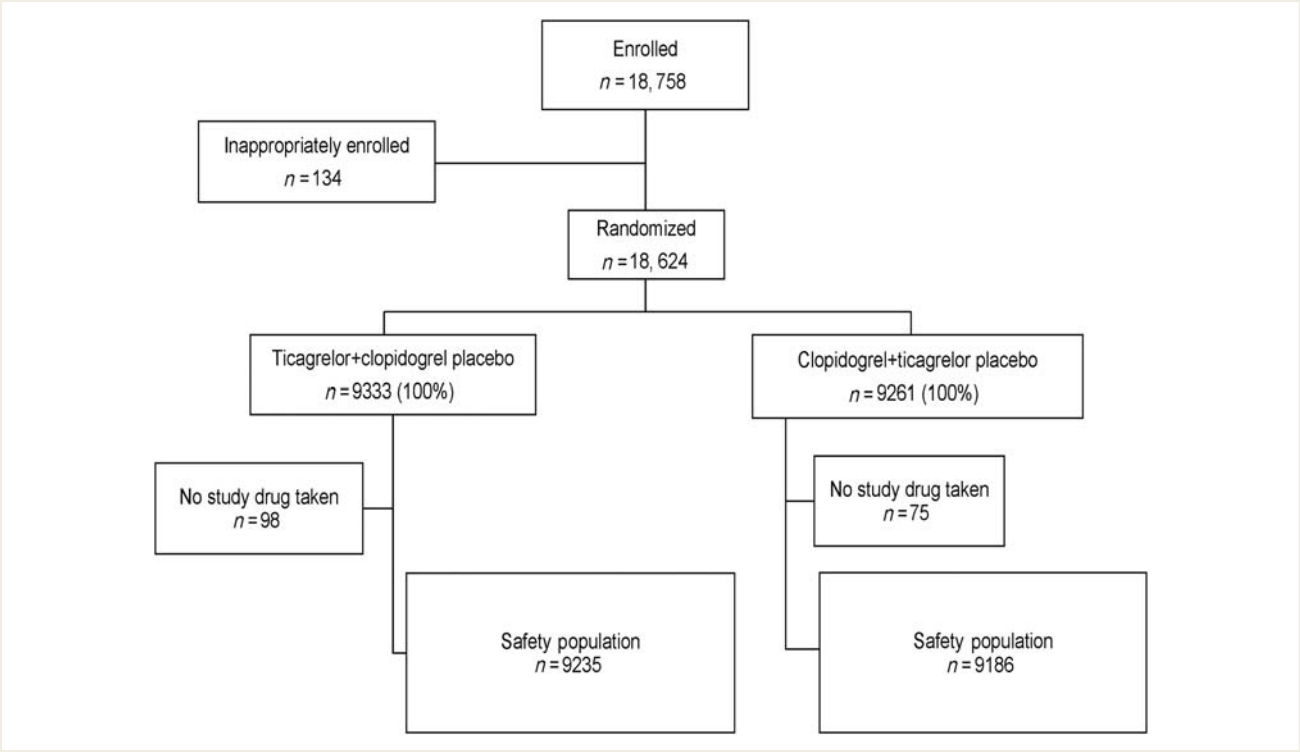


Figure 1 Consort diagram of patients in the PLATO trial and those included in the safety population.

associated with a decrease in haemoglobin of >50 g/L (29 vs. 38), transfusion of four or more units of packed red blood cells (39 vs. 39), disabling bleeding (40 vs. 22), clinically overt or apparent bleeding with a decrease in haemoglobin >30–50 g/L (120 vs. 85) and bleeding requiring local pressure or packing or intravenous fluid for volume expansion (38 vs. 26). Transfusion of either packed red blood cells or whole blood for all clinical contexts did not differ between the treatment groups (8.5 vs. 8.3%, $P = 0.81$).

Fatal bleeding was infrequent in PLATO and the rates did not differ between the treatment groups (0.3 vs. 0.3%, $P = 0.66$). The primary sites of fatal bleeding are summarized in *Table 3*. There was a numerically greater number of fatal intracranial bleeds with ticagrelor (11; 55%, CI 34.2–74.2 vs. 2; 8.7%, CI 2.4–26.8; $P = 0.02$) and a greater number of fatal GI bleeds with clopidogrel (0; 0.0%, CI 0.0–16.1 vs. 5; 21.7%, CI 9.7–41.9; $P = 0.16$).

Patient subgroups

There were no significant interactions for non-CABG-related major bleeding (*Figure 2*) or non-CABG major or minor bleeding (*Figure 3*) between treatment groups and age, weight, region, chronic kidney disease, creatinine clearance, or concomitant medications. Similarly, there were no significant interactions for treatment and aspirin dose on the day of randomization, pre-randomization clopidogrel administration, or clopidogrel loading dose.

