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Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: Data from the PLATO Trial

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Abstract

Aims: To determine the effect of ticagrelor compared to clopidogrel in patients with peripheral artery disease (PAD) and acute coronary syndromes (ACS).

Methods and results: PLATO (n = 18,624) was a multicentre, double-blind, randomized trial in ACS, that showed a 16% reduction in cardiovascular death (CV-death), myocardial infarction (MI) and stroke with ticagrelor compared with clopidogrel, without significant increase in overall major bleeding. We performed a post-hoc analysis of cardiovascular and bleeding outcomes in PLATO according to reported PAD status at baseline.

At one year, CV death, MI or stroke occurred in 19.3% of patients with PAD (n = 1144) compared to 10.2% in patients without PAD ($p < 0.001$). The Kaplan-Meier one year event rate for the primary endpoint of CV death, MI or stroke in PAD patients treated with ticagrelor as compared with clopidogrel, was 18% vs 20.6% (HR: 0.85 95% CI 0.64–1.11; for PAD status by treatment interaction, $p = 0.99$) and for death from any cause 8.7% vs 11.9%, (HR: 0.74 95% CI 0.50–1.08; interaction $p = 0.73$). PLATO-defined major bleeding event rates at one year were 14.8% for ticagrelor compared to 17.9% for clopidogrel, (HR: 0.81 95% CI 0.59–1.10; interaction $p = 0.09$).

Conclusion: PAD patients have a high rate of ischaemic and bleeding events post ACS. The reduction of CV death, MI or stroke with ticagrelor compared with clopidogrel in PAD patients was consistent with the overall trial result although it did not reach statistical significance. Overall major bleeding was similar between the therapies.

Keywords

Peripheral artery disease, acute coronary syndrome, ticagrelor

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Introduction

Patient with polyvascular disease, such as the combination of PAD and/or CVD with CAD, are at increased risk for cardiovascular events compared to patients with disease in only one vascular territory.[1] Moreover, at the time of an acute coronary syndrome (ACS), the presence of PAD increases the risk of cardiovascular procedures and adverse clinical events.[2] The optimal antiplatelet therapy for patients with PAD is unknown, with the current ACC/AHA guidelines for the management of PAD recommending the use of an anti-platelet agent.[3,4]

Clopidogrel is a thienopyridine that has a clinical indication, as part of dual antiplatelet therapy with aspirin, for use in patients with ACS,[5] and is also indicated for use as monotherapy in stable patients with PAD.[6] The efficacy of clopidogrel is limited by its pharmacology, which is characterized by variable transformation of the prodrug into the active metabolite leading to inconsistent platelet inhibition and limited clinical efficacy in some patients.

Ticagrelor is an oral, reversibly-bound inhibitor of the adenosine diphosphate $P2Y_{12}$ receptor that has a rapid onset of action directly related to the plasma concentration and a greater and more consistent inhibition of platelet aggregation than clopidogrel.[7,8] Ticagrelor was recently shown in the PLatelet inhibition And patienT Outcomes (PLATO) trial to reduce vascular death, myocardial infarction, or stroke without an increase in bleeding compared to clopidogrel in patients with acute coronary syndromes.[9] Therefore, we performed a post-hoc analysis to evaluate the risk of cardiovascular events and bleeding in patients with ACS and PAD and to determine if the response to ticagrelor compared with clopidogrel was consistent in this subgroup with the overall population.

Methods

Study design

The study design of the PLATO study has been previously published.[9,10] Briefly, 18,624 patients with ACS, either ST-segment elevation myocardial infarction (STEMI) or non-ST segment elevation ACS (NSTE-ACS), with onset of symptoms within 24 hours were enrolled. For patients with NSTE-ACS, at least two of three criteria were required: ST-segment depression or transient elevation $\geq$1 mm in two or more contiguous leads, positive biomarkers for myocardial necrosis, or one additional risk indicator such as age >60 years, previous MI, coronary artery bypass graft (CABG), carotid artery disease, stroke, transient ishaemic attack (TIA), PAD or chronic kidney disease with creatinine clearance (CrCl) <60 ml/min.

