Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial

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Aims
The optimal platelet inhibition strategy for ACS patients managed without revascularization is unknown.

We aimed to evaluate efficacy and safety of ticagrelor vs. clopidogrel in the non-ST-elevation acute coronary syndrome (NSTE-ACS) subgroup of the PLATO trial, in the total cohort, and in the subgroups managed with and without revascularization within 10 days of randomization.

Methods and results
We performed a retrospective analysis of the primary endpoint of cardiovascular death/myocardial infarction/stroke. Among 18 624 PLATO patients, 11 080 (59%) were categorized as NSTE-ACS at randomization. During the initial 10 days, 74% had angiography, 46% PCI, and 5% CABG. In NSTE-ACS patients, the primary endpoint was reduced with ticagrelor vs. clopidogrel (10.0 vs. 12.3%; hazard ratio (HR) 0.83; 95% confidence interval (CI) 0.74–0.93), as was myocardial infarction (6.6 vs. 7.7%; HR 0.86; 95% CI = 0.74–0.99), cardiovascular death (3.7 vs. 4.9%; HR 0.77; 95% CI = 0.64–0.93), and all-cause death (4.3 vs. 5.8%; HR 0.76; 95% CI = 0.64–0.90). Major bleeding rate was similar between treatment groups (13.4 vs. 12.6%; HR 1.07; 95% CI = 0.95–1.19), but ticagrelor was associated with an increase in non-CABG major bleeding (4.8 vs. 3.8%; HR 1.28; 95% CI = 1.05–1.56). Within the first 10 days, 5366 (48.4%) patients were managed without revascularization. Regardless of revascularization or not, ticagrelor consistently reduced the primary outcome (HR 0.86 vs. 0.85, interaction P = 0.93), and all-cause death (HR 0.75 vs. 0.73, interaction P = 0.89) with no significant increase in overall major bleeding.

Conclusion
In patients with NSTE-ACS, benefit of ticagrelor over clopidogrel in reducing ischemic events and total mortality was consistent with the overall PLATO trial, independent of actually performed revascularization during the initial 10 days.

Keywords
Platelet inhibition • Acute coronary syndrome

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Introduction

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is standard of care in acute coronary syndromes (ACS).1-3 Ticagrelor is the first reversibly binding direct P2Y12 inhibitor. As opposed to clopidogrel and prasugrel, it does not require enzymatic activation, and causes faster, greater, and more consistent platelet inhibition compared with clopidogrel.3,4 The Platelet Inhibition and Patient Outcomes (PLATO) trial compared ticagrelor with clopidogrel in patients with ACS. Ticagrelor was superior in preventing ischemic events (the composite of death from vascular causes, myocardial infarction, and stroke), as well as death from any cause, without a significant increase in all-cause major bleeding. PLATO included both invasively and non-invasively managed patients. The decision on which management strategy to pursue was made by the investigator.5

The third-generation thienopyridine prasugrel is, like clopidogrel, an irreversible P2Y12 inhibitor, but with faster and more consistent platelet inhibition.6 Prasugrel, when compared with clopidogrel, reduced ischemic events in patients with ACS planned for PCI in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON),7 but in non-ST-elevation acute coronary syndrome (NSTE-ACS) patients planned for management without revascularization, prasugrel showed no benefit over clopidogrel in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial.8

The aim of the present study was to explore the effect of ticagrelor vs. clopidogrel in the total NSTE-ACS subgroup of the PLATO trial and also stratified by initial management with or without revascularization.

Methods

Study design

The PLATO trial (ClinicalTrials.gov No. NCT00391872) was an international randomized double-blind, double-dummy phase III study comparing ticagrelor with clopidogrel in ACS. Details of the study design and overall results have been published previously.3,9 Briefly, a total of 18 624 patients were randomized to receive either ticagrelor or clopidogrel on background treatment with aspirin. The study included patients ≥18 years of age, previous myocardial infarction or coronary artery disease with ≥50% stenosis in ≥2 vessels, previous ischemic stroke, transient ischemic attack (TIA), carotid stenosis, cerebral revascularization, diabetes mellitus, peripheral artery disease, or chronic renal dysfunction.