Patient-related clinical and treatment variables associated with non-CABG-related major bleeding were evaluated to determine a potential differential effect of ticagrelor when compared with clopidogrel-treated patients. The only statistically significant interaction ($P = 0.017$) was between treatment and the use of GP IIb/IIIa antagonists on the day of randomization. In the clopidogrel treatment group, patients receiving GP IIb/IIIa antagonists were at significantly higher risk of non-CABG-related major bleeding (HR 2.02; 95% CI 1.53–2.67), while in the ticagrelor group there was a numerical increase in the risk of this type of bleeding in patients receiving GP IIb/IIIa antagonists (HR 1.26; 95% CI 0.96–1.66).

Location of non-procedure-related major bleeding

The primary location of all non-procedure-related bleeding is highlighted in *Table 4*. In decreasing order of frequency, the most common locations were: GI (the primary site in one-third of all events), nose, urinary tract, subcutaneous/dermal, and intracranial. These five sites collectively represented three-quarters of all non-procedure-related bleeding events.

Intracranial bleeding and haemorrhagic stroke

Intracranial bleeding was uncommon in PLATO, being reported in 26 (0.34%) of ticagrelor-treated patients and 15 (0.19%) of clopidogrel-treated patients ($P = 0.08$). All haemorrhagic strokes were counted not only as bleeding events but also in the primary efficacy endpoint. There were 11 (0.21%) and 2 (0.03%) fatal intracranial events, respectively ($P = 0.02$). Haemorrhagic stroke was reported in 22 (0.26%) of ticagrelor-treated patients

Table 2 Bleeding events according to PLATO, TIMI, and GUSTO criteria

	Ticagrelor ($n = 9235$), *n* (%)	Clopidogrel ($n = 9186$), *n* (%)	Hazard ratio (95% CI)	*P*-value
PLATO major bleeding				
Total	961 (11.6)	929 (11.2)	1.037 (0.947–1.135)	0.43
Non-procedure-related (spontaneous)	235 (3.1)	180 (2.3)	1.314 (1.082–1.596)	0.01
Procedure related	756 (9.0)	775 (9.3)	0.975 (0.882–1.078)	0.62
Coronary procedure related	732 (8.7)	745 (8.9)	0.982 (0.887–1.088)	0.73
Non-coronary procedure related	27 (0.3)	37 (0.5)	0.733 (0.446–1.204)	0.22
Total non-CABG related	362 (4.5)	306 (3.8)	1.188 (1.020–1.384)	0.03
Non-CABG-related procedural	143 (1.7)	133 (1.6)	1.075 (0.849–1.361)	0.55
CABG related	619 (7.4)	654 (7.9)	0.945 (0.847–1.055)	0.31
PCI related	93 (1.0)	68 (0.8)	1.364 (0.997–1.864)	0.05
Coronary angiography related	23 (0.3)	28 (0.3)	0.819 (0.472–1.422)	0.48
PLATO major or minor bleeding				
Total	1339 (16.1)	1215 (14.6)	1.110 (1.027–1.200)	0.01
Non-procedure related (spontaneous)	457 (5.9)	332 (4.3)	1.390 (1.207–1.601)	<0.0001
Procedure related	938 (11.1)	936 (11.2)	1.004 (0.917–1.099)	0.93
Coronary procedure related	895 (10.6)	887 (10.5)	1.011 (0.921–1.109)	0.82
Non-coronary procedure related	53 (0.7)	66 (0.9)	0.806 (0.561–1.157)	0.24
Non-CABG related	713 (8.7)	567 (7.0)	1.269 (1.137–1.417)	<0.0001
Non-CABG related procedural	294 (3.3)	256 (3.0)	1.149 (0.972–1.359)	0.10
CABG-related	666 (8.0)	712 (8.6)	0.933 (0.840–1.037)	0.20
PCI-related	193 (2.1)	138 (1.6)	1.397 (1.123–1.739)	0.01
Coronary angiography related	51 (0.6)	56 (0.6)	0.907 (0.621–1.326)	0.61
TIMI bleeding				
Major	657 (7.9)	638 (7.7)	1.032 (0.926–1.151)	0.57
Major non-CABG related	221 (2.8)	177 (2.2)	1.254 (1.029–1.529)	0.02
Major CABG related	446 (5.3)	476 (5.8)	0.937 (0.824–1.066)	0.32
Major or minor	946 (11.4)	906 (10.9)	1.047 (0.955–1.146)	0.33
Minor	314 (3.9)	288 (3.5)	1.092 (0.931–1.282)	0.28
GUSTO bleeding				
Severe	253 (2.9)	264 (3.1)	0.923 (0.773–1.102)	0.37
Moderate	388 (4.6)	338 (4.0)	1.145 (0.987–1.329)	0.07
Mild	929 (10.6)	820 (9.5)	1.139 (1.034–1.255)	0.01
Transfusion				
PRBC or whole blood	705 (8.5)	697 (8.3)	1.013 (0.912–1.124)	0.81

