Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Impact of Procedural Bleeding in Peripheral Artery Disease

An Analysis From EUCLID Trial

Aman Kansal, BS
Zhen Huang, MS
Frank W. Rockhold, PhD
Iris Baumgartner, MD
Jeffrey S. Berger, MD, MS
Juuso I. Blomster, MD, PhD
F. Gerry Fowkes, MBChB, PhD
Brian Katona, PharmD
Kenneth W. Mahaffey, MD
Lars Norgren, MD, PhD
William R. Hiatt, MD
Manesh R. Patel, MD
W. Schuyler Jones, MD

BACKGROUND: The relationship between invasive vascular procedures and bleeding in patients with peripheral artery disease has not been well described in the literature. This post hoc analysis from the EUCLID trial (Examining Use of Ticagrelor in Peripheral Artery Disease) aimed to describe the incidence of major and minor postprocedural bleeding and characterize the timing and severity of bleeding events relative to the procedure.

METHODS: EUCLID was a multicenter, randomized controlled trial of 13 885 patients with symptomatic peripheral artery disease that tested the efficacy and safety of ticagrelor compared with clopidogrel for the prevention of major adverse cardiovascular events. A total of 2661 patients underwent 3062 coronary revascularization, peripheral revascularization, and amputation during the study. The primary safety end point was Thrombolysis in Myocardial Infarction major or minor bleeding. All bleeding events were formally adjudicated by a clinical end point classification group.

RESULTS: Major bleeding events most often occurred ≤7 days following the procedure. The incidence of Thrombolysis in Myocardial Infarction major or minor bleeding ≤7 days following peripheral revascularization (3.3%; 95% CI, 2.5%–4.1%) was similar to rates after coronary revascularization (4.0%; 95% CI, 2.6%–5.4%) and lower extremity amputation (2.3%; 95% CI, 0.8%–3.8%). The severity of bleeding events (as graded by drop in hemoglobin, need for transfusion, bleeding in a critical location, and fatal bleeding) was also similar following peripheral, coronary revascularization, and lower extremity amputation.

CONCLUSIONS: The incidence of Thrombolysis in Myocardial Infarction major/minor bleeding following peripheral revascularization is comparable to rates after coronary revascularization and lower extremity amputation, and the majority of bleeding events occur within 7 days following the procedure. The severity of periprocedural bleeding is also similar after procedures, with the most frequently adjudicated reason being a drop in hemoglobin ≥2 g/dL. Future studies should be performed to enhance our understanding of bleeding risk related to revascularization and amputation procedures in peripheral artery disease patients.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: amputation ■ hemoglobins ■ incidence ■ lower extremity ■ peripheral arterial disease

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WHAT IS KNOWN

- Peripheral revascularization is a class I recommendation for patients with critical limb ischemia and for those with intermittent claudication who have failed medical therapy and exercise training and performance continues to increase.
- Although risk of bleeding has been studied extensively in coronary revascularization, there have been limited studies evaluating the occurrence, severity, and impact of periprocedural bleeding in patients with peripheral artery disease.

WHAT THE STUDY ADDS

- This is the largest peripheral artery disease cohort study analyzing procedural bleeding that has been performed; there were 3 main findings.
- The majority of periprocedural bleeding occurred within 7 days and was similar between peripheral revascularization, coronary revascularization, and amputation.
- The severity of bleeding events (as graded by drop in hemoglobin, need for transfusion, bleeding in a critical location, and fatal bleeding) was also similar following peripheral, coronary revascularization, and lower extremity amputation.

Peripheral artery disease (PAD) is a manifestation of atherosclerosis that affects the lower extremities. It is a major health concern affecting >200 million people worldwide.[1] Many patients with PAD have functional limitations and are at high risk of poor cardiovascular outcomes, including myocardial infarction, ischemic stroke, amputation, and death.[2] Peripheral revascularization is a class I recommendation for patients with critical limb ischemia and for those with intermittent claudication who have failed medical therapy and exercise training.[1] While the performance of peripheral revascularization continues to increase, the occurrence, severity, and impact of periprocedural bleeding has not been well studied in patients with PAD.

In contrast, the risk of bleeding has been studied extensively in patients with coronary artery disease undergoing coronary artery bypass graft surgery and percutaneous coronary intervention. Major bleeding postpercutaneous coronary intervention has been shown to be independently associated with increases in both short- and long-term risk of mortality and major adverse cardiovascular events.[3–5] Previous studies have also demonstrated the association of antiplatelet and antithrombotic medications with an increased risk of bleeding in patients with PAD.[6–8] Although some patients in these studies did undergo endovascular revascularization, the relationship between procedure and bleeding has not been prospectively assessed. A retrospective analysis from the Society of Vascular Surgery Vascular Quality Initiative evaluated the incidence and risk factors for access site hematomas and pseudoaneurysms after peripheral vascular interventions, reporting that access site complications occurred in 3.5% of procedures and of those, 9.7% were moderate requiring transfusion, 5.4% were moderate requiring thrombin injection, and 10.5% were severe requiring surgery.[9] Importantly, these events were not adjudicated and the timing of events was not reported.

