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Case Study: Ticagrelor in PLATO and Prasugrel in TRITON-TIMI 38 and TRILOGY-ACS Trials in Patients With Acute Coronary Syndromes

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Cross-trial comparisons are typically inappropriate as there are often numerous differences in study designs, populations, end points, and loading doses of the study drugs. These differences are clearly reflected in the most recent updates to the European Society of Cardiology (ESC) non-ST elevation acute coronary syndrome (NSTE-ACS) and ST elevation myocardial infarction (STEMI) guidelines, which include recommendations for the use of the antiplatelet agents ticagrelor, prasugrel, and clopidogrel, based in part on results from the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38, TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY-ACS) and PLATelet inhibition and patient Outcomes (PLATO) trials. Here, we describe each of these trials in detail and explain the differences between them that make direct comparisons difficult. In conclusion, this information, along with the current guidelines and recommendations, will assist clinicians in deciding the most appropriate treatment pathway for their patients with NSTE-ACS and STEMI.

Keywords: acute coronary syndromes, ticagrelor, prasugrel, trial comparison

INTRODUCTION

In clinical practice, physicians frequently base their decisions on data from well-controlled, randomized, comparative clinical trials. However, these clinical decisions can be difficult in the absence of head-to-head trials that definitively demonstrate a treatment benefit of one agent over another.

Clinical decision making based on cross-trial comparison is an important issue for the antiplatelet drugs ticagrelor and prasugrel, as both have shown superiority over clopidogrel in the treatment of patients with acute coronary syndromes (ACS), but in separate studies. There are no available data from direct head-to-head clinical comparisons of ticagrelor and prasugrel, although the ongoing ISAR-REACT-5 trial (NCT01944800) aims to evaluate whether ticagrelor is superior to prasugrel in patients with ACS for whom an invasive treatment strategy is planned. Elsewhere, Biondi-Zoccai et al[1] undertook a clopidogrel-adjusted

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comparative meta-analysis of ticagrelor versus prasugrel using data from the PLATelet inhibition and patient Outcomes (PLATO), DISPERSE-2, and TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 studies. The validity of such adjusted indirect comparisons depends on a number of factors, including the overall similarities of the study designs, hospital setting, inclusion/exclusion criteria, treatment strategies, study duration, and end point definitions.

This review examines the similarities and differences between the design of PLATO, TRITON-TIMI-38, and TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY-ACS), and assesses whether cross-trial comparisons are appropriate in the case of ticagrelor and prasugrel. This may help to optimize the use of these drugs and to target treatment to the patient populations deriving most benefit.

MAIN RESULTS OF MAJOR TRIALS

In the PLATO trial (Table 1), 18,624 patients with ACS were randomized to ticagrelor (180 mg loading dose, 90 mg twice-daily maintenance dose) or clopidogrel (300–600 mg loading dose, 75 mg/d maintenance dose).[2] At 12 months, ticagrelor significantly reduced the primary end point {composite of death from vascular causes, myocardial infarction [MI], or stroke compared with clopidogrel [9.8% vs. 11.7%, respectively; hazard ratio (HR): 0.84; 95% confidence interval (CI), 0.77–0.92; $P < 0.001$]}. Predefined hierarchical testing of individual secondary efficacy end points showed ticagrelor was associated with significant reductions in rates of MI (5.8% with ticagrelor vs. 6.9% with clopidogrel, $P = 0.005$), death from vascular causes (4.0% vs. 5.1%, $P = 0.001$), and death from any cause (4.5%, vs. 5.9%, $P < 0.001$).[2] Ticagrelor did not increase the rate of overall major bleeding, but a statistically significant increase in noncoronary artery bypass grafting (non-CABG) major bleeding (4.5% vs. 3.8%; HR: 1.19; 95% CI, 1.02–1.38; $P < 0.03$) was observed.[2] Dyspnea was more common in the ticagrelor group than in the clopidogrel group (13.8% of patients vs. 7.8%), although few patients discontinued treatment due to dyspnea (0.9% vs. 0.1%) and no effect of ticagrelor on pulmonary function was seen in a substudy of PLATO.[2,6] In the first week of treatment, a higher incidence of ventricular pauses was observed with ticagrelor compared with clopidogrel. However, pauses were rarely associated with symptoms, and the treatment groups did not differ significantly with respect to the incidence of syncope or pacemaker implantation.[2,7] The number needed to treat (NNT) to prevent 1 cardiovascular death, MI, or stroke in 12 months was 54.[8]

The TRITON-TIMI 38 trial randomized 13,608 patients with moderate-to-high-risk ACS with scheduled percutaneous coronary intervention (PCI) to prasugrel (60 mg loading dose, 10 mg/d maintenance dose) or clopidogrel (300 mg loading dose, 75 mg/d maintenance dose).[3] At 15 months, prasugrel significantly reduced the primary composite end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke compared with clopidogrel (9.9% vs. 12.1%, respectively; HR: 0.81; 95% CI, 0.73–0.90; $P < 0.001$) with an NNT within 15 months of 46.[3,9] Compared with clopidogrel, prasugrel also reduced the rates of MI (9.7% for clopidogrel vs. 7.4% for prasugrel; $P < 0.001$) and urgent target vessel revascularization (3.7% vs. 2.5%; $P < 0.001$), but not death from any cause (3.3% vs. 3.0%, $P = 0.64$). There was a statistically significant increase in non–CABG-related TIMI major bleeding (1.8% vs. 2.4%, HR: 1.32; 95% CI, 1.03–1.68; $P = 0.03$), including fatal bleeding, with prasugrel.