'%' represents the Kaplan–Meier estimate at 360 days.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PRBC, packed red blood cells; *n*, number of patient events during the study.

and 13 (0.15%) of clopidogrel-treated patients ($P = 0.13$). Further analysis of cases failed to identify any subgroup at increased risk for intracranial haemorrhage, with the exception of a prior intracranial haemorrhage which was associated with increased risk in both treatment groups. Although a prior history of intracranial haemorrhage was an exclusion criterion for PLATO, 15 ticagrelor patients and 13 clopidogrel patients with prior intracranial haemorrhage were randomized and received the study drug. Of these, 1 and 2 patients, respectively, experienced an intracranial haemorrhage. Of the 564 and 588 patients with a past history of either transient ischaemic attack or non-haemorrhagic stroke in ticagrelor and clopidogrel-treated patients, respectively, only four patients in each group experienced a non-fatal intracranial haemorrhage.

Timing of major bleeding and influence of aspirin dose

The relationship between study drug treatment and the occurrence of either non-CABG-related major bleeding or non-procedure-related major bleeding is summarized in *Table 5*. The rates of major bleeding during the first 30 days did not differ between the treatment groups. In contrast, ticagrelor-treated patients were more likely to experience non-CABG or non-procedure-related major bleeding after 30 days on study

Table 3 Fatal bleeding: sites and management

	Ticagrelor	Clopidogrel
Total	20	23
Primary location of bleed[a]		
Intracranial	11	2
Pericardial	2	4
Gastrointestinal	0	5
Cardiac cath/percutaneous coronary intervention access site	2	2
Subcutaneous/dermal	0	2
Retroperitoneal	0	2
Haemoptysis	1	0
Other bleeding site[b]	5	7
Not reported	0	2
Bleeding characteristics[c]		
Intracranial	11	2
Intrapericardial bleed with cardiac tamponade	1	3
Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery	4	5
Clinically overt or apparent bleeding associated with a decrease in haemoglobin of >50 g/L	2	4
Clinically overt or apparent bleeding associated with a decrease in haemoglobin of >30–50 g/L	2	4
Transfusion of 4 or more units	1	2
Transfusion of 2–3 units	2	4
Transfusion of ≤1 units	0	1
Other reason for bleeding	0	1

[a]In three patients, multiple primary sites were reported: in two patients, two primary sites were reported (one in ticagrelor arm and one in clopidogrel arm). For one patient in clopidogrel arm, three primary sites were reported.
[b]In ticagrelor group, the following bleeding sites were reported: aorta, abdominal, oropharyngeal, right lung, and sternotomy. In the clopidogrel group, the following bleeding sites were reported: abdominal aneurysm, CABG access site, bleeding from tissues of the surgical site, chest drains, lung, and sternotomy wounds.
[c]Multiple sites were reported for some patients.

drug—even when adjusting for repeated bleeding, bleeding within the first 30 days, and PCI within the first 30 days of drug administration. An aspirin dose ≥300 mg daily was associated with a greater risk for non-CABG-related major bleeding than lower doses among both ticagrelor- and clopidogrel-treated patients (data not shown).

Models were constructed for non-CABG-related major bleeding and major or minor bleeding for the first 30 days and beyond 30 days on study drug. After adjustment for laboratory values, baseline demographics, concomitant treatments, past medical history, and clinical variables, non-CABG-related major bleeding in ticagrelor-treated patients in the first 30 days of treatment did not achieve statistical significance for an increased risk (2.45 vs. 2.00%; HR 1.23; 95% CI 0.98–1.54; $P = 0.073$). After 30 days, ticagrelor increased the risk of non-CABG-related major bleeding by 45% relative to clopidogrel (2.29 vs. 1.59%; HR 1.45; 95% CI 1.09–1.92; $P = 0.011$). Ticagrelor was associated with increased non-CABG-related major or minor bleeding during both the first 30 days (5.11 vs. 4.02%; HR 1.28; 95% CI 1.10–1.501; $P = 0.002$) and after 30 days of study treatment (3.98 vs. 2.97%; HR 1.35; 95% CI 1.09–1.67; $P = 0.006$).