In the current analysis, NSTE-ACS was in the data-base defined as absence of either persistent ST-segment elevation of 1 mV for 20 min in two contiguous leads or new (or presumed new) left bundle branch block in entry ECG. In addition to the overall NSTE-ACS population, we also analysed outcomes in the subgroups of NSTE-ACS patients who initially underwent revascularization and those who were treated without early revascularization. Both cohorts required endpoint-free survival for 10 days post-randomization to determine revascularization status. The no-revascularization subgroup was defined as NSTE-ACS patients who did not undergo any revascularization procedure (PCI or CABG) with or without angiography during the first 10 days.

Endpoints

The primary efficacy endpoint of the present study was the composite of cardiovascular death, myocardial infarction, (excluding silent infarctions) and stroke. Each component alone and all-cause death were secondary efficacy endpoints. Major bleeding by PLATO criteria9 and life-threatening/fatal bleeding were the primary safety endpoints. Secondary safety endpoints were CABG-related major bleeding, non-CABG-related major bleeding, minor bleeding, intracranial bleeding, and fatal bleeding. Additional secondary safety outcomes were bleeding events as defined by TIMI (major, minor, and non-CABG related major) and GUSTO (severe and moderate). An independent central adjudication committee, unaware of treatment assignments, assessed all endpoints. Major bleeding as defined by TIMI was recorded from the electronic case report form, where a drop of 50 g/L in haemoglobin was used as a cut-off, but this did not necessarily require clinical evidence of bleeding.

Statistical analyses

Patient characteristics and medical history, in-hospital procedures and medications, discharge ACS status, and post-discharge medications are presented by treatment in the NSTE-ACS patient cohort as well as by revascularization status subgroup. Continuous variables are presented as median and 25th–75th percentiles; categorical variables are presented as number and percentage. The treatment effect of ticagrelor vs. clopidogrel on the primary and secondary endpoints was compared within the subgroup of NSTE-ACS patients. Kaplan–Meier estimated event rates at 360 days and total number of observed events during the study were presented for each endpoint. Hazard ratios (HR), confidence intervals (CI), and P-values from unadjusted Cox proportional hazards regression models were presented. Kaplan–Meier estimated event rates were plotted by treatment for the primary efficacy endpoint, all-cause death, major bleeding, and non-CABG related major bleeding.

To examine whether the effect of ticagrelor in patients with NSTE-ACS differed based on early revascularization, Cox proportional hazards models were fitted for each endpoint using a treatment-by-revascularization interaction term. In these models, we adjusted for region of the world to account for differences in revascularization practice and the time-to-event was measured from a landmark at 10 days post-randomization. Kaplan–Meier rates 350 days post-landmark are presented for each treatment/revascularization category along with HR for ticagrelor vs. clopidogrel in the revascularization and medical management subgroups. Interaction P-values assess whether the treatment effect is different depending on revascularization status. Kaplan–Meier event rates adjusted for region are plotted by the four treatment/revascularization categories for the primary efficacy endpoint, all-cause death, major bleeding, and non-CABG related major bleeding. For consistency with the PLATO design paper,9 we also performed a 30-day landmark analysis; and as a sensitivity analysis, we also performed a 10-day landmark analysis.

Patients

Two or more of the following inclusion criteria were required for patients enrolled without ST-elevation ACS at admission: (1) ST-segment changes on ECG indicating ischaemia (ST-segment depression or transient elevation ≥1 mm) in at least two contiguous leads; (2) positive biomarker indicating myocardial necrosis (troponin I or T or CK-MB above the upper limit of normal); (3) one of the following: ≥60 years of age, previous myocardial infarction or coronary artery bypass surgery, coronary artery disease with ≥50% stenosis in ≥2 vessels, previous ischemic stroke, transient ischemic attack (TIA),...
landmark analysis of the full study population. Finally, the association of treatment with the primary efficacy endpoint was evaluated within several patient cohorts using Cox proportional hazards models, separately within the revascularization and non-revascularization subgroups. Forest plots present the HR for ticagrelor vs. clopidogrel in each subgroup cohort. Endpoints are defined using intent to treat and a P-value of 0.05 is used to denote statistical significance. Data were analysed using SAS version 9.2 for all analyses.

**Results**

**Patient characteristics**

The PLATO trial included 18,624 patients with ACS, of which 11,080 patients were classified as NSTE-ACS at randomization. Of these, 5,581 were randomized to ticagrelor and 5,499 to clopidogrel (Figure 1). The baseline and in-hospital characteristics were similar between groups in the overall NSTE-ACS population (Table 1). In the overall NSTE-ACS group, 74% of patients had a coronary angiography performed, 46% underwent PCI, and 5% CABG. The discharge diagnosis (in this population categorized as NSTE-ACS at admission) was NSTEMI in 65%, STEMI in 8%, and unstable angina/other in 27%.