In the more recent TRILOGY-ACS trial, 9326 medically managed patients (ie, without revascularization) with unstable angina or non-ST elevation myocardial infarction (NSTEMI) were randomized to prasugrel 10 mg/d (5 mg/d if aged ≥75 years or with body weight <60 kg) or clopidogrel 75 mg/d. Clopidogrel-naive patients who underwent randomization within 72 hours after first medical contact received a loading dose of prasugrel 30 mg or clopidogrel 300 mg, followed by daily blinded maintenance therapy. Patients who did not undergo randomization within 72 hours were treated with open-label clopidogrel before randomization and then received daily maintenance study drug. In the 7243 patients <75 years (primary efficacy and safety cohort), no significant difference in the primary end point of death from vascular causes, MI, or stroke was observed between treatment groups over 6–30 months; no significant increase in non-CABG major bleeding events was observed.[10]

A prespecified exploratory analysis of PLATO demonstrated a net clinical benefit of ticagrelor, based on time to first occurrence of any event from cardiovascular death, MI, stroke, and any major bleeding event, excluding non–life-threatening bleeding during CABG.[2,11] This composite efficacy and safety end point demonstrated statistically significant superiority of ticagrelor over clopidogrel for ≤12 months after index ACS events (15.7% vs. 17.0%; HR: 0.92; 95% CI, 0.86–0.99; $P = 0.026$). A net clinical benefit of prasugrel over clopidogrel was also demonstrated in TRITON-TIMI 38 for the composite of death from

Table 1. Summary of characteristics and outcomes from 3 major trials of antiplatelet agents (PLATO, TRITON-TIMI-38, and TRILOGY-ACS).[2–4]

			TRILOGY-ACS‡	
	PLATO*	TRITON-TIMI 38†	Patients <75 yrs	Overall
Type of ACS	Any ACS: 43% NSTEMI, 38% STEMI, 17% UA	ACS with scheduled PCI: NSTEMI or UA 74%, 26% STEMI	Medically managed: 67% NSTEMI; 33% UA	Medically managed: 70% NSTEMI; 30% UA
No. patients	18,624	13,608	7243	9326
Age (yrs; median)	62	61 (IQR, 53–70)	62	66
Female (%)	28	26	36	39
Symptom duration	<24 h	<72 h NSTE, <12 h PPCI, <14 d other STE	<10 d	<10 d
ST deviation ≥1 mm or elevated biomarker at entry (%)	89 and 86, respectively	100	Without ST-elevation	Without ST-elevation
Prior MI (%)	21	18	44	43
Diabetes (%)	25	23	39	38
Major exclusion criteria	Fibrinolysis <24 h, OAC, c.i. to CLO, drugs strongly affecting CYP-450 3A, risk of bradycardia	High bleeding risk, anemia, thrombocytopenia, intracranial disease, any thienopyridine <5 d	History of TIA or stroke, PCI, or CABG within previous 30 d, renal failure requiring dialysis, concomitant OAC	
Treatment A	ASA, 75–100 mg (325 mg permitted) once daily + TIC (180 mg LD + 90 mg twice daily ± 90 mg at PCI)	ASA, 75–162 mg once daily + PRA (60 mg LD + 10 mg once daily) up to 1 h post-PCI but not before angiography	ASA, ≤100 mg once daily + PRA (30 mg LD + 5–10 mg once daily)§	ASA, ≤100 mg once daily + PRA (30 mg LD + 5 mg once daily)§
Treatment B	ASA, 75–100 mg once daily + CLO (300 mg LD + 75 mg ± 300 mg for PCI >24 h)	ASA, 75–162 mg once daily + CLO (300 mg LD + 75 mg once daily) up to 1 h post-PCI but not before angiography	ASA, ≤100 mg once daily + CLO (300–600 mg LD + 75 mg once daily)§	ASA, ≤100 mg once daily + CLO (300–600 mg LD + 75 mg once daily)§
Clopidogrel before coronary angiography	Allowed	Not allowed unless PPCI	Allowed	Allowed
Length of follow-up (minimum–maximum)	Up to 12 mo (6–12, event-driven)	Median, 14.5 mo (6–15)	Not stated	Median, 17.1 mo (6–30)
In-hospital PCI and use of GPI (%), respectively	61 and 27	99 and 55	6%; % GPI use not stated	Not stated
Use of >1 DES (%)	19	47	Not stated	Not stated
CABG (%)	10 during study	2.7 during study	2	Not stated
PEEP definition	CVD, NF MI, NF stroke	CVD, NF MI, or NF stroke	CVD, NF MI, NF stroke	
PEEP in A vs. B (%)	9.8 vs. 11.7, $P < 0.001$	9.9 vs. 12.1, $P < 0.001$	13.9 vs. 16.0, $P = 0.21$	18.7 vs. 20.3, $P = 0.45$

(*Continued on next page*)

Table 1. (*Continued*) Summary of characteristics and outcomes from 3 major trials of antiplatelet agents (PLATO, TRITON-TIMI-38, and TRILOGY-ACS).[2–4]