Net clinical benefit, defined as the composite of cardiovascular death, MI (myocardial infarction), stroke, and major bleeding (CABG or non-CABG related) was greater for ticagrelor compared with clopidogrel during the conduct of the study. The greatest relative difference was observed after 30 days of study treatment (7.86 vs. 8.97%; HR 0.87; 95% CI 0.77–0.98; $P = 0.026$). The difference between the treatment groups persisted after adjustment for patient-related, clinical, and laboratory variables, including region, age, final diagnosis, history of TIA (transient ischaemic attack) or stroke, aspirin on the day of randomization, creatinine clearance, baseline haemoglobin, and Killip classification (data not shown).

Independent predictors of major bleeding

Increasing age (HR 1.44, 95% CI 1.077–1.215 for a 5-year increase) as well as decreasing creatinine clearance (HR 0.899, 95% CI: 0.841–0.961 for a 5 mL/min increase in patients with creatinine clearance under 60 mL/min and HR 0.965, 95% CI 0.933–0.999 for a 5 mL/min increase in patients with creatinine clearance of 60 mL/min or more) and haemoglobin (HR 0.789, 95% CI 0.731–0.851 for a 10 g/L increase in patients with haemoglobin under 150 g/L), female sex (HR 0.765, 95% CI 0.587–0.996), and treatment with ticagrelor (HR 1.460, 95% CI 1.170–1.823) were associated with higher risks of non-procedure-related major bleeding. Weight <60 kg, race, and prior TIA or ischaemic stroke were not associated with this type of bleeding. Age (HR 1.272, 95% CI 1.140–1.420 for a 5-year increase), female sex (HR 2.245, 95% CI 1.416–3.559) and weight (HR 0.898, 95% CI 0.818–0.986 for a 5 kg increase in patients with weight of 60 kg or more) were each associated with PCI-related major bleeding. Ticagrelor was not independently associated with this type of bleeding.

Applying the CRUSADE bleeding model to the PLATO population of patients with non-ST-segment elevation, MI revealed a trend towards increased non-CABG-related major bleeding in-hospital, at 30 days, and at 1 year with an increasing risk score.[9] Patients with a very low risk score (≤20) ($n = 2797$) experienced cumulative non-CABG-related major bleeding rates of 0.5, 1.0, and 2.7% in-hospital, at 30 days, and at 1 year, respectively, while those with very high risk scores (>50) ($n = 356$) had rates of 3.7, 6.8, and 9.7%, respectively. There were no significant CRUSADE risk score by treatment interactions.

Discussion

In the PLATO study, major non-CABG-related bleeding was more common in patients receiving ticagrelor compared with those given clopidogrel—primarily after 30 days on study drug. Increasing age, decreasing creatinine clearance, low admission haemoglobin, female sex, prior GI bleeding, GP IIb/IIIa inhibitor use and