At 10 days post-randomization, 5,366 patients were alive and had not undergone revascularization. There were regional differences in the proportion of patients undergoing revascularization during the initial 10 days (Asia/Australia 44%, Central/South America 40.3%, Europe/Middle East/Africa 49.8%, North America 71.6%). Non-revascularized and revascularized patients were of similar age (63 vs. 65), but patients who did not undergo revascularization were more likely to be of female gender (39 vs. 25%), and more likely to have comorbidities (e.g. previous myocardial infarction, heart failure, renal disease). Although non-revascularized patients had more comorbidities, they were less likely to be troponin I positive (Table 1). The proportion of patients with TIMI risk score >2 was slightly higher in the revascularization group (92 vs. 88%). During the first 10 days, 47% of non-revascularized patients underwent coronary angiography. When including only those who had angiography during the initial 10 days, female gender was more common in the non-revascularized (36%) than revascularized (25%). No significant coronary artery disease at angiography was noted in 32 and 0.7% of the non-revascularized and revascularized, respectively.

**Efficacy in the overall non-ST-elevation acute coronary syndrome population**

Efficacy and safety outcomes of the overall NSTE-ACS population are summarized in Table 2, and Kaplan–Meier curves are shown in Supplementary material online. The incidence of the primary composite endpoint was reduced with ticagrelor vs. clopidogrel (10.0 vs. 12.3%; HR 0.83; 95% CI = 0.74–0.93; P = 0.0013) (see Supplementary material online, Figure S1A). Cardiovascular death occurred less often in the ticagrelor group than in the clopidogrel group (3.7 vs. 4.9%; HR 0.77; 95% CI = 0.64–0.93; P = 0.0070), and myocardial infarction was also less common with ticagrelor vs. clopidogrel (6.6 vs. 7.7%; HR 0.86; 95% CI = 0.74–0.99; P = 0.0419), whereas stroke incidence did not differ significantly between treatment arms (1.3 vs. 1.4%; HR 0.95; 95% CI 0.69–1.33; P = 0.79). All-cause death was reduced in those treated with
Table 1  Baseline characteristics and invasive procedures by randomized treatment in the overall NSTE-ACS population, and by initial treatment strategy (within the first 10 days after randomization)