For STEMI, inclusion required planned primary PCI and patients with fibrinolysis within 24 hours were excluded. The presence of PAD was ascertained at time of enrolment by self-report and captured on the electronic case report form (eCRF); PAD status was not confirmed by objective testing at the time of enrolment. However, PAD was defined in the eCRF as intermittent claudication with prior objective confirmation, either as prior revascularization or ankle-brachial index less than 0.9.

Patients were randomized in a double-blind, double-dummy fashion to either ticagrelor at a 180 mg loading dose followed by 90 mg twice daily or clopidogrel with a 300–600 mg loading dose, for those patients who were not already treated with the drug, followed by 75 mg daily. All patients also received aspirin therapy at a daily dose of 75–100 mg, with daily doses up to 325 mg allowed for 6 months after stent placement. The median duration of treatment was 9.1 months. The PLATO trial was approved by ethical review boards and adhered to the ethical principles of the Declaration of Helsinki. All patients gave a written informed consent.

Endpoints

The primary endpoint was time to any component of the composite of cardiovascular death (CV death), myocardial infarction (MI) and stroke. Individual components of the composite primary endpoint served as secondary endpoints. PLATO-defined bleeding was the primary safety endpoint. TIMI-defined major bleeding was programmed from the eCRF.

Statistical analysis

Baseline characteristics and outcomes for PAD patients were compared with patients without PAD in the entire study population combining treatment groups. Categorical baseline variables by randomized treatment in PAD patients are presented as frequencies and percentages with Fisher's exact test used to evaluate differences. For continuous baseline variables, medians and quartiles are presented, and comparisons are performed with the Wilcoxon test.

Event rates are provided as unadjusted Kaplan Meier estimates at one year post-randomization. The interaction between randomized treatment and PAD was tested using the Cox regression model. A significant PAD by treatment interaction indicates that the treatment effect is different in patients with and without PAD.

Adjustment models were derived for the efficacy endpoints, CV death/MI/stroke (primary endpoint) and

all-cause death, and safety endpoints, PLATO major bleeding and PLATO non-CABG major bleeding and used to compare patients with and without PAD. Variables presented in Table 1 were considered for inclusion along with biochemistry values. Continuous variables were assessed for linearity on the log-hazard scale for each outcome separately and linear splines were used when appropriate. For each endpoint, model selection was based on a backward algorithm repeated in 200 bootstrap samples. For each sample, the significance level to stay in the model was set to 0.05. Models selected in each of the 200 bootstrap samples were summarized and variables included in 75% or more of the models were selected for inclusion in the final model. Variables not included in the final model were considered individually and they were added if

Table 1. Baseline characteristics of PLATO PAD population by treatment.