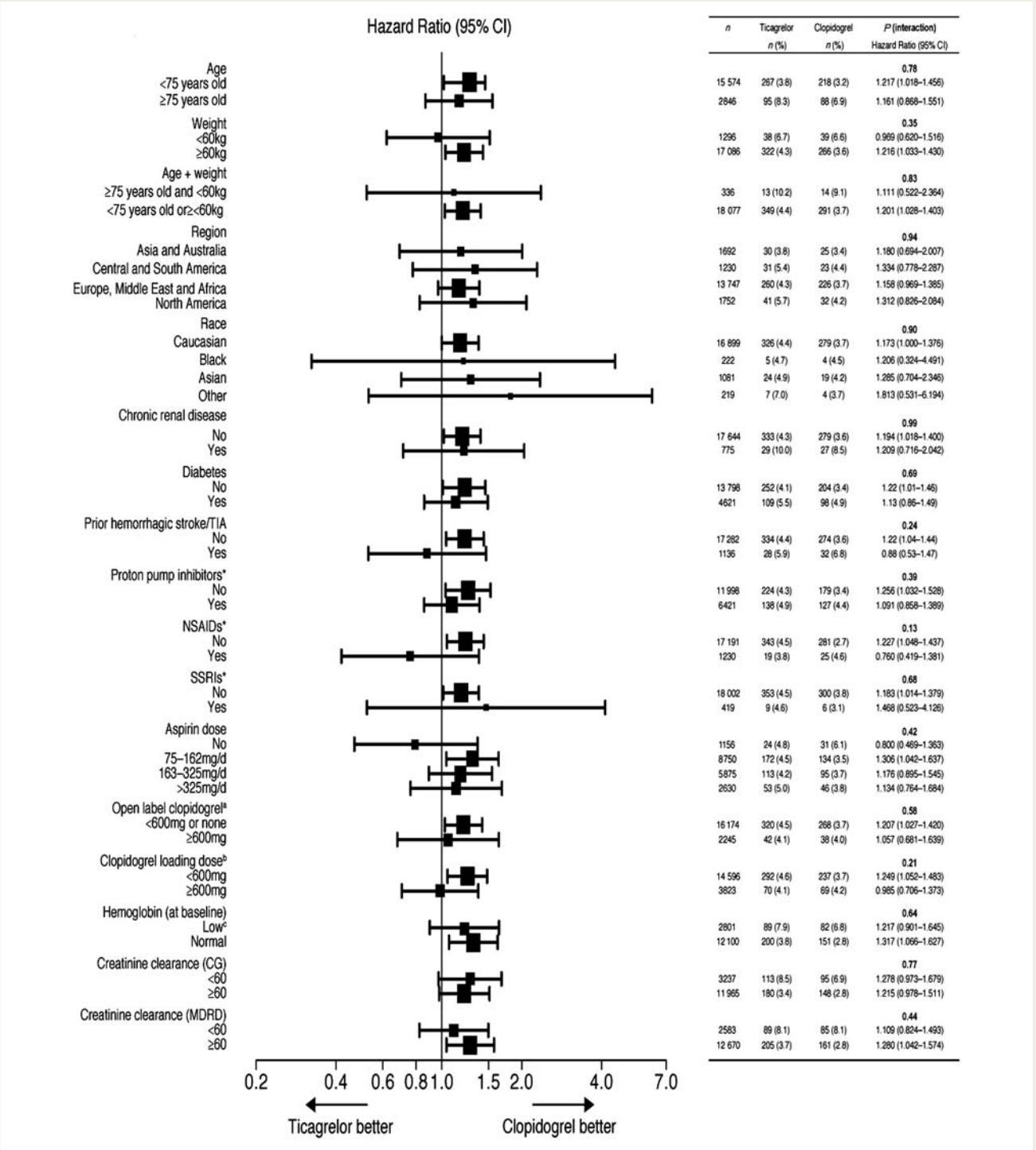
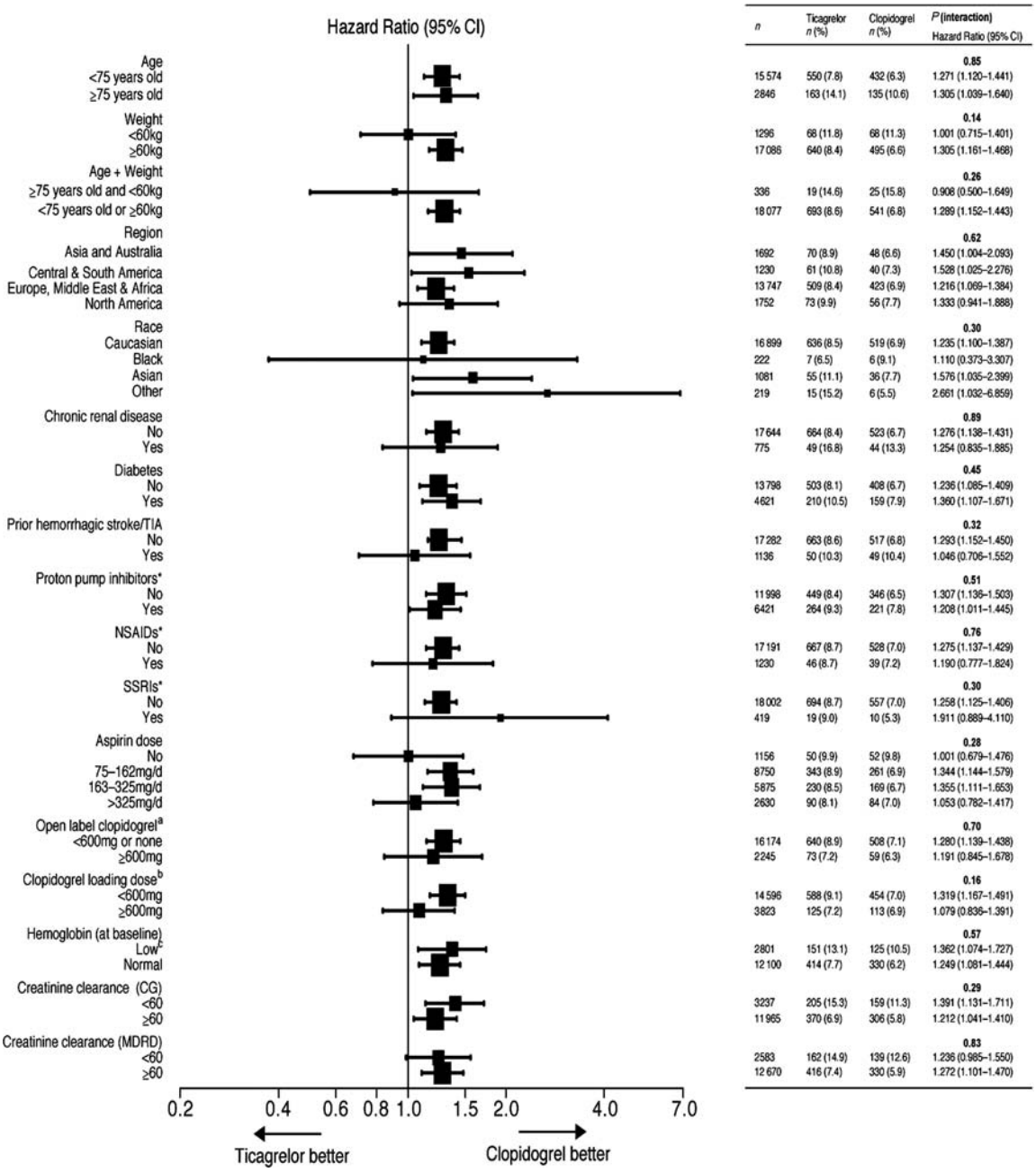