| Demographics | Overall NSTE-ACS | NSTE-ACS with revascularization | NSTE-ACS without revascularization |
|--------------|-----------------|--------------------------------|-----------------------------------|
| Ticagrelor (N = 5581) | Clopidogrel (N = 5499) | Ticagrelor (N = 2873) | Clopidogrel (N = 2841) | Ticagrelor (N = 2708) | Clopidogrel (N = 2658) |
| Age, median (25th–75th percentile), years | 64 (56–72) | 64 (56–72) | 63 (55–71) | 63 (55–71) | 65 (57–73) | 65 (57–73) |
| Age ≥ 75 years, n (%) | 955 (17.1) | 1024 (18.6) | 420 (14.6) | 460 (16.2) | 535 (19.8) | 564 (21.2) |
| Female gender, n (%) | 1746 (31.3) | 1746 (31.8) | 706 (24.6) | 716 (25.2) | 1040 (38.4) | 1030 (38.8) |
| Body weight < 60 kg, n (%) | 398 (7.2) | 389 (7.1) | 165 (5.8) | 172 (6.1) | 233 (8.6) | 217 (8.2) |
| Body mass index, median (25th–75th percentile), kg/m² | 27.5 (24.8–30.8) | 27.4 (24.8–30.5) | 27.5 (24.9–30.5) | 27.5 (24.9–30.5) | 27.5 (24.7–30.6) | 27.3 (24.6–30.5) |
| GRACE risk score nomogram | 130 (112–150) | 130 (112–149) | 128 (110–145) | 127 (110–145) | 133 (114–154) | 134 (116–153) |
| Cardiovascular risk factors, n (%) | | | | | | |
| Current smoking | 1636 (29.4) | 1640 (29.9) | 1000 (34.8) | 960 (33.8) | 636 (23.6) | 680 (25.6) |
| Hypertension | 3915 (70.2) | 3835 (69.8) | 1881 (65.5) | 1886 (66.4) | 2034 (75.3) | 1949 (73.4) |
| Dyslipidaemia | 2885 (51.8) | 2852 (51.9) | 1515 (52.8) | 1569 (55.2) | 1370 (50.7) | 1283 (48.3) |
| Diabetes mellitus | 1608 (28.9) | 1522 (27.7) | 756 (26.3) | 747 (26.3) | 852 (31.6) | 773 (29.1) |
| Medical history, n (%) | | | | | | |
| Angina pectoris | 2932 (52.6) | 2890 (52.6) | 1337 (46.5) | 1356 (47.7) | 1595 (59.1) | 1534 (57.8) |
| Myocardial infarction | 1400 (25.1) | 1410 (25.7) | 609 (21.2) | 608 (21.4) | 791 (29.3) | 802 (30.2) |
| Congestive heart failure | 397 (7.1) | 429 (7.8) | 99 (3.4) | 103 (3.6) | 298 (11.0) | 326 (12.3) |
| Percutaneous coronary intervention (PCI) | 944 (16.9) | 918 (16.7) | 537 (18.7) | 517 (18.2) | 407 (15.1) | 401 (15.1) |
| Coronary artery bypass graft (CABG) | 434 (7.8) | 474 (8.6) | 214 (7.4) | 218 (7.7) | 220 (8.1) | 256 (9.6) |
| Transient ischaemic attack | 185 (3.3) | 189 (3.4) | 82 (2.9) | 74 (2.6) | 103 (3.8) | 115 (4.3) |
| Non-hemorrhagic stroke | 246 (4.4) | 243 (4.4) | 81 (2.8) | 98 (3.5) | 165 (6.1) | 145 (5.5) |
| Peripheral arterial disease | 400 (7.2) | 413 (7.5) | 174 (6.1) | 204 (7.2) | 226 (8.4) | 209 (7.9) |
| Chronic renal disease | 273 (4.9) | 279 (5.1) | 117 (4.1) | 108 (3.8) | 156 (5.8) | 171 (6.4) |
| Physical findings, median (25th–75th percentile) | | | | | | |
| Heart rate (bpm) | 72 (64–80) | 72 (64–81) | 71 (62–80) | 72 (63–80) | 72 (64–82) | 72 (64–82) |
| Systolic blood pressure (mmHg) | 135 (120–150) | 134 (120–150) | 135 (120–150) | 135 (120–150) | 134 (120–150) | 132 (120–150) |
| Diastolic blood pressure (mmHg) | 80 (70–89) | 80 (70–87) | 80 (70–89) | 80 (70–87) | 80 (70–89) | 80 (70–87) |
| Risk indicators, n (%) | | | | | | |
| Troponin positive, n (%) | 4356 (80.8) | 4323 (81.3) | 2522 (89.6) | 2486 (89.3) | 1834 (71.3) | 1837 (72.4) |
| ST depression (≥ 1 mm) | 3158 (56.8) | 3201 (58.4) | 1547 (54.0) | 1535 (54.2) | 1611 (59.8) | 1666 (62.8) |
| TIMI risk score > 2 | 4838 (89.7) | 4785 (89.8) | 2584 (91.3) | 2566 (91.8) | 2254 (88.0) | 2219 (87.7) |
| Type of ACS at discharge, n (%) | | | | | | |
| STEMI | 449 (8.1) | 437 (8.0) | 330 (11.5) | 305 (10.7) | 119 (4.4) | 132 (5.0) |
| NSTEMI | 3605 (64.8) | 3525 (64.3) | 2045 (71.2) | 2025 (71.3) | 1560 (58.0) | 1500 (56.7) |
| UA/other | 1509 (27.1) | 1524 (27.8) | 497 (17.3) | 510 (18.0) | 1012 (37.6) | 1014 (38.3) |
| Antithrombotic treatment during index hospitalization, n (%) | | | | | | |
| Aspirin | 5386 (96.6) | 5316 (96.8) | 2797 (97.4) | 2797 (97.8) | 2589 (95.9) | 2537 (95.8) |
| Unfractionated heparin | 2910 (52.1) | 2856 (51.9) | 1845 (64.2) | 1845 (64.9) | 1065 (39.3) | 1011 (38.0) |

Continued
ticagrelor vs. clopidogrel (4.3 vs. 5.8%; HR 0.76; 95% CI = 0.64–0.90; P = 0.0020) (see Supplementary material online, Figure S1B).