			TRILOGY-ACS‡	
	PLATO*	TRITON-TIMI 38†	Patients <75 yrs	Overall
Relative (absolute) risk reduction (%)	16 (1.9)	19 (2.2)	9 (2.1)	4 (1.6)
Death in A vs. B (%)	4.5 vs. 5.9, $P < 0.001$	3.0 vs. 3.2	7.8 vs. 8.1, $P = 0.63$	11.6 vs. 12.2, $P = 0.40$
CVD in A vs. B (%)	4.0 vs. 5.1, $P = 0.001$	2.1 vs. 2.4	6.6 vs. 6.8, $P = 0.48$	9.9 vs. 10.2, $P = 0.38$
NF MI in A vs. B (%)	5.8 vs. 6.9, $P = 0.005$	7.3 vs. 9.5, $P < 0.001$	8.3 vs. 10.5, $P = 0.21$	10.7 vs. 12.3, $P = 0.58$
Definite + probable ST in A vs. B (%)	2.2 vs. 2.9, $P = 0.02$	1.1 vs. 2.4, $P < 0.001$	Not stated	Not stated
NF stroke in A vs. B (%)	1.5 vs. 1.3	1.0 vs. 1.0	1.5 vs. 2.2, $P = 0.08$	2.2 vs. 2.6, $P = 0.52$
Major bleed definition¶	PLATO (and TIMI)	TIMI	TIMI non-CABG‖	TIMI non-CABG‖
Major bleed in A vs. B (%)	11.6 vs. 11.2 (TIMI, 7.9 vs. 7.7)	Not reported	2.1 vs. 1.5, $P = 0.27$	2.5 vs. 1.8, $P = 0.29$
Non-CABG major bleed in A vs. B (%)¶	4.5 vs. 3.8 (2.8 vs. 2.2), $P = 0.03$	2.4 vs. 1.8, $P = 0.03$	2.1 vs. 1.5, $P = 0.27$	2.5 vs. 1.8, $P = 0.29$
CABG-related major bleed in A vs. B (%)	7.4 vs. 7.9 (5.3 vs. 5.8) of all A and B treated	13.4 vs. 3.2 of CABG treated, $P < 0.001$	Not stated	Not stated
Life-threatening bleed in A vs. B (%)	5.8 vs. 5.8 (study criteria)	1.4 vs. 0.9 (non-CABG), $P = 0.01$	0.9 vs. 0.8, $P = 0.88$	1.1 vs. 1.1, $P = 0.85$
Intracranial bleed in A vs. B (%)	0.3 vs. 0.2	0.3 vs. 0.3 (non-CABG)	0.7 vs. 0.5, $P = 0.39$	0.8 vs. 0.7, $P = 0.42$
Fatal bleed in A vs. B (%)	0.3 vs. 0.3	0.4 vs. 0.1 (non-CABG), $P = 0.002$	0.5 vs. 0.2, $P = 0.99$	0.6 vs. 0.4, $P = 0.68$
NNT and (non-CABG) NNH for A vs. B	54 and 167, respectively	46 and 167, respectively	NA	NA

*The end point percentages are Kaplan–Meier estimates of the rate of each end point at 12 months.
†The end point percentages are Kaplan–Meier estimates of the rate of each end point at 15 months.
‡The end point percentages are Kaplan–Meier estimates of the rate of each end point at 30 months.
§Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of study drug. The prasugrel maintenance dose was 10 mg, which was adjusted to 5 mg once daily for patients who weighed <60 kg or were aged ≥75 years.
¶TIMI-defined non-CABG major bleeding was the primary safety end point in TRITON-TIMI 38, but not in PLATO. However, TIMI-defined and GUSTO-defined bleeds were also adjudicated in PLATO and are comprehensively reported by Becker et al.[5]
‖End points presented use TIMI criteria for major bleeding not related to CABG. Key bleeding end points were also analyzed using GUSTO criteria for severe or life-threatening bleeding not related to CABG.
ACS, acute coronary syndrome; ASA, aspirin; CABG, coronary artery bypass surgery; c.i., contraindication; CLO, clopidogrel; CVD, cardiovascular death; CYP, cytochrome P; GPI, glycoprotein inhibitor; IQR, interquartile range; LD, loading dose; MI, myocardial infarction; NF, nonfatal; NNH, number needed to harm; NNT, number needed to treat; NSTE, non-ST elevation; OAC, oral anticoagulant; PEEP, primary efficacy end point; PLATO, PLATelet inhibition and patient Outcomes; PRA, prasugrel; ST, stent thrombosis; STE, ST elevation; TIC, ticagrelor; TIMI, thrombolysis in myocardial infarction; TRITON, TRIal to assess improvement in Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel; UA, unstable angina.

any cause, nonfatal MI, nonfatal stroke, and major non-CABG bleeding (12.2% vs. 13.9%; HR: 0.87; 95% CI, 0.79–0.95; $P = 0.004$).[3,9]

Based on the results of these studies, ticagrelor is indicated for the reduction of thrombotic cardiovascular events in patients with ACS (NSTE-ACS or STEMI) who are managed either with an ischemia-guided strategy or with PCI or CABG,[8,12] and prasugrel is indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS (NSTE-ACS or STEMI) to be managed with PCI.[13] Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage, active pathological bleeding, severe hepatic impairment, or hypersensitivity to ticagrelor or any of its components.[12] Prasugrel is contraindicated in individuals with active pathological bleeding, prior transient ischemic attack (TIA) or stroke, or hypersensitivity to prasugrel or any of its components.[13] Of note, the most recent American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for patients with NSTE-ACS now recommend ticagrelor over clopidogrel for patients treated with an early invasive or ischemia-guided strategy, and prasugrel over clopidogrel in those undergoing PCI who are not considered to be at high risk of bleeding complications.[14]

