Major bleeding in patients with peripheral artery disease: Insights from the EUCLID trial

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Background Rates and predictors of major bleeding in patients with peripheral artery disease (PAD) treated with antiplatelets have not been well studied. This post hoc analysis of EUCLID aimed to determine the incidence of major/minor bleeding, predictors of major bleeding, and risk of major adverse cardiovascular events (MACE) following major bleeding events.

Methods EUCLID, a multicenter randomized controlled trial of 13,885 patients with symptomatic PAD, compared ticagrelor with clopidogrel for the prevention of MACE. The primary safety end point was Thrombolysis in Myocardial Infarction (TIMI) major bleeding. Baseline characteristics were used to develop a multivariable model to determine factors associated with TIMI major bleeding. The occurrence and timing of MACE relative to a first major bleeding event were determined.

Results TIMI major bleeding occurred in 2.3% of participants overall (0.94 event/100 patient-years). There was no significant difference in major bleeding rates by treatment assignment. Factors associated with TIMI major bleeding included older age, geographic region, Rutherford class, and β-blocker use. Patients with TIMI major bleeding postrandomization had an increased risk of MACE (hazard ratio [HR] 4.46; 95% CI 3.40-5.84; $P < .0001$) compared with those without major bleeding; the association was strongest within 30 days after a bleeding event.

Conclusions In patients with symptomatic PAD, 0.94 major bleeding event/100 patient-years was observed and associated with older age, residing in North America, disease severity, and β-blocker use. Patients who had a major bleeding event were significantly more likely to experience MACE, especially within the first 30 days, when compared with patients who did not have major bleeding. (Am Heart J 2020;220:51-58.)

Peripheral artery disease (PAD) is a manifestation of atherosclerotic disease that affects arteries of the lower extremities. PAD affects more than 200 million people worldwide with a global prevalence between 3% and 12%.[1] Importantly, PAD is associated with poor cardiovascular outcomes (eg, myocardial infarction, ischemic stroke, and death) when compared with patients without PAD.[2] Although antiplatelet therapy with aspirin or clopidogrel in patients with PAD is a class I recommendation, little is known about the rates and predictors of major bleeding in patients with PAD.[3,4] There remains a need to better understand the balance between bleeding risk and the therapeutic benefits of antiplatelet agents in patients with PAD.

The occurrence of major adverse cardiovascular events (MACE) and bleeding events with the use of antiplatelet agents in patients with PAD has been described in subgroup analyses of earlier studies,[5-8] yet little data are available for stable, symptomatic patients with PAD. Risk factors for bleeding and the occurrence of MACE following bleeding events have been well described in patients with acute coronary syndrome and percutaneous coronary intervention.[9-11] Yet in patients with PAD, there remains a need to better understand the balance between bleeding risk and the therapeutic benefits of antiplatelet agents. The primary aim of this post hoc analysis of the

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Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial is to describe the incidence of major bleeding events (according to multiple major bleeding classification systems) in symptomatic patients with PAD treated with ticagrelor or clopidogrel. The second aim is to determine the baseline demographic and clinical characteristics associated with major bleeding. The third aim is to assess the relationship of an index major bleeding event on the occurrence of subsequent MACE.

Methods

Study design and population

The design and results of the EUCLID (NCT01732822) trial have been previously published.[1,7] In brief, EUCLID was a double-blind, multicenter, randomized controlled trial designed to evaluate the efficacy and safety of ticagrelor (90 mg twice daily) compared with clopidogrel (75 mg once daily) for the prevention of MACE in patients with symptomatic PAD.[1] *Symptomatic PAD* in EUCLID was defined as an ankle-brachial index ≤0.80 and lower extremity symptoms (n = 6,010), or prior lower extremity revascularization (n = 7,875). Key exclusion criteria included planned use of dual antiplatelet therapy, requirement for aspirin, history of bleeding diathesis, treatment with anticoagulation, or *poor metabolizer status for CYP2C$_{19}$*, defined as possessing a genotype consisting of 2 loss-of-function alleles. A total of 13,885 patients were randomized and followed for all clinical end points and serious adverse events until the end of the study. All patients provided written informed consent, and institutional review boards at each participating center approved the protocol.