Safety
With ticagrelor when compared with clopidogrel, there was no significant difference in PLATO major bleeding (13.4 vs. 12.6%; HR 1.07; 95% CI = 0.95–1.19; P = 0.26), but a higher rate of non-CABG-related major bleeding (4.8 vs. 3.8%; HR 1.28; 95% CI = 1.05–1.56; P = 0.0139) (see Supplementary material online, Figure S2A and B). There was no significant difference in the rate of life-threatening or fatal bleeding (6.6 vs. 6.5%; HR 1.05; 95% CI = 0.90–1.22, P = 0.56), nor any significant difference in the rate of intracranial bleeding with ticagrelor compared with clopidogrel (0.3 vs. 0.2%; HR 2.01; 95% CI = 0.81–4.99; P = 0.13). The composite of major or minor bleeding (by PLATO criteria) occurred more often in the ticagrelor group (18.2 vs. 16.3%; HR 1.14; 95% CI = 1.03–1.25, P = 0.0078). When assessed by TIMI criteria, there was no significant difference in major or minor bleeding (13.2 vs. 12.3%; HR 1.08; 95% CI = 0.97–1.21; P = 0.16). TIMI major bleeding, GUSTO severe, and GUSTO moderate or severe bleeding also did not appear to differ significantly between ticagrelor and clopidogrel, whereas TIMI non-CABG-related major bleeding was more common in the ticagrelor group (Table 2).

Efficacy and safety according to treatment strategy
Event rates were considerably higher in NSTE-ACS patients treated without revascularization compared with patients undergoing revascularization during the initial 10 days. For both revascularized and non-revascularized patients, there were similar proportional reductions of the primary endpoint with ticagrelor compared with clopidogrel (HR 0.86 vs. 0.85, interaction P = 0.93) (Figure 2A, Table 3) consistent with the overall trial. There was also a consistent reduction in all-cause death (HR 0.75 vs. 0.73; interaction P = 0.89) (Figure 2B). No significant difference in overall major bleeding was seen with ticagrelor vs. clopidogrel within each treatment strategy (revascularization/no revascularization) (Figure 3A). There was a higher incidence of non-CABG-related major bleeding with ticagrelor vs. clopidogrel in patients with NSTE-ACS with no significant interaction by invasive treatment strategy (HR 1.32 vs. 1.07; interaction P = 0.43) (Figure 2B). The primary outcome was reduced in both revascularized and non-revascularized patients, as well as in major subgroups in both revascularized and non-revascularized patients (see Supplementary material online, Figures S3 and S4). The results were consistent with a 30-day landmark for revascularization (see Supplementary material online, Table S1), as well as in the full study population (see Supplementary material online, Table S2). In patients who underwent angiography during the initial
Discussion

In this subgroup analysis, ticagrelor compared with clopidogrel reduced the composite endpoint of cardiovascular death, myocardial infarction, and stroke as well as the individual endpoints of cardiovascular death, myocardial infarction, and all-cause death without any significant difference in major bleeding in patients with an entry diagnosis of NSTE-ACS. The event curves for the primary composite endpoint and total mortality separated continuously for the duration of the trial. The benefits with ticagrelor were observed both in patients who underwent and in those who did not undergo early revascularization, regardless whether angiography was performed or not. These results are consistent with the previously reported subgroup analysis of all ACS patients with an intended strategy (prior to randomization) of no revascularization, where about one-fifth still underwent PCI and about 4% had CABG surgery before discharge.10

Although current guidelines advocate early invasive management in NSTE-ACS,12 a large proportion of patients are managed non-invasively.11 Patients who are managed without revascularization usually have more comorbidities, higher risk of bleeding, and inferior outcome than patients who are revascularized.13 The optimal platelet inhibition strategy in these patients has been uncertain. P2Y12 inhibition has previously been shown to reduce ischaemic events in NSTE-ACS patients managed without revascularization. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which randomized NSTE-ACS patients to receive either clopidogrel or placebo (on background aspirin treatment), 64% of patients did not undergo revascularization after randomization. There were almost identical relative reductions in CV death/MI/stroke with clopidogrel in the non-invasive and invasive subgroups.14 The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial studied the addition of clopidogrel to aspirin in a stable, more heterogeneous population at risk for atherothrombotic events. Overall, the combination was not more effective than aspirin monotherapy, but a trend towards benefit was noted in those with symptomatic atherosclerotic disease, whereas a trend towards harm was seen in those included based only on multiple cardiovascular risk factors.15