Figure 2 Forest plot for non-CABG-related major bleeding.

randomization to ticagrelor were independently associated with non-CABG-related major bleeding. There were no significant interactions for non-CABG-related major bleeding between the treatment groups and age ≥75 years, weight <60 kg, chronic kidney disease, creatinine clearance <60 mL/min, aspirin dose >325 mg at randomization or during study treatment or pre-randomization clopidogrel loading dose. Similarly, an interaction for region was not observed. Fatal bleeding events were uncommon in the PLATO study and did not differ between the treatment groups. Net clinical benefit, adjusted for patient-related, clinical, and laboratory variables, including region, age, final diagnosis, history of TIA or stroke, aspirin on the day of randomization, creatinine clearance, baseline haemoglobin and Killip classification, favoured ticagrelor throughout the study, particularly after 30 days on treatment.



n	Ticagrelor n (%)	Clopidogrel n (%)	P (interaction) Hazard Ratio (95% CI)
			0.85
15 574	550 (7.8)	432 (6.3)	1.271 (1.120–1.441)
2846	163 (14.1)	135 (10.6)	1.305 (1.039–1.640)
			0.14
1296	68 (11.8)	68 (11.3)	1.001 (0.715–1.401)
17 086	640 (8.4)	495 (6.6)	1.305 (1.161–1.468)
			0.26
336	19 (14.6)	25 (15.8)	0.908 (0.500–1.649)
18 077	693 (8.6)	541 (6.8)	1.289 (1.152–1.443)
			0.62
1692	70 (8.9)	48 (6.6)	1.450 (1.004–2.093)
1230	61 (10.8)	40 (7.3)	1.528 (1.025–2.276)
13 747	509 (8.4)	423 (6.9)	1.216 (1.069–1.384)
1752	73 (9.9)	56 (7.7)	1.333 (0.941–1.888)
			0.30
16 899	636 (8.5)	519 (6.9)	1.235 (1.100–1.387)
222	7 (6.5)	6 (9.1)	1.110 (0.373–3.307)
1081	55 (11.1)	36 (7.7)	1.576 (1.035–2.399)
219	15 (15.2)	6 (5.5)	2.661 (1.032–6.859)
			0.89
17 644	664 (8.4)	523 (6.7)	1.276 (1.138–1.431)
775	49 (16.8)	44 (13.3)	1.254 (0.835–1.885)
			0.45
13 798	503 (8.1)	408 (6.7)	1.236 (1.085–1.409)
4621	210 (10.5)	159 (7.9)	1.360 (1.107–1.671)
			0.32
17 282	663 (8.6)	517 (6.8)	1.293 (1.152–1.450)
1136	50 (10.3)	49 (10.4)	1.046 (0.706–1.552)
			0.51
11 998	449 (8.4)	346 (6.5)	1.307 (1.136–1.503)
6421	264 (9.3)	221 (7.8)	1.208 (1.011–1.445)
			0.76
17 191	667 (8.7)	528 (7.0)	1.275 (1.137–1.429)
1230	46 (8.7)	39 (7.2)	1.190 (0.777–1.824)
			0.30
18 002	694 (8.7)	557 (7.0)	1.258 (1.125–1.406)
419	19 (9.0)	10 (5.3)	1.911 (0.889–4.110)
			0.28
1156	50 (9.9)	52 (9.8)	1.001 (0.679–1.476)
8750	343 (8.9)	261 (6.9)	1.344 (1.144–1.579)
5875	230 (8.5)	169 (6.7)	1.355 (1.111–1.653)
2630	90 (8.1)	84 (7.0)	1.053 (0.782–1.417)
			0.70
16 174	640 (8.9)	508 (7.1)	1.280 (1.139–1.438)
2245	73 (7.2)	59 (6.3)	1.191 (0.845–1.678)
			0.16
14 596	588 (9.1)	454 (7.0)	1.319 (1.167–1.491)
3823	125 (7.2)	113 (6.9)	1.079 (0.836–1.391)
			0.57
2801	151 (13.1)	125 (10.5)	1.362 (1.074–1.727)
12 100	414 (7.7)	330 (6.2)	1.249 (1.081–1.444)
			0.29
3237	205 (15.3)	159 (11.3)	1.391 (1.131–1.711)
11 965	370 (6.9)	306 (5.8)	1.212 (1.041–1.410)
			0.83
2583	162 (14.9)	139 (12.6)	1.236 (0.985–1.550)
12 670	416 (7.4)	330 (5.9)	1.272 (1.101–1.470)