End points

The end points for this analysis were derived from the primary safety end point of the EUCLID trial: Thrombolysis in Myocardial Infarction (TIMI) major bleeding. Bleeding events were also adjudicated using the Study of Platelet Inhibition and Patient Outcomes (PLATO), Bleeding Academic Research Consortium (BARC), and International Society on Thrombosis and Haemostasis (ISTH) bleeding definitions. Adjudication of these events was performed according to standard definitions as recorded in the EUCLID Clinical Endpoints Committee charter and annotated in the Appendix. All potential bleeding events were reported by site investigators in an electronic Web-based capture system with submission of supporting source documentation when applicable. Additionally, an automatic trigger process was implemented during the duration of the study to identify potential bleeding events when hemoglobin dropped more than 3 g/dL. The primary efficacy end point in EUCLID was MACE, described as cardiovascular death, myocardial infarction, or ischemic stroke. The occurrence of MACE following a major bleeding event was investigated in this report.

Statistics

The analysis was conducted using the intention-to-treat population in the EUCLID trial. We analyzed all events that occurred after randomization through the end of the study. Baseline characteristics are presented as means with SD and medians with corresponding 25th and 75th percentiles for continuous variables, and counts and percentages for categorical variables. Incidence (number and proportion of participants with event) and the exposure-adjusted event rate of overall bleeding and major bleeding in the population were calculated. For participants with multiple bleeding events, the first event of interest was analyzed. Baseline demographic and clinical characteristics associated with TIMI major bleeding were first evaluated by univariate analyses, for which hazard ratios (HRs) and corresponding 95% CIs were estimated using Cox proportional hazards models. Multivariate analysis was then performed with factors selected by stepwise and backward selection processes. A cutoff of a nominal *P* value of .05 was required for inclusion in the final model. Collinearity of continuous factors was assessed, and randomized treatment (ticagrelor and clopidogrel) was added to the final model. The *C*-index was estimated as a measure of model performance.

To evaluate the association of a major bleeding event on subsequent MACE, we used a multivariate analysis in which having a postrandomization bleeding event was included in the Cox model as a time-dependent covariate along with baseline covariates.[8] As a postrandomization risk factor, bleeding occurred at different time points for different participants. The bleeding status of a participant was examined at each time point since randomization, where all participants were first classified as "no bleeding." A participant would remain in this category until a bleeding event occurred and would then be reclassified as "bleeding." Under this framework, participants who experienced a MACE event prior to a bleeding event would have reached the end point without bleeding. A piecewise hazard function was built representing periods before day 30 and after day 30 postbleeding to evaluate the risk of early ischemic events versus later ischemic events. Wald χ^2 tests were carried out to examine whether the HRs were consistent across these periods. HRs and associated 95% CIs and *P* values were calculated.

All analyses were conducted using SAS software version 9.4 (SAS Institute, Inc, Cary, NC). *P* values were not adjusted for multiple comparisons.

Results

A total of 321 patients had a TIMI major bleeding event. The current analysis was conducted using the intention-to-treat population from the EUCLID trial. Previously published results reported 222 patients with TIMI major bleeding events; however, that analysis included patients

Table I. Baseline characteristics of EUCLID patients with and without TIMI major bleeding

Characteristic	TIMI major bleeding (n = 321)	No TIMI major bleeding (n = 13,564)	*P* value
Age group, y			
<65	113 (35.2%)	5772 (42.6%)	.0004
65-75	136 (42.4%)	5639 (41.6%)	
>75	72 (22.4%)	2153 (15.9%)	
Female sex	85 (26.5%)	3803 (28.0%)	.533
Geographic region			
Europe	120 (37.4%)	7378 (54.4%)	<.0001
Asia	42 (13.1%)	1560(11.5%)	
North America	129 (40.2%)	2911 (21.5%)	
Central/South America	30 (9.3%)	1710 (12.6%)	
BMI, mean (kg/m^2)	27.1 (5.4)	27.2 (5.0)	.453
Medical history			
History of coronary or carotid revascularization	112 (34.9%)	3703 (27.3%)	.003
Prior PCI	57 (17.8%)	1911 (14.1%)	.073
Prior CABG	47 (14.6%)	1489 (11.0%)	.037
Prior TIA	18 (5.6%)	489 (3.6%)	.066
Prior stroke	26/321 (8.1%)	1117/13,562 (8.2%)	.970
Prior CAD*	116 (36.1%)	3916 (28.9%)	.004
History of hyperlipidemia	259 (80.7%)	10,221 (75.4%)	.054
History of diabetes mellitus	132 (41.1%)	5213 (38.4%)	.239
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	95 (30.4%)	3210 (24.4%)	.006
Medications at baseline			
Prior antiplatelet use	277 (86.3%)	11,418 (84.2%)	.338
Statin	240 (74.8%)	9941 (73.3%)	.737
β-Blocker	164 (51.1%)	5476 (40.4%)	<.001
Clopidogrel	118 (36.8%)	4355 (32.1%)	.082
PPI	76 (23.7%)	2656 (19.6%)	.064
Rutherford classification at baseline†			
Asymptomatic	74 (23.1%)	2527 (18.6%)	.022
Mild/moderate claudication	156 (48.6%)	7254 (53.5%)	
Severe claudication	69 (21.5%)	3159 (23.3%)	
CLI	22 (6.9%)	621 (4.6%)	
Inclusion criterion met for randomization			
ABI/TBI criterion	108 (33.6%)	5902 (43.5%)	<.001
Prior revascularization	213 (66.4%)	7662 (56.5%)	
Number of prior vascular beds‡			
1	157 (48.9%)	7647 (56.4%)	.018
2	122 (38.0%)	4566 (33.7%)	
3	42 (13.1%)	1351 (10.0%)	
Smoking status at baseline			
Current smoker	99 (31.0%)	4190 (31.1%)	.439
Former smoker	161 (50.5%)	6369 (47.2%)	
Never smoked	59 (18.5%)	2925 (21.7%)	