Characteristic	All PAD N = 1144	Ticagrelor N = 566	Clopidogrel N = 578	*P* value
Age, median (25^{th}–75^{th}) (years)	66 (58–73)	66 (57–72)	66 (58–73)	0.1861
Female (%)	287 (25.1)	143 (25.3)	144 (24.9)	0.8909
Body mass index, median (25^{th}–75^{th}) ($kg/m^{2)}$	27.0 (24.5–29.8)	27.0 (24.5–30.0)	26.9 (24.6–29.8)	0.7073
Race – Caucasian	1093 (95.5)	541 (95.6)	552 (95.5)	0.4872
Smoking status				
Non-smoker	302 (26.4)	149 (26.3)	153 (26.5)	
Ex-smoker	408 (35.7)	200 (35.3)	208 (36.0)	0.9589
Habitual smoker	434 (37.9)	217 (38.3)	217 (37.5)	
Hypertension	904 (79.0)	452 (79.9)	452 (78.2)	0.4911
Dyslipidaemia	750 (65.6)	373 (65.9)	377 (65.2)	0.8098
Diabetes mellitus	431 (37.7)	204 (36.0)	227 (39.3)	0.2595
Family history of CHD	396 (34.7)	218 (38.6)	178 (30.8)	0.0057
Prior history				
Angina pectoris	714 (62.4)	341 (60.3)	373 (64.5)	0.1346
Myocardial infarction	386 (33.7)	193 (34.1)	193 (33.4)	0.8001
Coronary artery disease	563 (49.2)	276 (48.8)	287 (49.7)	0.7632
Percutaneous coronary intervention	295 (25.8)	146 (25.8)	149 (25.8)	0.9913
Coronary artery bypass graft	173 (15.1)	77 (13.6)	96 (16.6)	0.1561
Transient ischaemic attack	75 (6.6)	44 (7.8)	31 (5.4)	0.0996
Non-haemorrhagic stroke	92 (8.1)	47 (8.3)	45 (7.8)	0.7537
Carotid stenosis ($\geq$50%)	130 (11.4)	59 (10.4)	71 (12.3)	0.3166
Clinical presentation				
Blood pressure, median (25^{th}–75^{th}) (mmHg)				
Systolic	134 (120–150)	135 (120–150)	133 (120–150)	0.7265
Diastolic	78 (70–85)	79 (70–85)	77 (69–85)	0.4057
Heart rate	73 (65–82)	75 (64–84)	73 (65–82)	0.2797
ST Elevation/new LBBB on ECG at entry	331 (28.9)	166 (29.3)	165 (28.6)	0.7706
Final diagnosis				
Unstable angina pectoris	258 (22.6)	121 (21.4)	137 (23.7)	0.6915
STEMI	273 (23.9)	142 (25.1)	131 (22.7)	
NSTEMI	591 (51.7)	292 (51.6)	299 (51.8)	
Other	21 (1.8)	11 (1.9)	10 (1.7)	
ST depression	653 (57.2)	297 (52.6)	356 (61.7)	0.0018
Transient ST elevation	71 (6.2)	36 (6.4)	35 (6.1)	0.8306
Persistent ST elevation	291 (25.5)	147 (26.0)	144 (25.0)	0.6808
T-wave Inversion	405 (35.5)	202 (35.8)	203 (35.2)	0.8404
New left bundle branch block	46 (4.0)	21 (3.7)	25 (4.3)	0.5924

they were statistically significant ($\alpha = 0.05$). After a main effects model was selected, interactions were assessed for inclusion. The effect of variable on the outcome was presented as hazard ratios with their 95% confidence intervals. Goodness of fit of each model was assessed with the Hosmer-May statistic based on the comparison of observed and expected rates of events. The C-index was used to quantify the model's ability to distinguish events from non-events.

Results

Baseline characteristics

PAD was identified at baseline in 1144 (6.1%) patients in the PLATO trial. Patients with PAD were older (66 vs 62 years, $p < 0.0001$) and more often had hypertension (79.0% vs 64.6%, $p < 0.0001$), diabetes (37.7% vs 24.2%, $p < 0.001$) and prior myocardial infarction (MI) (33.7% vs 24.2%, $p < 0.001$) (online Supplement Table 1**).** Baseline characteristics were similar for patients with PAD randomized to treatment with ticagrelor compared with clopidogrel, although patients randomized to receive ticagrelor were less likely to have ST-segment depression on presentation (52.6% vs 61.7%, $p = 0.001$) when compared to clopidogrel (Table 1).

Clinical outcomes by PAD status

Patients with PAD in the PLATO trial had significantly higher rates of cardiovascular and bleeding events compared to patients without PAD (Table 2). The Kaplan Meier event rate at one year for the primary endpoint of death from vascular causes (CV death), MI or stroke was 19.3% in patients with PAD compared to 10.2% in patients without PAD ($p < 0.001$). The rate of death from any cause was 10.3% of PAD patients compared to 4.9% of patients without PAD ($p < 0.0001$). PLATO-defined major bleeding also occurred more often in patients with PAD (16.4%) as compared to patients without PAD (11.4%) ($p < 0.0001$). The rate of CABG at one year was higher in PAD patients (12.7%) compared to non-PAD patients (10.6%) ($p = 0.010$).

Adjusted clinical outcomes by PAD status

After adjustment, the clinical outcomes by PAD status for the primary, secondary and safety endpoints

Table 2. Outcomes by PAD status.