This issue was also recently studied in the TRILOGY-ACS trial, in which NSTE-ACS patients intended for management without revascularization were prospectively randomized to receive either prasugrel or clopidogrel (both irreversible P2Y12 inhibitors). The results showed no significant overall benefit of prasugrel over clopidogrel during 24 months, even though the Kaplan–Meier curves for the efficacy endpoints tended to separate after 1 year,8 and with a

| Table 2 | Efficacy and safety outcomes in patients with NSTE-ACS |
|-----------------------------------------------|-----------------|-----------------|-----------------|--------|
| Efficacy endpoints                          | Ticagrelor % (n) | Clopidogrel % (n) | HR (95% CI) | P-value |
| CV death/MI (excluding silent)/stroke       | 10.0 (533)       | 12.3 (630)       | 0.83 (0.74, 0.93) | 0.0013 |
| All-cause death/MI(excl. silent)/stroke     | 10.5 (557)       | 13.0 (664)       | 0.82 (0.73, 0.92) | 0.0006 |
| CV death/MI(all)/stroke/severe recurrent ishaemia/recurrent ishaemia/TIA/arterial thrombotic event | 15.5 (824) | 17.8 (918) | 0.88 (0.80, 0.96) | 0.0058 |
| Myocardial infarction (excluding silent)    | 6.6 (345)        | 7.7 (392)        | 0.86 (0.74, 0.99) | 0.0419 |
| Cardiovascular death (includes vascular and unknown deaths) | 3.7 (194) | 4.9 (247) | 0.77 (0.64, 0.93) | 0.0070 |
| Stroke                                       | 1.3 (69)         | 1.4 (71)         | 0.95 (0.69, 1.33) | 0.79   |
| All-cause death                              | 4.3 (224)        | 5.8 (290)        | 0.76 (0.64, 0.90) | 0.0020 |

Safety endpoints

| Safety endpoints                          | Ticagrelor % (n) | Clopidogrel % (n) | HR (95% CI) | P-value |
|-------------------------------------------|-----------------|-----------------|-------------|--------|
| Major bleeding (study criteria)           | 13.4 (660)      | 12.6 (618)      | 1.07 (0.95, 1.19) | 0.26   |
| Major or minor bleeding (study criteria)  | 18.2 (900)      | 16.3 (794)      | 1.14 (1.03, 1.25) | 0.0078 |
| Non-CABG related major bleeding (study criteria) | 4.8 (225) | 3.8 (176) | 1.28 (1.05, 1.56) | 0.0139 |
| Fatal bleeding                            | 0.3 (13)        | 0.4 (18)        | 0.72 (0.35, 1.47) | 0.37   |
| Life threatening or fatal bleeding (study criteria) | 6.6 (331) | 6.5 (315) | 1.05 (0.90, 1.22) | 0.56   |
| Intracranial bleeding                     | 0.3 (14)        | 0.2 (7)         | 2.01 (0.81, 4.99) | 0.13   |
| Other major bleeding                      | 7.2 (344)       | 6.6 (318)       | 1.08 (0.93, 1.25) | 0.34   |
| Major bleeding (TIMI criteria)            | 9.2 (452)       | 8.7 (422)       | 1.07 (0.94, 1.22) | 0.33   |
| Major or minor bleeding (TIMI criteria)   | 13.2 (653)      | 12.3 (602)      | 1.08 (0.97, 1.21) | 0.16   |
| Non-CABG related major bleeding (TIMI criteria) | 2.9 (137) | 2.2 (99) | 1.39 (1.07, 1.80) | 0.0131 |
| GUSTO severe bleeding                     | 3.1 (146)       | 3.2 (151)       | 0.96 (0.77, 1.21) | 0.74   |
| GUSTO moderate or severe bleeding         | 8.6 (416)       | 7.8 (382)       | 1.08 (0.94, 1.25) | 0.25   |

Each treatment group is summarized as Kaplan–Meier rates at 360 days and total number of events during the study. P-values and hazard ratios (95% CI) come from unadjusted Cox models testing ticagrelor vs. clopidogrel.