Data presented as n (%).
BMI, body mass index; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *TIA*, transient ischemic attack; *CAD*, coronary artery disease; *eGFR*, estimated glomerular filtration rate; *PPI*, proton pump inhibitor; *CLI*, critical limb ischemia; *ABI*, ankle-brachial index; *TBI*, toe-brachial index.
* *Prior CAD* is defined as the patient having had a prior MI, prior PCI, or prior CABG.
† Rutherford classification is a commonly used clinical staging system for describing PAD.
‡ A *vascular bed* is defined as either PAD; prior CAD (defined as above); or *prior cerebrovascular disease* defined as prior stroke, prior TIA, prior carotid artery stenosis, or prior carotid revascularization. The variable for patients in EUCLID can hence receive values from 1 to 3.

in the safety population who received at least 1 dose of study drug during the treatment period.[8] Demographics of patients according to whether or not they had TIMI major bleeding are shown in Table I. Patients with major bleeding events were generally older, more commonly resided in North America, were more likely to have a history of coronary or carotid revascularization, had a higher Rutherford classification, had a prior history of coronary artery or cerebrovascular disease, and were more likely to be treated with β-blockers at baseline compared with patients without major bleeding events.

Major bleeding according to classification

The incidence of any bleeding and major bleeding based on multiple bleeding definitions can be found in Table II. The incidence of TIMI major bleeding during

Table II. Incidence and rate of bleeding in the EUCLID cohort by bleeding definition

Bleeding definition	Randomized population (N = 13,882)	
	Number of patients with bleeding events n (%)	Bleeding event rate (per 100 pt-y)
TIMI		
Any (major/minor/requiring medical attention/minimal)	2064 (14.9%)	7.08
Major	321 (2.3%)	0.94
PLATO		
Any (major/minor/minimal/other)	2064 (14.9%)	7.08
Major	583 (4.2%)	1.73
ISTH		
Any (major/minor)	2044 (14.7)	6.99
Major	647 (4.7%)	1.93
BARC		
Any (BARC 1-5)	2064 (14.9)	7.08
Major (BARC 3 or greater)	657 (4.7)	2.01

Table III. Multivariate analysis evaluating association between baseline characteristics and TIMI major bleeding among EUCLID patients

Parameter for multivariate analysis	Parameter estimate	Standard error	χ^2	*P* value	HR (95% CI)
Every 10-y increase in age	0.22	0.07	10.98	.0009	1.25 (1.10-1.43)
Region (compared with North America)				.0001	
Asia	–0.44	0.18	5.76	.0163	0.64 (0.45-0.92)
Europe	–0.88	0.13	45.39	<.0001	0.42 (0.32-0.54)
South America	–0.75	0.21	13.07	.0003	0.472 (0.31-0.71)
Rutherford classification at baseline* (compared with "asymptomatic" category)				<.0001	
Mild/moderate claudication	–0.268	0.14	3.41	.06	0.77 (0.58-1.02)
Severe claudication	–0.23	0.17	1.86	.17	0.79 (0.57-1.11)
CLI	0.25	0.24	1.07	.30	1.29 (0.80-2.08)
β-Blocker treatment at baseline	0.31	0.12	7.21	.01	1.36 (1.09-1.71)
Ticagrelor vs. clopidogrel	–0.09	0.12	0.63	.43	0.92 (0.74-1.14)