	Overall	No PAD	PAD	Hazard ratio	
	KM% (n)	KM% (n)	KM% (n)	(95% CI)[a]	*P* value
Efficacy outcomes					
Death from vascular cause, MI or stroke	10.8 (1871)	10.2 (1663)	19.3 (208)	1.975 (1.710–2.281)	<0.0001
Death from any cause	5.3 (902)	4.9 (795)	10.3 (107)	2.082 (1.702–2.548)	<0.0001
Death from any cause or MI	9.9 (1719)	9.4 (1525)	18.1 (194)	2.003 (1.725–2.326)	<0.0001
MI	6.4 (1095)	6.1 (973)	11.7 (122)	1.976 (1.637–2.385)	<0.0001
Stroke	1.4 (228)	1.3 (202)	2.5 (26)	1.981 (1.317–2.979)	0.0010
TIA	0.25 (40)	0.26 (39)	0.09 (1)	0.389 (0.053–2.825)	0.3504
Definite stent thrombosis	1.7 (176)	1.6 (160)	3.0 (16)	1.877 (1.123–3.138)	0.0163
Probable or definite stent thrombosis	2.5 (275)	2.4 (249)	4.7 (26)	1.964 (1.312–2.942)	0.0011
Possible, probable or definite stent thrombosis	3.4 (355)	3.2 (319)	6.8 (36)	2.130 (1.509–3.005)	<0.0001
Safety outcomes					
Major bleeding, study criteria	11.4 (1868)	11.1 (1723)	16.4 (163)	1.515 (1.290–1.778)	<0.0001
Major bleeding, TIMI criteria	7.9 (1292)	7.7 (1188)	10.3 (104)	1.392 (1.139–1.701)	0.0012
Intracranial bleeding	0.27 (39)	0.27 (37)	0.21 (2)	0.827 (0.200–3.425)	0.7933
Non-CABG-related major bleeding, study criteria	4.2 (665)	4.0 (596)	7.3 (69)	1.829 (1.425–2.346)	<0.0001
Non-CABG-related major bleeding, TIMI criteria	2.5 (395)	2.4 (359)	3.8 (36)	1.574 (1.118–2.218)	0.0094
CABG-related major bleeding, study criteria	7.7 (1272)	7.6 (1176)	9.4 (96)	1.297 (1.054–1.597)	0.0142
CABG-related major bleeding, TIMI criteria	5.6 (922)	5.5 (853)	6.7 (69)	1.282 (1.003–1.639)	0.0469
Major or minor bleeding, study criteria	15.4 (2548)	15.0 (2331)	21.5 (217)	1.504 (1.309–1.729)	<0.0001

[a]CI denotes confidence interval.

remained significant (online Supplement Table 2). Patients with PAD had a higher risk of CV death, MI and stroke (HR 1.43; 95% CI 1.207–1.693), all cause death (HR 1.55; 95% CI 1.223–1.961), and major bleeding (HR 1.27; 95% CI 1.05–1.53).

Ticagrelor compared with clopidogrel in PAD patients

The Kaplan-Meier estimated rates for primary efficacy events at one year (Figure 1) show that patients treated with ticagrelor had lower absolute rates that did not reach statistical significance. The numerical reduction in the rate of CV death, MI and stroke with ticagrelor compared to clopidogrel in PAD patients – 18.0% vs 20.6% (HR 0.846, 95% CI 0.64–1.11) – was similar to the reduction observed in patients without PAD (by PAD status interaction, $p = 0.99$). Similar results were found for all primary and secondary efficacy endpoints as evaluated by ticagrelor vs clopidogrel treatment and PAD status (Figure 2). In the PAD cohort, the rate of death from any cause was 8.7% in ticagrelor-treated patients compared to 11.9% in clopidogrel-treated patients, (HR 0.74, 95% CI 0.50–1.083, interaction $p = 0.12$).