10 days with or without significant coronary disease, the effect of ticagrelor vs. clopidogrel was consistent (see Supplementary material online, Table S3).
reduction of the primary outcome in the subgroup who underwent angiography.\textsuperscript{16} In the no revascularization subgroup of the current PLATO NSTE-ACS substudy, there were consistent benefits with ticagrelor when compared with clopidogrel concerning both mortality and non-fatal ischaemic events. Although the no revascularization subgroup of the present PLATO substudy seems similar to the TRILOGY-ACS population, it is impossible to compare the effect of the respective new P2Y\textsubscript{12} inhibitor vs. clopidogrel across the two studies. Patients with intention for treatment without revascularization were prospectively studied in TRILOGY-ACS, while the present PLATO substudy was a post hoc stratification with subgroups of revascularization/no revascularization defined post randomization and post procedures. The TRILOGY-ACS population also was of higher risk with more prevalent comorbidities such as hypertension, dyslipidaemia, and diabetes, and had higher rates of previous myocardial infarction and revascularization procedures.

In ACS patients managed with revascularization, more potent P2Y\textsubscript{12} inhibition has been associated with better outcomes, as shown in the intention for invasive management subgroup analysis of PLATO for ticagrelor\textsuperscript{17} and in TRITON for prasugrel.\textsuperscript{7} In the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT OASIS-7) trial also, intensified P2Y\textsubscript{12} inhibition with double dose clopidogrel for the first 7 days showed no significant difference in outcome in the overall population,\textsuperscript{18} but a reduction in cardiovascular events, including stent thrombosis in the pre-specified (albeit post-randomization) subgroup undergoing PCI.\textsuperscript{19}
Table 3  Interaction of ticagrelor treatment and revascularization within 10 days (adjusting for region)

| Efficacy endpoints | NSTE-ACS with revascularization | NSTE-ACS without revascularization | Interaction |
|--------------------|----------------------------------|------------------------------------|-------------|
|                    | N  | Ticagrelor KM rate | Clopidogrel KM rate | HR (95% CI) | N  | Ticagrelor KM rate | Clopidogrel KM rate | HR (95% CI) | p  |
| CV death/MI (excluding silent)/stroke | 5416 | 5.11 | 6.10 | 0.86 (0.68, 1.09) | 5189 | 9.63 | 11.60 | 0.85 (0.72, 1.01) | 0.93 |
| All-cause death/MI (excl. silent)/stroke | 5416 | 5.44 | 6.60 | 0.85 (0.67, 1.06) | 5189 | 10.15 | 12.53 | 0.84 (0.71, 0.99) | 0.94 |
| CV death/MI (all)/stroke/severe recurrent ischaemia/recurrent ischaemia/TIA/arterial thrombotic event | 5290 | 8.73 | 10.31 | 0.86 (0.71, 1.03) | 5109 | 14.14 | 15.16 | 0.97 (0.84, 1.13) | 0.29 |
| Myocardial infarction (excluding silent) | 5438 | 3.52 | 3.88 | 0.90 (0.68, 1.21) | 5201 | 6.04 | 6.68 | 0.94 (0.75, 1.17) | 0.85 |
| Cardiovascular death (includes vascular and unknown deaths) | 5648 | 1.64 | 2.33 | 0.76 (0.52, 1.13) | 5217 | 4.07 | 5.44 | 0.75 (0.58, 0.98) | 0.95 |
| Stroke | 5632 | 0.67 | 0.59 | 1.18 (0.60, 2.34) | 5209 | 1.48 | 1.69 | 0.92 (0.58, 1.46) | 0.56 |
| All-cause death | 5648 | 2.03 | 2.88 | 0.75 (0.53, 1.07) | 5217 | 4.77 | 6.65 | 0.73 (0.57, 0.93) | 0.89 |