C-index 0.65.
* Rutherford Classification is a commonly used clinical staging system for describing PAD.

study follow-up (median 30 months) was 2.3% with an event rate of 0.94 per 100 patient-years of follow-up. The rates of major bleeding according to the PLATO (4.2%, event rate 1.73 per 100 patient-years), ISTH (4.7%, event rate 1.93 per 100 patient-years), and BARC definitions (4.7%, event rate 2.01 per 100 patient-years) were similar. The site of bleeding is shown in Supplemental Table I, including total bleeding events and stratified based on treatment assignment.

Factors associated with major bleeding

Factors associated with major bleeding in a univariate analysis included age, geographic region (North America, specifically), history of coronary or carotid revascularization, prior coronary artery bypass graft surgery, treatment with β-blockers, Rutherford classification, baseline indication for inclusion (ankle-brachial index or prior revascularization), prior coronary artery disease, and number of diseased vascular beds. The results of a multivariate analysis to identify independent risk factors are shown in Table III. Age (10-year increase), geographic region, Rutherford classification at baseline, and β-blocker treatment remained significant factors associated with TIMI major bleeding after adjustment. The discriminative power of the model as measured by the *C*-index was 0.65.

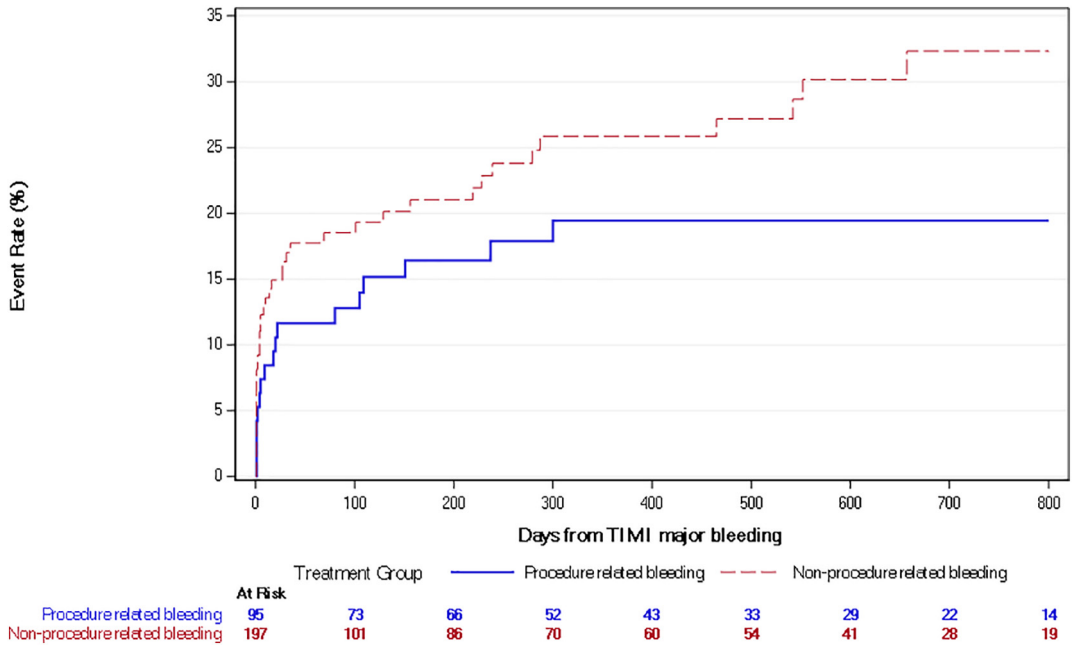
Treatment effect on bleeding

There was no difference in risk of TIMI major bleeding between patients randomized to ticagrelor or clopidogrel (HR 0.915; 95% CI 0.735-1.139; $P = .4273$). In the overall EUCLID trial, about 28% of all participants discontinued study treatments prematurely. Ticagrelor was prematurely discontinued more often than clopidogrel (30% vs 26%; $P < .001$). Supplemental Figure 1 shows the Kaplan-Meier curves for major bleeding in the intention-to-treat population (all patients [right panel]) and on-treatment population (those patients still taking study medication at visit before major bleeding event [left panel]). Adverse events leading to permanent discontinuation of study