The PLATO-defined total major bleeding rate in PAD patients was 14.8% in the ticagrelor arm as compared to 17.9% in the clopidogrel arm (HR 0.81; 95% CI 0.59–1.10), treatment by PAD status interaction ($p = 0.09$) (Figure 3). Similarly the non-CABG related PLATO major bleeding rate was 7.3% with ticagrelor as compared to 7.4% for clopidogrel (HR 0.99; 95% CI 0.62–1.58, interaction $p = 0.40$). Similar results were seen for total bleeding and non-CABG major bleeding when the TIMI criteria were used (Figure 3).

Discussion

There are two principal findings from this post-hoc analysis of patients with PAD in the PLATO trial. The first is that the presence of PAD in the entire randomized population of patients at the time of an ACS event was associated with significantly higher rates of cardiovascular death, myocardial infarction and stroke compared to patients without PAD presenting with ACS. This increased risk persisted after adjustment for baseline factors. The second finding was the lack of a significant interaction between the PAD patient subgroup and the overall PLATO trial. Specifically, the overall trial results with ticagrelor compared with clopidogrel were consistent in PAD patients with ACS, although the risk reduction in ischaemic events did not reach statistical significance. It should also be noted that there was not a statistically significant interaction for PAD patients treated with ticagrelor compared with

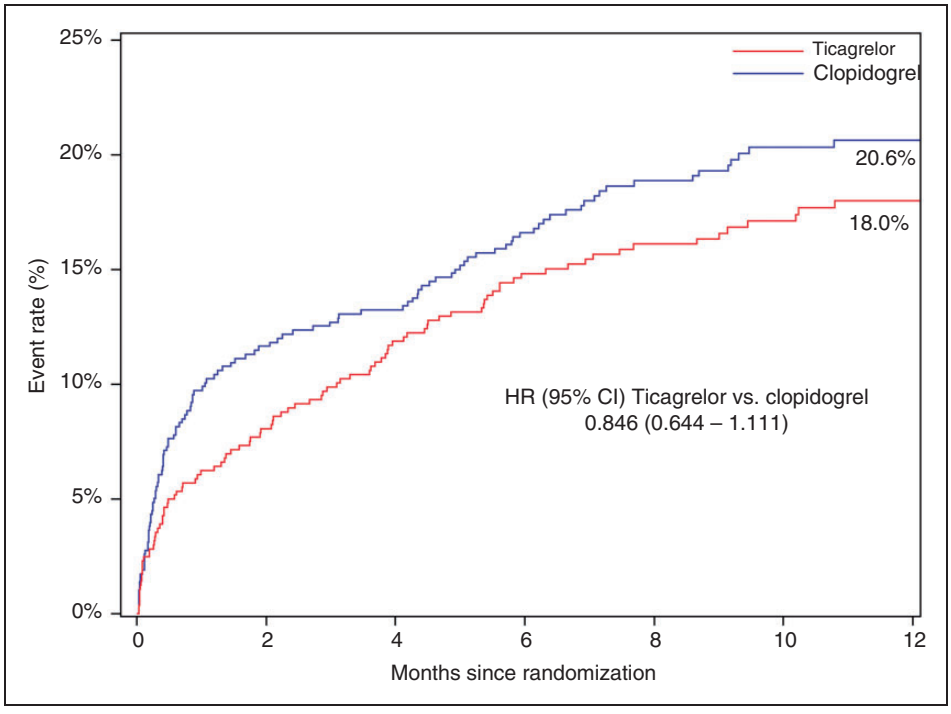

Figure 1. Primary outcome in PAD patients-Ticagrelor vs. Clopidogrel.
Figure Caption-kaplan-Meir Curves for CV death, MI, and stroke in PAD patients treated with ticagrelor versus. clopidogrel.