Safety endpoints

| Safety endpoints | NSTE-ACS with revascularization | NSTE-ACS without revascularization | Interaction |
|------------------|----------------------------------|------------------------------------|-------------|
|                  | N  | Ticagrelor KM rate | Clopidogrel KM rate | HR (95% CI) | N  | Ticagrelor KM rate | Clopidogrel KM rate | HR (95% CI) | p  |
| Major bleeding (study criteria) | 4983 | 5.25 | 4.68 | 1.10 (0.84, 1.44) | 4931 | 11.83 | 11.43 | 1.05 (0.88, 1.26) | 0.82 |
| Major or minor bleeding (study criteria) | 4842 | 7.76 | 6.35 | 1.22 (0.97, 1.54) | 4847 | 14.59 | 13.96 | 1.07 (0.91, 1.25) | 0.34 |
| Non-CABG major bleeding (study criteria) | 5270 | 3.14 | 2.38 | 1.32 (0.92, 1.90) | 4933 | 2.78 | 2.79 | 1.07 (0.74, 1.56) | 0.43 |
| Fatal or life-threatening major bleeding (study criteria) | 5173 | 2.25 | 2.01 | 1.18 (0.79, 1.76) | 4962 | 5.77 | 6.11 | 0.95 (0.75, 1.22) | 0.37 |
| Other major bleeding (study criteria) | 5178 | 3.10 | 2.85 | 1.02 (0.72, 1.45) | 4945 | 6.50 | 5.68 | 1.16 (0.91, 1.49) | 0.55 |
| Major bleeding (TIMI criteria) | 5102 | 3.42 | 2.79 | 1.21 (0.86, 1.70) | 4952 | 8.04 | 8.39 | 0.97 (0.79, 1.20) | 0.28 |
| Major or minor bleeding (TIMI criteria) | 4990 | 5.24 | 4.56 | 1.12 (0.85, 1.47) | 4933 | 11.78 | 11.16 | 1.08 (0.91, 1.29) | 0.85 |
| Non-CABG major bleeding (TIMI criteria) | 5316 | 1.88 | 1.19 | 1.66 (1.01, 2.72) | 4952 | 2.05 | 1.84 | 1.19 (0.76, 1.87) | 0.34 |
| GUSTO severe bleeding | 5286 | 1.16 | 1.49 | 0.75 (0.45, 1.26) | 4946 | 2.75 | 2.46 | 1.13 (0.77, 1.65) | 0.22 |
| GUSTO moderate or severe bleeding | 5134 | 3.93 | 3.30 | 1.13 (0.82, 1.55) | 4945 | 7.18 | 5.96 | 1.19 (0.95, 1.51) | 0.78 |

Kaplan–Meier (KM) rates 350 days after day 10 post-randomization.
With more potent platelet inhibition, bleeding complications have usually been increasing. In TRITON-TIMI 38, where prasugrel vs. clopidogrel was evaluated in ACS, prasugrel demonstrated a reduction in thrombotic events, but at the cost of significantly increased rates of major bleeding, including fatal bleeding, particularly in patients at high bleeding risk defined as high age and low body weight. In TRILOGY-ACS on the other hand, which included a lower maintenance dose, prasugrel did not cause any increased major bleeding rate, including patients >75 years of age. In the present analysis, there was no significant difference in PLATO-defined total major bleeding with ticagrelor compared with clopidogrel. However, the incidence of non-CABG-related major bleeding was significantly higher in the ticagrelor group. There was no significant difference in life-threatening or fatal bleeding or major bleeding as defined by the TIMI criteria, but the composite of PLATO major/minor bleeding was increased with ticagrelor.

**Study limitations**

There are several limitations to this work. The sample size is large, which gives high power to detect even relatively small differences in effect that may or may not be clinically important. The revascularization/no revascularization analyses were post hoc investigations of subgroups identified post-randomization, which makes the analyses subject to potential bias. Because landmark analyses were used, the risk of time-dependent confounding is acknowledged. As sensitivity analyses, we also performed landmark analyses at 30 days instead of 10 days, with consistent results. Nevertheless, the findings reported with regard to revascularization status should be
interpreted strictly as exploratory and hypothesis generating. The present results based on actual revascularization strategy support and complement those of our previous analysis based on pre-randomization intention to treat with invasive or conservative management, and the results based on performed revascularization or not are consistent with the overall NSTE-ACS results, as well as the overall PLATO results.

Conclusions

In this substudy of the PLATO trial, ticagrelor compared with clopidogrel consistently reduced the rates of ischaemic events and mortality without any difference in overall major bleeding in patients with an entry diagnosis of NSTE-ACS, and this effect was independent of whether or not early revascularization was performed. These results harmonize with the European Society of Cardiology (ESC) NSTE-ACS guidelines, which recommend ticagrelor in all patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy.

Supplementary material

Supplementary material is available at European Heart Journal online.

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