Table IV. MACE event rate in EUCLID and after TIMI major bleeding event

	Cumulative event rate (%) of MACE (95% CI)		
Study population		Postrandomization	
	Day 30	1 y	Overall
	0.4% (0.3-0.5)	4.2% (3.9-4.5)	4.4 per 100 pt-y
After TIMI major bleeding		Post-TIMI major bleeding event	
	Day 30	1 y	Overall
	14.1% (9.7-18.5)	22.6% (16.9-28.3)	22.7 per 100 pt-y

Figure 1



and Central Figure. Cumulative incidence of MACE post-TIMI major bleeding.

drug were primarily dyspnea (4.8% vs 0.8%; $P < .0001$) and discontinuation of study drug due to a bleeding event that was documented by the investigator on the case report form, which included unadjudicated minimal bleeding (2.4% in the ticagrelor group vs 1.6% in the clopidogrel group; $P < .0001$).

MACE following a major bleeding event

The occurrence of MACE in patients following a TIMI major bleeding event was assessed compared with the occurrence of MACE in the overall study population without TIMI major bleeding at different time points (Table IV). The cumulative event rates of MACE for the entire study population at 30 days and 1 year postrandomization were 0.4% and 4.2%, respectively. The rate was 14.1% at 30 days and 22.6% at 1 year after the first TIMI major bleeding event. The MACE curve as a function of time after TIMI major bleeding event is depicted in Figure 1. There is an increase of events observed shortly after the bleeding event.

The relationship between TIMI major bleeding and MACE adjusting for baseline covariates is summarized in Table V. Overall, the risk of MACE increased following a postrandomization major bleeding event (HR 4.46; 95% CI 3.40-5.84; $P < .0001$). More specifically, the association of major bleeding with MACE within 30 days was greater than the association of major bleeding with MACE after 30 days (HR 38.51; 95% CI 27.70-53.54 vs HR 1.67; 95% CI 1.07-2.60; $P < .0001$).

Discussion

This post hoc analysis from the EUCLID trial provides deeper insights into the occurrence and impact of major bleeding in patients with PAD treated with ticagrelor and clopidogrel. The incidence and rates of TIMI major bleeding were 0.94 event/100 patient-years and similar in patients randomized to ticagrelor and clopidogrel. The factors associated with TIMI major bleeding after

Table V. Relationship between TIMI major bleeding and risk of MACE both independent and dependent of time after bleeding event

Exposure	HR (95% CI)	*P* value testing Estimated HR = 1	*P* value short- vs long-term effect of bleeding
Model 1: risk of MACE is independent of time after bleeding			
TIMI major bleeding at any time	4.46 (3.40-5.84)	<.0001	
Model 2: risk of MACE is dependent upon time after bleeding			
Short-term (≤30 d) effect of TIMI major bleeding	38.51 (27.70-53.54)	<.0001	<.0001
Long-term (>30 d) effect of TIMI major bleeding	1.67 (1.07-2.60)	0.0243	

adjustment included older age, geographic region, Rutherford class, and β-blocker use. Patients with TIMI major bleeding who did not have a MACE prior to a bleeding event had a higher percentage of postbleeding MACE compared with patients without TIMI major bleeding. The association of major bleeding and MACE was greater in the short term than the long term, with MACE more frequently occurring within 30 days following an index major bleeding event.

Previous studies, including CAPRIE, CHARISMA, TRA2°P-TIMI 50, and PEGASUS-TIMI 54, showed increased rates of bleeding in patients with PAD treated with antiplatelet agents compared with patients without PAD.[10-13] In the Reduction of Atherothrombosis for Continued Health registry, patients with or at risk for atherothrombosis were assessed to develop a risk score to quantify bleeding risk in outpatients receiving a broad range of antithrombotic therapies.[14] This was the first study to develop a risk score in patients with stable atherothrombosis; other risk scores were designed for patients with atrial fibrillation, those with acute coronary syndromes, or those undergoing percutaneous coronary intervention. Baseline variables were analyzed as potential predictors of bleeding and assessed using modified regression analysis. The bleeding risk score included 1 demographic factor (age), 2 predictors related to medical history (PAD, congestive heart failure), 4 comorbidities of lifestyle characteristics (diabetes mellitus, hypercholesterolemia, hypertension, smoking), and 2 medication regimens (antiplatelets, oral anticoagulants).