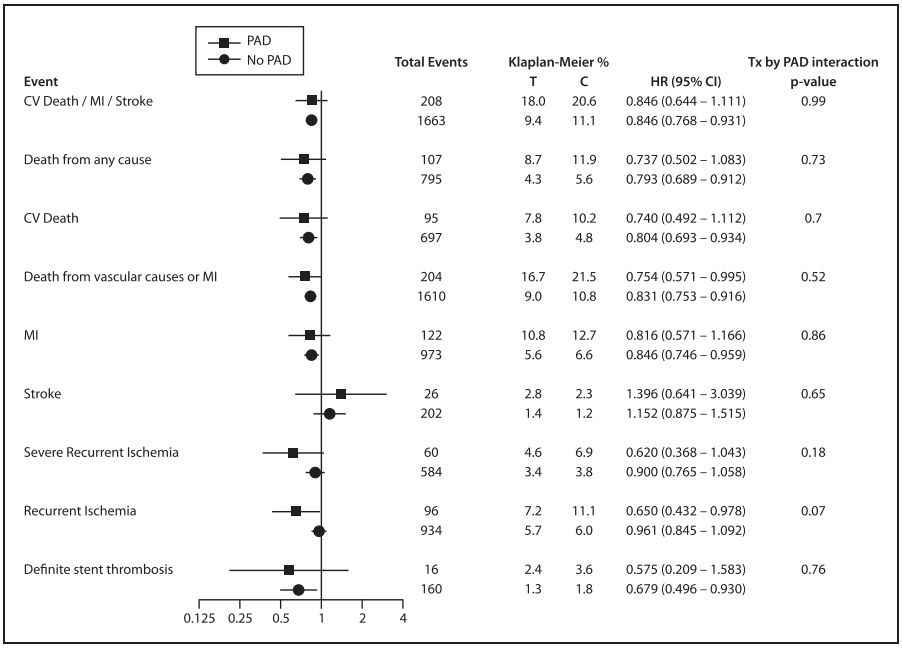

Figure 2. Efficacy outcomes by PAD status and treatment by Ticagrelor vs. Clopidogrel.
Figure Caption-forest plot of clinical efficacy outcomes in patients with and without PAD treated with ticagrelor versus. clopidogrel in the PLOT trial. Figures includes total events, HR Hazard Ratio, and p value for treatment interaction for each sub group.

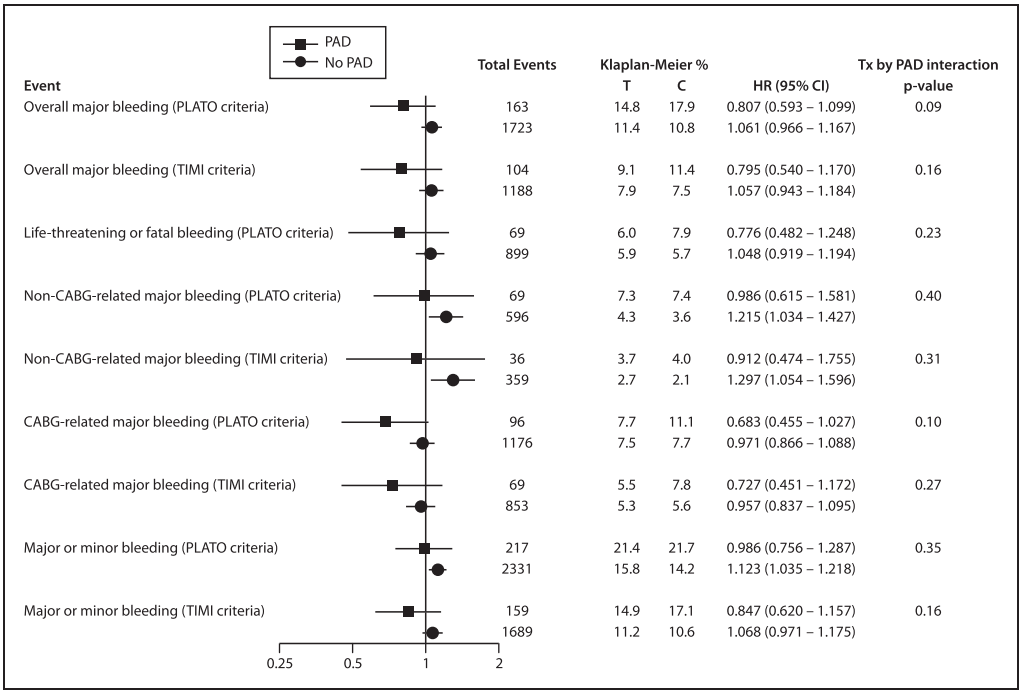

Figure 3. Safety outcomes by PAD status and treatment by Ticagrelor vs. Clopidogrel.
Figure Caption-forest plot of clinical efficacy outcomes in patients with and without PAD treated with ticagrelor versus. clopidogrel in the PLOT trial. Figures includes total events, HR Hazard Ratio, and p value for treatment interaction for each sub group.