SUBGROUP ANALYSES OF THE MAJOR CLINICAL TRIALS

A number of subgroup analyses of PLATO, TRITON-TIMI 38, and TRILOGY-ACS have been performed. Patients with diabetes mellitus (DM) are known to have high platelet reactivity and an increased risk of ischemic events and bleeding post-ACS. In PLATO, ticagrelor compared with clopidogrel reduced ischemic events irrespective of diabetic status and glycemic control, without an increase in major bleeding events.[15] Diabetic status, however, seemed to be a differentiator in TRITON-TIMI 38: the reduction in ischemic events observed with prasugrel versus clopidogrel was numerically greater in patients with DM than in those without DM, although there was no significant interaction between treatment effect and diabetes status ($P_{\text{interaction}} = 0.09$).[16]

The elderly represent another group with an increased risk of recurrent ischemic events and death.[17] In PLATO, the antithrombotic benefits of ticagrelor applied to both patients aged ≥75 and <75 years, with respect to the composite of cardiovascular death, MI, or stroke.[17] An exploratory post hoc subgroup analysis of TRITON-TIMI 38 demonstrated that prasugrel had less clinical efficacy and greater absolute levels of bleeding in patients aged ≥75 years than the overall study cohort.[3] In TRILOGY-ACS, a reduced maintenance dose of prasugrel (5 mg) in a cohort of 2083 patients aged ≥75 years showed no difference in ischemic or bleeding outcomes compared with clopidogrel. No significant interactions among weight, pharmacodynamic response in an ex vivo platelet function substudy, and bleeding risk were observed between reduced-dose prasugrel and clopidogrel in elderly patients.[4]

Patients with ACS and a history of stroke or TIA are known to have an increased rate of recurrent cardiac events and intracranial hemorrhages,[18] as demonstrated in PLATO.[19] Despite the numerical increase in event rates, the effect of ticagrelor was consistent with the overall PLATO results and demonstrated a favorable net clinical benefit and decreased mortality. TRITON-TIMI 38 also demonstrated a higher rate of death from cardiovascular causes, nonfatal MI, or nonfatal stroke in patients with a history of stroke or TIA, relative to those without.[20] The numerical increase in recurrent cardiac events and intracranial hemorrhage in these patients resulted in a net harm from prasugrel (HR: 1.54; 95% CI, 1.02–2.32; $P = 0.04$), and these results were not consistent with the overall study population.

Patients with STEMI are at greater risk of side effects as they need to undergo PCI shortly after diagnosis; oral antiplatelet agents are not fully effective by the time of PCI and are often delayed until after PCI is completed.[21,22] Results of a subgroup analysis of the PLATO trial in patients with STEMI or left bundle-branch block and intended for reperfusion with primary PCI were consistent with the main results of the PLATO trial; ticagrelor plus aspirin reduced cardiovascular and total death, MI, and stent thrombosis and improved survival without an increase in major bleeding compared with clopidogrel plus aspirin.[21] In a TRITON-TIMI 38 subgroup analysis of patients with STEMI undergoing primary PCI (PPCI) or late PCI, prasugrel plus aspirin was also more effective than clopidogrel plus aspirin in preventing ischemic events, without an increase in bleeding.[23]

Another potential risk is the concomitant use of oral antiplatelet agents and proton pump inhibitors (PPIs), although available data are conflicting.[24] Previous studies have shown that certain PPIs reduce platelet inhibition when administered with clopidogrel.[24] Results of a subanalysis of the PLATO trial demonstrated that PPI use was independently associated with a higher rate of cardiovascular events in patients receiving both clopidogrel and ticagrelor.[25] This analysis suggests that the association between PPI use and adverse events in the PLATO trial may be a result of confounding, and that PPI use is a marker for higher

rates of cardiovascular events, as opposed to the cause of these events. In a TRITON-TIMI 38 subgroup analysis, no association was found between PPI use and risk of the composite of cardiovascular death, MI, or stroke for patients treated with clopidogrel or prasugrel.[26]

STUDY PATIENTS

The characteristics of study patients differed between PLATO, TRITON-TIMI 38, and TRILOGY-ACS. Each study enrolled patients with ACS, although the target populations were different (Table 1). PLATO enrolled a broad spectrum of patients with ACS (NSTE-ACS or STEMI) who were identified within 24 hours after hospitalization for the index event. Planned treatment intention (invasive vs. medical management) was prespecified by the investigator. No restrictions were placed on the type of patients with ACS, the proportion of patients with NSTE-ACS or STEMI, pretreatment with clopidogrel, or the prespecified treatment strategy (PCI or CABG or medical management).

In general, PLATO patients represented a typical ACS population, as demonstrated by large-scale registry data from European and American practices. In the Swedish ACS Registry (RIKS-HIA), 64% of patients from 1998 to 2005 (n = 205,269) and 79% of patients from 2007 (n = 24,695) met PLATO inclusion criteria.[27] Comparisons of the Global Registry of Acute Coronary Events (GRACE) with the PLATO patients support these findings.[27,28]

TRITON-TIMI 38 enrolled patients with ACS (NSTE-ACS or STEMI) with planned PCI. Patients with ACS with planned medical management were excluded, as were those who had received treatment with any thienopyridine within 5 days of randomization, which were the main differences in design compared with PLATO. In TRITON-TIMI-38, NSTE-ACS patients were enrolled within 72 hours of symptom onset and randomization took place on the catheterization table, immediately before scheduled PCI. STEMI patients were enrolled within 12 hours of symptom onset if PPCI was planned, or within 14 days after receiving medical therapy for STEMI. Recruitment of NSTE-ACS and post-STEMI patients was restricted to patients whose anatomy was considered amenable to PCI before randomization, and recruitment of STEMI patients was capped at 26% of the overall cohort (n = 3534 enrolled).