Figure 3 Forest plot for non-CABG-related major or minor bleeding.

Intensity of platelet inhibition and clinical outcomes

Platelet $P2Y_{12}$ receptor inhibition with ticagrelor occurs more rapidly than with clopidogrel and achieves a higher degree of adenosine diphosphate (ADP)-mediated inhibition of platelet aggregation as well.[10] Differences in the degree of platelet inhibition between drugs persist during the maintenance phase of daily treatment.[11] At 24 h after drug cessation, mean inhibition of platelet aggregation is 58% for ticagrelor and 52% for clopidogrel, and by Day 3 after cessation of ticagrelor the degree of platelet inhibition is comparable with that of clopidogrel at Day 5.

Several different scales provide a general categorization of bleeding severity with antiplatelet agents. Our analysis determined bleeding complications using three different scales, according to the PLATO, TIMI, and GUSTO-based definitions. The PLATO primary bleeding outcomes definition, evolved from those employed in previous trials of clopidogrel in ACS, capture both in-hospital events, where changes in haemoglobin concentration are documented, and out-of-hospital events. As such, they match well the treatment period of up to 12 months in the PLATO trial. Similarly, the primary bleeding outcome for PLATO comprised both CABG-related and non-CABG-related bleeding.

More than 1 in 10 ACS patients underwent CABG during the study period. A comprehensive analysis of these patients has been reported previously.[12] By not excluding CABG-related bleeding, PLATO total major bleeding includes ACS patients experiencing the intravascular volume and haemoglobin concentration changes that accompany CABG and may also impact their outcome. The present analysis also considered the highly relevant clinical outcome of non-CABG-related bleeding.

Table 4 Non-procedure-related bleeding according to primary location

	Ticagrelor (n = 9235)	Clopidogrel (n = 9186)
Any spontaneous bleeding (major)		
Patients	235	180
Events	664	483
Primary location of bleeding	664 (100.0)	483 (100.0)
Gastrointestinal	209 (31.5)	178 (36.9)
Epistaxis	133 (20.0)	70 (14.5)
Urinary	58 (8.7)	54 (11.2)
Subcutaneous/dermal	64 (9.6)	44 (9.1)
Intracranial	36 (5.4)	18 (3.7)
Pericardial	15 (2.3)	15 (3.1)
Haemoptysis	16 (2.4)	11 (2.3)
Intraocular	3 (0.5)	4 (0.8)
Retroperitoneal	4 (0.6)	3 (0.6)
Intra-articular	2 (0.3)	1 (0.2)
Cardiac cath/PCI access site	2 (0.3)	0 (0.0)
Other bleeding site	122 (18.4)	85 (17.6)

PCI, percutaneous coronary intervention; Cath, catheterization.

A majority of non-coronary procedures in PLATO associated with bleeding were GI in nature, including upper endoscopy and colonoscopy with or without biopsy and polypectomy. While a dedicated study of bridging therapy with ticagrelor would be required to define its utility and safety in this setting, one could broadly speculate that peri-procedural management of antiplatelet therapy may be less complicated with a drug displaying rapid onset and reversible pharmacodynamic characteristics. The time frame of study drug cessation prior to performing procedures in the PLATO trial varied widely. While the basis for a relatively greater proportion of GI bleeding events, including fatal bleeds among patients randomized to clopidogel, is not known, common genetic polymorphisms may at least contribute.[13] Regardless, we believe that antiplatelet therapy should be used cautiously in patients with a recent history of peptic ulcer disease, known GI pathology, or prior GI bleeding. A strategy of drug cessation prior to scheduled procedures must take the patient, risk for thrombosis, and anticipated risk of bleeding into careful consideration.