clopidogrel. The numerical overall bleeding rates were lower with ticagrelor compared with clopidogrel; however again this finding was not statistically significant and did not represent a significant interaction. These findings raise the possibility of ticagrelor as a possible treatment for patients with PAD, although well-powered trials would need to test this in the context of current clinical care.

In PLATO, 6% of the patients presenting with ACS had a diagnosis of PAD at randomization. This contemporary rate appears lower than those previously reported as 9–15% of ACS patients.[2,11,12] However, the observed increased rates of cardiovascular events including CV death, MI and stroke are consistent with descriptions of increased risk in both non-ST-segment and ST-segment elevation ACS populations.[1,13–15] Additionally, PAD has been identified as a risk predictor in patients undergoing percutaneous coronary intervention[16] and outpatients with atherosclerosis.[17,18] Unfortunately, despite these repeated observations regarding the risk of patients with PAD, the available risk scores for patients presenting with ACS do not include PAD, a potentially easy-to-ascertain risk factor associated with substantially increased patient risk for adverse events.[19–21]

This lack of emphasis on PAD as a risk factor for adverse outcomes may in part explain the suboptimal use of proven evidence-based therapies for PAD patients hospitalized with ACS.[14,22,23] Another possible explanation may simply be the lack of awareness of PAD status in clinical practice. The PARTNERS study demonstrated that, in primary care, the presence of PAD often goes unrecognized.[24] In an effort to improve PAD patient outcomes for both inpatients and outpatients, performance measures have been developed to improve and standardize the care of these patients.[4] These measures recommend lipid-lowering therapy, blood pressure reduction and antiplatelet therapy.

Optimal antiplatelet therapy for patients with PAD is unknown, with the current ACC/AHA guidelines for the management of PAD recommending the use of an antiplatelet agent. Although aspirin is often used in PAD patients, the existing evidence does not clearly demonstrate a clinical benefit.[25] Clopidogrel does have an indication for PAD based on the CAPRIE trial in which clopidogrel 75 mg once daily was found to reduce CV death, MI and ischaemic stroke compared to 325 mg daily of aspirin, in all patients including the PAD subgroup.[6] The PAD subgroup of the CHARISMA trial found that dual therapy of clopidogrel and aspirin reduced MI and ischaemia hospitalizations at the cost of minor bleeding.[26] Hence, it is with this background that the findings of ticagrelor treatment compared with clopidogrel in the PLATO PAD patients should be considered.

The ischaemic event findings are in keeping with the results in the entire PLATO population and demonstrate reductions similar to those of the overall trial for CV death, MI and stroke with ticagrelor. Although numerically fewer ischaemic events occurred with ticagrelor, this was not statistically significant and could simply represent no true difference. With regards to bleeding, the numerically lower rates of major bleeding, defined by either PLATO trial criteria or TIMI criteria, although not statistically significant are reassuring. The ischaemic findings may be due to the more consistent and potent as well as reversible $P2Y_{12}$ inhibition afforded by ticagrelor, as opposed to clopidogrel, which is hampered by variable conversion of the prodrug into the active irreversibly acting metabolite. However, the numerically lower major bleeding findings are encouraging but are not statistically significant and likely represent a chance finding in a subgroup of the main trial that is noted to have much higher overall bleeding rates. These findings represent a potential step forward for these high-risk patients where the atherosclerotic burden is high and prior studies have demonstrated both elevated thrombotic and bleeding rates. It should be noted that a large ongoing trial – EUCLID (Examining Use of tiCagreLor In paD) – compares monotherapy ticagrelor to clopidogrel in decreasing the risk of thrombotic CV events in patients with PAD (ClinicalTrials.gov # NCT01732822).