During index hospitalization in PLATO, 34% of patients with ACS were managed medically and 4.5% underwent CABG[2]; however, only 1% of patients in TRITON-TIMI 38 underwent CABG as the index procedure, as patients with planned CABG were excluded from this study.[3] Furthermore, no patients were managed medically in TRITON-TIMI 38, whereas the TRILOGY-ACS study examined the use of prasugrel within 10 days of an event in NSTE-ACS patients who were selected for a final treatment strategy of medical management. Patients were also required to have at least one of the 4 risk criteria: age of ≥60 years; presence of DM; previous MI; or previous revascularization with PCI or CABG.[10,29] The primary TRILOGY analysis considered the 7243 patients aged ≤75 years. Of these, 571 patients (7.9%) underwent revascularization with PCI, CABG, or both, during follow-up. A secondary TRILOGY analysis considered the primary cohort plus an additional 2083 patients aged ≥75 years receiving a reduced maintenance dose of prasugrel 5 mg daily.

Initially, data from the STEMI cohort of PLATO and TRITON-TIMI 38 may seem suitable for comparison. However, the PLATO analysis included patients with persistent ST-elevation and planned PPCI (defined as PCI within 24 hours of symptom onset) or new bundle-branch block and planned PPCI.[21,30] In contrast, in TRITON-TIMI 38, the subanalysis of STEMI patients included data from patients who underwent PPCI (n = 2438; within 12 hours of symptom onset) and those who underwent secondary PCI (n = 1094; between 12 hours and 14 days of symptom onset), as prespecified in the protocol.[23,31]

As the TRITON-TIMI 38 study was exclusively interventional, the overall proportion of patients receiving a stent (95%) was higher than in PLATO (61%). Moreover, the proportion of the overall study population receiving drug-eluting stents (DES) versus bare-metal stents (BMS) differed between PLATO (DES = 19%; BMS = 42%), and TRITON (DES = 47%; BMS = 48%).[2,3] The type of stent (DES vs. BMS) deployed may be particularly relevant due to other differences in study design between PLATO and TRITON-TIMI 38. For example, as patients in TRITON-TIMI 38 were randomized "on the catheterization table," clopidogrel-mediated inhibition of platelet aggregation may not have been established by the time of intervention. This may have contributed to the high rate of periprocedural events reported in TRITON-TIMI 38 (independent of treatment, 69% of all cardiovascular events occurring in the first 30 days of TRITON were periprocedural). In fact, in the ONSET/OFFSET study of 123 patients with stable coronary artery disease receiving either clopidogrel (600 mg loading dose, 75 mg/d maintenance dose) or ticagrelor (180 mg loading dose, 90 mg twice-daily maintenance dose), plus aspirin (75–100 mg/d), the time to maximum inhibition of platelet aggregation was nearly 7.8 hours after the

loading dose for clopidogrel, whereas it took 2 hours after the loading dose for ticagrelor.[32] As such, in this scenario a DES (vs. BMS) may be more beneficial in protecting against cardiovascular events.[33] The type of stent may also be important when it comes to risk of late stent thrombosis. The incidence of stent thrombosis within 1 year of DES or BMS deployment is similar given patients also receive the recommended dual antiplatelet therapy of aspirin plus a $P2Y_{12}$ receptor inhibitor for ≥12 months.[34] However, there may be a slight increase in risk for late stent thrombosis (thrombosis occurring after 1 year of deployment) with DES partially due to delayed neointimal coverage.[35]

In some respects, the baseline characteristics of PLATO, TRITON-TIMI 38, and TRILOGY-ACS patients were similar. However, there were also some notable differences. TRILOGY-ACS, for example, only enrolled patients with NSTE-ACS, whereas approximately 9% of PLATO patients intended for noninvasive management were diagnosed with STEMI at discharge. Also, approximately, a third of PLATO patients intended for noninvasive management actually underwent PCI or CABG during follow-up, whereas only 7.9% of the primary TRILOGY cohort underwent revascularization during follow-up.

Current guidelines (Table 2) for the treatment of ACS reflect the different inclusion criteria and patient populations of PLATO and TRITON-TIMI-38. The European Society of Cardiology (ESC) NSTE-ACS guidelines[37] and the AHA/ACC NSTE-ACS guidelines[14] have been revised recently (Table 2). Although the levels of evidence for the use of prasugrel and ticagrelor are the same (level 1B), ticagrelor is recommended regardless of initial treatment strategy (including patients pretreated with clopidogrel), whereas prasugrel is limited to $P2Y_{12}$ inhibitor–naive patients (especially patients with diabetes) with known coronary anatomy and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications. The revised ESC STEMI guidelines[38] also recommend the use of ticagrelor and prasugrel (both evidence level 1B). The use of prasugrel is restricted to patients who are clopidogrel naive without an increased risk of bleeding (Table 2).