In our study, we included all baseline characteristics to be analyzed as potential bleeding risk factors. Ultimately, we found that baseline characteristics, such as age, geographic region, disease severity, and medications used throughout the trial, were also important factors associated with major bleeding events. One perplexing finding in our analysis is the significant association of β-blocker use and TIMI major bleeding. This relationship is unlikely to be causal because β-blocker use is not known to be associated with major bleeding in this population, but the significance of β-blocker use may be a marker of more complex atherothrombotic disease that may make these patients more susceptible to major bleeding.

During the design phase of EUCLID, trial leadership incorporated several bleeding scores used to define major, minor, and minimal bleeding (including TIMI, PLATO, ISTH, BARC). Full descriptions of these bleeding definitions are included in the Appendix. The abundance of bleeding definitions highlights the complexity of defining bleeding events in a large trial of stable patients with atherothrombosis. Thus, a decision was made to adjudicate all bleeding events using multiple classification schemes in EUCLID to ensure accurate comparisons across studies. The percentage of patients with major bleeding events was similar according to the BARC, ISTH, and PLATO scores but was significantly lower according to the TIMI definition. This finding can be partially explained by the more restrictive definition of major bleeding as defined using the TIMI criteria, yielding fewer positively adjudicated major bleeding events and lower event rates. These findings highlight the importance of taking into account which classification system was used when comparing event rates across studies, and lend support to the idea that at least 2 adjudication classifications should be used for studies designed to be generalizable across heterogeneous populations (eg, PAD).

The final aim of this study evaluated the occurrence of MACE following a major bleeding event. Not surprisingly, patients with PAD who experienced an index major bleeding event who did not have a MACE prior to their major bleed had a significantly higher hazard of MACE when compared with patients who did not have an index major bleeding event. When the association between major bleeding and MACE was evaluated, the hazard of MACE was more pronounced within the first 30 days of a bleeding event as compared with after 30 days. Whether these increased risks are directly related to the bleeding event, reflect a higher-risk group of patients, or are related to baseline hemoglobin or anemia remains to be determined. The association of MACE with hemoglobin drop, anemia, and transfusion has been described in the cardiovascular literature, particularly during hospitalization for acute coronary syndrome. In EUCLID, we primarily studied the effect of overt bleeding and did not collect hemoglobin values on all participants. Future studies of patients with PAD should evaluate this association in more detail.

Overall, these findings suggest that patients with PAD who are older, have more severe disease, and live in

certain geographic locations should be followed closely in the early period following major bleeding. Of note, our findings are within the parameters of the study, including the time from randomization to the time to the first major bleeding event, without full consideration of how long patients were previously taking antiplatelet medications.

Limitations

The current analysis from EUCLID has several limitations. First, patients in EUCLID were required to be symptomatic; thus, the rate of major bleeding does not reflect major bleeding event rates in asymptomatic patients with PAD. Furthermore, the US Food and Drug Administration recommended that the EUCLID trial include a cohort of patients with PAD who did not have a high degree of coronary artery disease; thus, our results are generalizable to patients with PAD but may not represent the event rate in a broader population of patients with atherosclerosis in multiple vascular beds. Our study does not address the potential confounding effect of antiplatelet discontinuation on the relationship between major bleeding events and MACE. Thus, there is no intention of implying causal inference from these findings. In addition, the relationship between bleeding and MACE applied only in patients who did not experience a MACE event prior to their bleed, which may further cloud the causal connection. Finally, the current study was limited by only including demographic and clinical characteristics that were known at baseline in the analysis; thus, no postrandomization factors or events were included in the model (eg, the impact of new medications, development of clinical conditions known to be associated with bleeding such as acute coronary syndrome).

Conclusions

In conclusion, in patients with symptomatic PAD, the rate of major bleeding was found to be 0.94 event/100 patient-years. Factors including older age, residing in North America, higher baseline Rutherford class, and β-blocker use were all significantly associated with TIMI major bleeding. Patients who had a first episode of postrandomization major bleeding were significantly more likely to experience MACE as compared with those with no major bleeding events, especially within the first 30 days after the bleeding event. Future studies should focus on patient and clinician perspectives on major and minor bleeding in patients with PAD taking antiplatelet agents, as they may shed light on antiplatelet discontinuation in this population. Studies of the use of bleeding avoidance strategies, treatment options for bleeding (eg, transfusion), and other methods to mitigate the occurrence of MACE following major bleeding events in patients with PAD are also warranted given the findings of this study. It is critical for vascular patients to better understand the balance between ischemic and bleeding risks, and this should be further explored to guide clinicians and patients in clinical decision making.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.11.007.

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