Our study has some limitations that should be considered when reviewing the results. Importantly, the current study is a post-hoc analysis, and therefore all the findings should be considered as hypothesis generating. The presence of PAD was defined in the eCRF as intermittent claudication with prior objective confirmation, either as prior revascularization or ankle-brachial index less than 0.9. This may have lead to underreporting of PAD in the study. Unmeasured confounders cannot be excluded, and given the small size of the PAD subgroup adjustment for all confounders may be limited. Furthermore, the PAD population is a small subgroup and all results are underpowered and should not be used to make clinical decisions. The lack of significant effect in this higher risk population also raises the possibility of no clinical effect. Prospective well-powered studies in PAD patients are required to direct treatment decisions. However, PLATO is a large randomized trial and the analysis by treatment and PAD status show effects across multiple adjudicated clinical endpoints that are in line with the overall study findings.

In conclusion, patients with PAD and ACS represent a unique cohort of patients. These patients suffer a large atherosclerotic burden, with evidence of polyvascular disease, and they display a high rate of adverse cardiovascular events including CV death, MI and

stroke. The reduction of CV death, MI or stroke with ticagrelor compared with clopidogrel in PAD patients was consistent with the overall trial result although it did not reach statistical significance. Overall major bleeding was similar between the therapies. Further research is needed to determine if ticagrelor provides significant clinical benefit in patients with peripheral artery disease without ACS.

Funding

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Conflicts of interest

MRP reports receiving research grants from Johnson & Johnson, Bayer, AstraZeneca, NHBLI, AHRQ and Pluristem; Consultant/Advisory Board for Jansen, Bayer, Genzyme and Otsuka. RCB reports scientific advisory for Merck, Portola, Boehringer Ingelheim, Bayer and Daiichi-Sankyo. DMW reports no conflicts of interest. HE reports being an employee of AstraZeneca. WRH reports receiving research grants from AstraZeneca, GlaxoSmithKline, Aastrom, Biosense, Kyushu University, Osiris, Otsuka, Pluristem, Reneuron, Takeda and TheraVasc. JH reports being an employee of AstraZeneca. SH reports being an advisory board member for AstraZeneca, Bristol-Myers Squibb, Pfizer and Bayer; research support from GlaxoSmithKline, Pfizer and Sanofi-Aventis. KWM has received research grant support from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Regado Biotechnologies Sanofi-Aventis, Shering Plough and The Medicines Company; speaking/consultant honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, Polymedix and Sanofi-Aventis. PGS reports having received research grants from NYU School of Medicine, Sanofi and Servier; consultancy fees/honoraria from Ablynx, Amarin, Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi/sankyo, Eisai, GlaxoSmithKline, Lilly, Medtronic, MSD, Novartis, Otsuka, Pfizer, Roche, Sanofi, Servier, The Medicines Company and Vivus; has equity ownership in Aterovax. RFS reports receiving research grants from AstraZeneca, Eli Lilly/Daiichi Sankyo and Merck; research support from Accumetrics; honoraria from AstraZeneca, Eli Lilly/Daiichi Sankyo, Merck, Iroko, Accumetrics and Medscape; consultancy fees from AstraZeneca, Merck, Novartis, Accumetrics, Sanofi-Aventis/Regeneron, Bristol-Myers Squibb and Eisai. LW reports receiving research grants from AstraZeneca, Merck/Schering-Plough, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer and GlaxoSmithKline; being a consultant for Merck/Schering-Plough, Regado Biosciences, Evolva, Portola, C.S.L. Behring, Athera Biotechnologies, Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline and Bristol-Myers Squibb/Pfizer; lecture fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline and Schering-Plough; honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline and Schering-Plough/Merck; travel support from Bristol-Myers Squibb/Pfizer. SKJ reports research grant from AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Terumo Inc, Medtronic and Vascular Solutions; honoraria from The Medicines Company, AstraZeneca, Eli Lilly, Bristol-Myers Squibb and IROKO; consultant/advisory board from AstraZeneca, Eli Lilly, Merck, Medtronic and Sanofi.

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