Prasugrel is suitable for a specific population of patients with ACS, as supported by a recent subanalysis of the TRITON-TIMI 38 data[20] and by the recent TRILOGY-ACS study.[10] The efficacy and safety of prasugrel was examined in a "core clinical cohort" (n = 10,804, 79% of TRITON-TIMI 38 patients), which excluded patients without a net clinical benefit because of an increased risk of bleeding complications (patients ≥75 years, <60 kg or with prior history of stroke or TIA). Patients receiving prasugrel had a clinically significant decrease in the primary end point of cardiovascular death, MI, or stroke compared with those receiving clopidogrel (8.3 vs. 11.0%; HR: 0.74; 95% CI, 0.66–0.84; $P < 0.0001$). However, patients ≥75 years and <60 kg (n = 2149, 16%) receiving prasugrel versus clopidogrel did not show a significant difference in efficacy in terms of the primary end point (15.3% vs. 16.3%; HR: 0.94; 95% CI, 0.76–1.18; $P = 0.61$), possibly caused by the increased risk of bleeding within these subgroups of patients. These patients received a lower dose of 5 mg in the later TRILOGY-ACS study (see below). However, it should be noted that effect estimates in several subgroups have wide confidence intervals, and the possibility of type II errors should not be ignored. The TRILOGY-ACS study enrolled patients with unstable angina/NSTEMI for whom a medical management strategy was selected. The prasugrel maintenance dose was 10 mg, but was adjusted to 5 mg for patients who weighed <60 kg or were ≥75 years of age. In patients aged <75 years, prasugrel did not significantly reduce the frequency of death from vascular causes, MI, or stroke compared with clopidogrel.[10] More recently, a subanalysis of TRILOGY-ACS found that the proportion of patients who experienced the primary end point was lower with prasugrel versus clopidogrel for those who had pre-enrollment angiography (10.7% vs. 14.9%, HR: 0.77; 95% CI, 0.61–0.98; $P = 0.032$), but did not differ between treatment groups in patients who did not have angiography (16.3% vs. 16.7%, HR: 1.01; 95% CI, 0.84–1.20; $P = 0.94$).[41] Of the patients who had angiography before treatment (n = 3085) and for whom CAD data were available, 2885 patients had at least 1 stenosis of more than 50%; 1892 of these 2885 patients (66%) did not have revascularization owing to a coronary anatomy that was judged to be unsuitable or without indication for PCI.[41]

Based on these results, prasugrel may not be the most appropriate option for NSTE-ACS patients treated with an ischemia-guided strategy, although further studies are warranted to corroborate the findings in patients who undergo angiography.

THE ACTIVE COMPARATOR: CLOPIDOGREL

PLATO, TRITON-TIMI 38, and TRILOGY-ACS all used clopidogrel as the control arm; however, the use of clopidogrel differed markedly between these trials. In PLATO, 46% of patients received open-label clopidogrel before randomization (including loading dose). Clopidogrel-randomized patients received a 300 mg loading dose, unless they had received

Table 2. International guideline recommendations for oral antiplatelet agents reflect the different patient populations studied in the PLATO and TRITON-TIMI 38 trials.

Recommendations		Class*	Level†
ESC/EACTS myocardial revascularization guidelines—Wijns et al[36]			
STEMI	Prasugrel‡	I	B
	Ticagrelor‡	I	B
	Clopidogrel§ (with 600 mg loading dose as soon as possible)	I	C
NSTE-ACS	Prasugrel‡	IIa	B
	Ticagrelor‡	I	B
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 mo after PCI)	I	B
ESC NSTE-ACS guidelines—Hamm et al[37]			
A P2Y12 inhibitor should be added to aspirin as soon as possible and maintained over 12 mo, unless there are contraindications such as excessive risk of bleeding		I	A
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischemic events (eg, elevated troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is commenced)		I	B
Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for $P2Y_{12}$ inhibitor–naive patients (especially patients with diabetes) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.		I¶	B
Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel		I	A
AHA/ACC NSTE-ACS guidelines—Amsterdam et al[14]			
Aspirin			
Non–enteric-coated aspirin to all patients promptly after presentation	162–325 mg	I	A
Aspirin maintenance dose continued indefinitely	81–162 mg/d	I	A
$P2Y_{12}$ inhibitors			
Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B
$P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy		I	B
Clopidogrel	300 mg or 600 mg loading dose, then 75 mg/d		
Ticagrelor‖	180 mg loading dose, then 90 mg twice daily		
$P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	NA	I	B

(*Continued on next page*)

Table 2. (*Continued*) International guideline recommendations for oral antiplatelet agents reflect the different patient populations studied in the PLATO and TRITON-TIMI 38 trials.

Recommendations		Class*	Level†
Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	NA	IIa	B
ESC STEMI guidelines—Steg et al[38]			
An ADP-receptor blocker is recommended in addition to aspirin. Options are		I	A
Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age <75 yrs		I	B
Ticagrelor		I	B
Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated		I	C
ACCP secondary prevention guidelines—Vandvik et al[39]			
For patients in the first year after an ACS who have not undergone PCI—dual antiplatelet therapy	Ticagrelor 90 mg twice daily plus low-dose aspirin 75–100 mg daily rather than single antiplatelet therapy	I	B
	Clopidogrel 75 mg daily plus low-dose aspirin 75–100 mg daily rather than single antiplatelet therapy	I	B
	Ticagrelor 90 mg twice daily plus low-dose aspirin rather than clopidogrel 75 mg daily plus low-dose aspirin	II	B
For patients in the first year after an ACS who have undergone PCI with stent placement—dual anti platelet therapy	Ticagrelor 90 mg twice daily plus low-dose aspirin 75–100 mg daily over single antiplatelet therapy	I	B
	Clopidogrel 75 mg daily plus low-dose aspirin 75–100 mg daily over single antiplatelet therapy	I	B
	Prasugrel# 10 mg daily plus low-dose aspirin over single antiplatelet therapy	I	B
	Ticagrelor 90 mg twice daily plus low-dose aspirin over clopidogrel 75 mg daily plus low-dose aspirin	II	B
ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention—Levine et al[40]			
Patients already taking daily aspirin therapy should take 81–325 mg before PCI		I	B
Patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI		I	B
After PCI, use of aspirin should be continued indefinitely		I	A
After PCI, it is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses		IIa	B
A loading dose of a $P2Y_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting (Level of evidence 1A). Options include	Clopidogrel 600 mg (ACS and non-ACS patients)	I	B
	Prasugrel 60 mg (ACS patients)	I	B
	Ticagrelor 180 mg (ACS patients)	I	B
In patients receiving a stent (BMS or DES) during PCI for ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 mo. Options include	Clopidogrel 75 mg daily	I	B
	Prasugrel 10 mg daily	I	B
	Ticagrelor 90 mg twice daily	I	B