Mechanism of platelet inhibition and clinical outcomes

The importance of ADP-induced platelet aggregation in maintaining haemostatic capacity following invasive procedures and in the setting of minor trauma probably reflects high local concentrations of ADP converted from adenosine triphosphate by ecto-ADPases.[14] The window of safety and efficacy for platelet $P2Y_{12}$ receptor antagonists may be determined not only by the intensity of platelet inhibition but also the mechanism of inhibition. While the high intensity of platelet inhibition achieved with ticagrelor at the dose employed in PLATO of 90 mg twice daily is similar to that of another $P2Y_{12}$ receptor antagonist, prasugrel,[15] there are distinct differences in the specific site and kinetics of receptor binding between thienopyridine and non-thienopyridine drugs, which may help to explain differences in their respective safety profiles—particularly fatal bleeding complications. Prasugrel causes an irreversible modification of the $P2Y_{12}$ receptor.[16]

Table 5 Landmark analyses: first 30 days on study drug vs. after 30 days on study drug

	Ticagrelor (n = 9235), n (%)	Clopidogrel (n = 9186), n (%)	Hazard ratio (95% CI)	P-value
Non-CABG-related major bleeding				
First 30 days on study drug	224 (2.47)	199 (2.21)	1.123 (0.928–1.360)	0.23
After 30 days on study drug	149 (2.17)	113 (1.65)	1.338 (1.048–1.708)	0.02
+Adjusting by bleeding events in first 30 days			1.329 (1.041–1.698)	0.02
+Adjusting by PCI in first 30 days			1.332 (1.043–1.701)	0.02
Non-procedure-related major bleeding				
First 30 days on study drug	112 (1.25)	93 (1.05)	1.201 (0.912–1.581)	0.19
After 30 days on study drug	129 (1.90)	89 (1.30)	1.471 (1.123–1.927)	0.01
+ Adjusting by bleeding events in first 30 days			1.466 (1.119–1.920)	0.01
+ Adjusting by PCI in first 30 days			1.469 (1.121–1.925)	0.01

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

In contrast, ticagrelor binds reversibly to the $P2Y_{12}$ receptor at a site different from the ADP-binding site, with half-life values for binding of 4 min and unbinding of 14 min.[17,18]

Despite the very low rate of intracranial bleeding in PLATO, there was still a greater number of events in the ticagrelor than the clopidogrel treatment group and included fatal events. This observation may reflect an inherently greater risk of intracranial bleeding with more intense platelet inhibition—at least theoretically related to an effect on capillary P2Y[13] receptor-mediated vascular integrity and healing, drug or metabolite permeability at the blood–brain barrier or localized differences in reverse transport. There was no overall difference in fatal bleeding between ticagrelor and clopidogrel and net clinical benefit favoured ticagrelor both within the initial 30 days of treatment and after 30 days. Similarly, we were not able to identify specific demographic or clinical risk indicators for fatal bleeding and the profiles for predicting non-CABG-related major bleeding did not differ for the two study drugs. The rate of intracranial bleeding among clopidogrel-treated patients in the TRITON study (0.31%) was similar to ticagrelor-treated patients in PLATO.[19] That said, we believe that it is prudent to avoid intense platelet inhibition in patients with a prior intracranial haemorrhage or established risk factors for this potentially life-threatening event.

In a previous trial comparing intense platelet inhibition with prasugrel and clopidogrel,[20] there was an apparent heightened risk of major and fatal bleeding in patients with a prior stroke or transient ischaemic attack, advanced age, and those with a low body weight (<60 kg). In the PLATO study, none of these factors identified patients at increased risk for bleeding with ticagrelor. Overall, similar risk factors for bleeding were identified in both clopidogrel- and ticagrelor-treated patients without any specific interactions other than GPIIb/IIIa receptor inhibitor administration among patients receiving clopidogrel. The basis for this observation is not clear, but has been reported previously.[21] It is also important to consider that some patients at risk for bleeding (e.g. renal insufficiency) are also at risk for thrombosis-related events and may concomitantly derive benefit from more intense platelet inhibition with ticagrelor.[22]

Conclusions

In the PLATO trial, ticagrelor exhibited similar rates of total major bleeding compared with clopidogrel, but a higher rate of non-CABG-related major bleeding that became statistically significant beginning 30 days after randomization. Fatal events were uncommon and occurred at a similar frequency between the treatment groups. Net clinical benefit favoured ticagrelor, particularly after 30 days on treatment. The mechanism(s) underlying a heightened risk for intracranial haemorrhage with long-term administration of drugs achieving robust platelet inhibition and drug-specific risk factors require further investigation.

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