(*Continued on next page*)

Table 2. (*Continued*) International guideline recommendations for oral antiplatelet agents reflect the different patient populations studied in the PLATO and TRITON-TIMI 38 trials.

Recommendations	Class*	Level†
If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (eg, <12 mo) of $P2Y_{12}$ inhibitor therapy is reasonable	IIa	C
Continuation of dual antiplatelet therapy beyond 12 mo may be considered in patients undergoing DES implantation	IIb	C
Prasugrel should not be administered to patients with a prior history of stroke or TIA	III HARM	B

*Class of recommendation.
†Level of evidence.
‡Depending on approval and availability. Direct comparison between prasugrel and ticagrelor is not available. Long-term follow-up is awaited for both drugs.
§Primarily if more efficient antiplatelet agents are contraindicated.
¶The overall class of recommendation for clopidogrel-pretreated patients and/or those with unknown coronary anatomy is IIa. The class I recommendation here refers to the specifically defined subgroup.
||The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg/d.
#Evidence suggests that prasugrel results in no benefit or net harm in patients with a body weight of <60 kg, age >75 years, or with a previous stroke or TIA. The effient prescribing information recommends a prasugrel dose of 5 mg for patients weighing <60 kg.[13]
ATC, Antithrombotic Trialists' Collaboration.

a loading dose of open-label clopidogrel or were taking clopidogrel (or ticlopidine) for at least 5 days before randomization. Patients undergoing PCI could receive an additional 300 mg clopidogrel loading dose at the discretion of the investigator. Between the time of the index event and up to 24 hours after randomization, 19.6% of the clopidogrel control group received ≥600 mg clopidogrel.[2] In a subset of patients with STEMI, 35.8% of patients in the clopidogrel group received a 600 mg total "intended" dose of clopidogrel (open label and blinded) within the 24-hour period after the first dose.[21] Clopidogrel study drug was started at a median of 5.3 hours after hospitalization and a median of 11.3 hours after the onset of chest pain. Furthermore, the median time from first dose of study drug to PCI was 0.25 hours for STEMI and 3.65 hours in NSTE-ACS patients.[2]

In TRITON-TIMI 38, patients were excluded if they had received clopidogrel within 5 days before PCI, and all patients randomized to clopidogrel received a loading dose of 300 mg. Although the investigators acknowledged that there were data supporting the use of a higher loading dose of clopidogrel, and that many physicians use a 600-mg loading dose in daily clinical practice, they concluded that data were insufficient to justify using a 600-mg loading dose in this study.[31] The loading dose could be given at any time after randomization, which took place on the catheterization table within 1 hour of the patient leaving the catheterization laboratory. Clopidogrel study drug was administered before the first coronary guide wire was placed in 25% of patients; during PCI or within 1 hour after PCI in 74%; and more than 1 hour after PCI in 1% of patients.[3] The median time from symptom onset until receiving the loading dose of prasugrel or clopidogrel study drug was 29.7 hours (range, 17.4–49.8 hours) in patients with unstable angina/NSTEMI, due to the protocol-specified delay until after angiography, and 7.0 hours (range, 3.7–28.5 hours) in patients with STEMI.[42]

Newer studies are providing further insights into clinical outcomes associated with the timing of the antiplatelet loading dose. Notably, the ACCOAST study demonstrated that among patients with NSTE-ACS who were scheduled to undergo catheterization, pretreatment with prasugrel at the time of diagnosis did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding complications, compared with administration in relation to coronary angiography.[43] Furthermore, the results of the ACCOAST, TRITON, and TRILOGY ACS trials are cited by the current AHA/ACC NSTE-ACS guidelines as the basis of prasugrel not being recommended for initial therapy in NSTE-ACS patients.[14] The

ATLANTIC study evaluated prehospital administration of ticagrelor in patients with STEMI, and although this was safe and reduced stent thrombosis, it did not demonstrate a significant effect on the primary efficacy end point of reperfusion.[44]

In TRILOGY-ACS, 26% of patients initiated clopidogrel treatment with a loading dose of 300–600 mg and a daily maintenance dose of 75 mg until randomization; 70% of patients received clopidogrel treatment for at least 5 days before randomization and continued with a 75-mg maintenance dose. Testing for the superiority of prasugrel over clopidogrel was performed with a 2-sided log-rank test and stratified by clopidogrel status at randomization. Notably, a lower loading dose of prasugrel (30 mg) was used in TRILOGY-ACS compared with that used in TRITON-TIMI-38 (60 mg) to test whether there was a reduced risk of acute bleeding in patients who, in the absence of a revascularization procedure, did not require immediate high-level platelet inhibition just after randomization. It is likely that the timing and initial dosing of study drug administration are important for the overall trial results. Therefore, the marked differences in the active comparator regime argue strongly against a cross-trial analysis for the prasugrel and ticagrelor studies.

STUDY END POINTS

The primary end points of PLATO and TRITON-TIMI 38—the composite of death from vascular causes, nonfatal MI, and nonfatal stroke—are identical. However, the impact of the different study designs on the ability to detect periprocedural MIs should be considered. Because of the short time between randomization and PCI in PLATO (49% of patients underwent PCI within 24 hours of randomization), there was generally only opportunity for 1 measurement of preprocedural cardiac ischemia marker level. As 86% of patients in PLATO had elevated troponin I level at study entry,[2] it was difficult to detect periprocedural MIs that are based on a "rise and fall" of cardiac biomarkers. In TRITON-TIMI 38, the end point of nonfatal MI had to be distinct from the index event.[31] Because of the time allowed between the onset of symptoms and PCI in this study, at least 2 cardiac biomarker measurements before PCI were generally allowed, and hence, MI adjudication was less confounded by the index event (at least in the NSTE-ACS and post-STEMI patients) than in PLATO. Furthermore, the high percentage of PCIs performed in the TRITON-TIMI 38 study led to a much greater representation of periprocedural MIs than in PLATO (Table 3).

Approximately, 19% of all MIs in PLATO were specifically related to a rise in biomarker.[47] However, more than half of the MIs in TRITON-TIMI-38 were classified as periprocedural, and by definition, classed as "enzymatic" events (classification by adjudication of laboratory values only[45]; Table 3). In TRITON-TIMI-38, in patients receiving at least 1 coronary stent (94% of the study patients), 65% of events occurred within the first 30 days, and of these, 69% were periprocedural.[48] Overall, 46% (median follow-up, 14.5 months) were classified as periprocedural. Despite the large number of biomarker-defined events in TRITON-TIMI 38, the net clinical benefit of prasugrel (in terms of the primary composite efficacy and safety end point) was maintained when periprocedural MIs were excluded from the analysis.[48]

The bleeding definitions also differed between studies: PLATO used both the PLATO-defined bleeding and TIMI bleeding definitions (although TIMI bleeding was derived from nonadjudicated events); TRITON-TIMI 38 used the TIMI bleeding definition; and TRILOGY-ACS used TIMI and Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definitions. Although Becker et al[5] reported comprehensive bleeding results from PLATO, including data described

Table 3. Summary of periprocedural MIs by trial.[45,46]

Study	Drug	Type 4a* (%)	Type 4b† (%)
PLATO‡	Ticagrelor	99/504 (19.6)	69/504 (13.7)
	Clopidogrel	124/593 (20.9)	103/593 (17.4)
TRITON-TIMI 38	Prasugrel	279/497 (56.1)§	48/497 (9.7)¶
	Clopidogrel	321/659 (48.7)§	107/659 (16.2)¶

Data are presented as number of MIs in subgroup/total number of MIs per treatment arm.
*Type 4a = MI associated with PCI.
†Type 4b = MI with stent thrombosis as documented by angiography or at autopsy (all type 4 events are PCI related).
‡All suspected MI events were adjudicated by a Clinical Events Committee; silent MI events were excluded.[46]
§Prasugrel versus clopidogrel HR, 0.86 (95% CI, 0.74–1.01), $P = 0.07$.
¶Prasugrel versus clopidogrel HR, 0.45 (95% CI, 0.32–0.63), $P < 0.001$.

according to various definitions, cross-trial comparison of bleeding data is still not recommended due to the other confounding factors discussed above.

CONCLUSIONS

The marked differences in study designs, patient populations and characteristics, assessment of end points, and loading dose of the comparator clopidogrel in PLATO, TRITON-TIMI 38, and TRILOGY-ACS render cross-trial comparisons inappropriate. Recent ESC updates to the NSTE-ACS and STEMI guidelines clearly reflect the differences between TRITON-TIMI 38 and PLATO. NSTE-ACS guidelines recommend the use of ticagrelor irrespective of initial treatment, including use in patients pretreated with clopidogrel. The guidelines limit the recommendation of prasugrel to $P2Y_{12}$ inhibitor–naive patients with known coronary anatomy and who are proceeding to PCI, unless there are other complications or a high risk of life-threatening bleeding.[14,37] The updated ESC STEMI guidelines also recommend use of either ticagrelor or prasugrel; however, prasugrel is only recommended for clopidogrel-naive patients who are not at increased risk for bleeding.[38]

Analysis of PLATO and TRITON-TIMI 38 indicates that the composite of efficacy and safety demonstrated statistically significant superiority of ticagrelor and prasugrel, respectively, over clopidogrel control.[2,3,9,11] The design of TRILOGY-ACS, which included a lower dose of prasugrel to reduce bleeding risk in elderly patients and those with a low body weight, may have contributed to the fact that the study failed to demonstrate superiority of prasugrel compared with clopidogrel in medically managed NSTE-ACS patients.[4,10] In general, indirect comparison meta-analyses adjusted by reference to a control that was used differently between trials are vulnerable to bias.

Given the differences between PLATO, TRITON-TIMI 38, and TRILOGY-ACS described above, in our view, cross-trial comparisons cannot be made appropriately. Clinicians therefore need to carefully evaluate the data from each of these trials to decide which oral antiplatelet agent is most appropriate for a particular patient and their condition.

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