The EUCLID trial (Examining Use of Ticagrelor in Peripheral Artery Disease) was a large, multicenter, multinational study of patients with symptomatic PAD.[10] A number of revascularization procedures and associated bleeding events occurred during study conduct. The ascertainment process for bleeding events was broad, and all bleeding events were adjudicated by a clinical end point classification group. The first aim of this report is to describe the incidence of both major and minor periprocedural bleeding events in patients with PAD undergoing peripheral revascularization, coronary revascularization, and lower extremity amputation. The second aim is to characterize the timing of bleeding events relative to the procedure. The third aim is to characterize the severity of bleeding events using formal adjudicated results.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

EUCLID was a double-blind, active-comparator, randomized controlled trial to test the hypothesis that monotherapy with ticagrelor would be superior to clopidogrel in preventing major adverse cardiovascular events (myocardial infarction, ischemic stroke, cardiovascular death) in patients with symptomatic PAD. Details from the EUCLID study have been previously published. From December 2012 through March 2014, a total of 16 237 patients were enrolled and screened for randomization at 811 clinical centers in 28 countries. A total of 13 855 patients underwent randomization and were followed for the occurrence of composite primary events through May 9, 2016.[10]

Patients were randomized in a 1:1 fashion to receive either ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). Randomization was performed via interactive voice-response or Web-response system. As the treatment effect on the primary end point was nearly identical between randomized groups, all participants were pooled for these analyses. The study protocol was approved by appropriate ethics committees at participating sites, and all patients provided written informed consent.

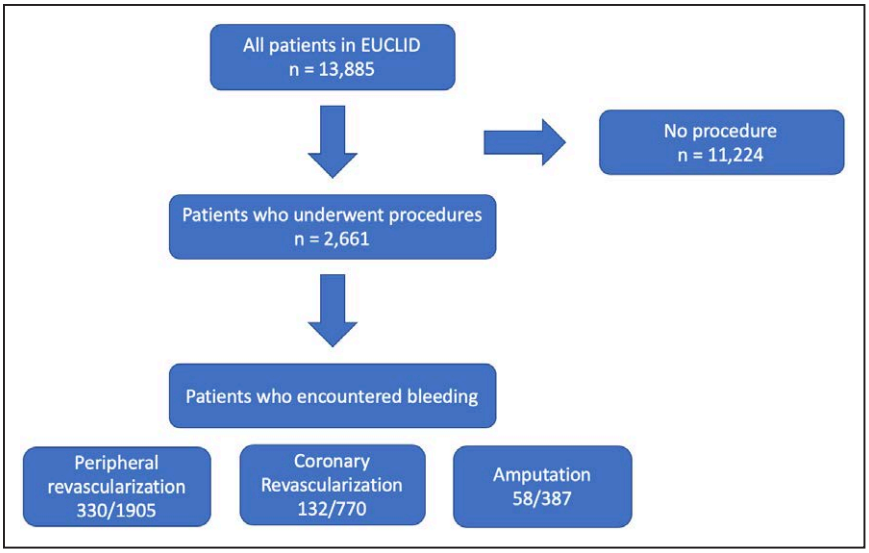

Figure 1. Flow diagram of patients in EUCLID trial (Examining Use of Ticagrelor in Peripheral Artery Disease) who experienced procedural bleeding.

End Points

The end points for this analysis include (1) major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria and (2) TIMI major/minor bleeding. The definition of procedural bleeding is a TIMI major/minor bleeding at the time of or following coronary revascularization (percutaneous coronary intervention and coronary artery bypass graft surgery), peripheral revascularization (lower extremity endovascular and surgical procedures), and lower extremity amputation. The performance of these procedures was allowed during the course of the study and was at the discretion of local clinical experts. All procedures and bleeding events were site-reported in an electronic Web-based capture system with submission of supporting source documentation where applicable. Automatic triggers were additionally used to identify potential bleeding events with a drop in hemoglobin. Adjudication of bleeding events was performed according to definitions in the EUCLID Clinical End points Classification Charter with board certification in cardiology as a prerequisite.

Statistical Analysis

The analysis population included randomized participants in the EUCLID trial. We analyzed all events that occurred during the study and used *P* to report intergroup comparisons. Baseline characteristics were summarized by mean and SD, median and 25th, 75th percentiles for continuous variables, and counts and percentages for categorical variables. Timing of TIMI major and minor bleeding events following procedures was analyzed for participants who had peripheral revascularization, coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention), and lower extremity amputation. Bleeding event rates and 95% CIs at 7, 30, 180 days, 1-year post-procedure, and up to 900 days were estimated using the Kaplan-Meier method. Cumulative event rates for bleeding were also compared using the log-rank test. For participants with multiple events or multiple procedures, only the first event following the first procedure of interest was analyzed. Further analyses using the International Society on Thrombosis and Haemostasis (ISTH) classification were carried out to investigate the severity of bleeding events within 30 days of a procedure because TIMI subcategories did not require grading the severity of bleeding events (eg, decrease in hemoglobin ≥2 g/dL, transfusion of ≥2 units of packed red blood cells, symptomatic bleed in a critical location, and fatal bleeding). Kaplan-Meier estimated event rates of ISTH major bleeding are reported for participants with a decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 units of whole blood or red cells, symptomatic bleed in a critical location, and fatal bleeding.

All analyses were conducted with the use of SAS software version 9.0 or higher (SAS Institute).

RESULTS

Of the 2661 patients undergoing peripheral/coronary revascularization or lower extremity amputation (a total of 3062 procedures were performed), 218 patients experienced TIMI major or minor bleeding periprocedurally. If the patient had both procedures, the bleeding associated with each individual procedure is reported and then analyzed separately. A diagram showing the patient flow from the overall EUCLID trial is shown in Figure 1. Demographic and clinical characteristics of patients according to whether or not they had TIMI major or minor bleeding are shown in Table 1. Patients with major or minor periprocedural bleeding events were more commonly older, female, enrolled in North America, and were more likely to have a history of smoking, coronary or carotid revascularization, coronary artery disease, or dyslipidemia. These patients were also more commonly on antiplatelet, statin, or β-blocker therapy at baseline. In addition, bleeding events were more common in patients randomized to ticagrelor over clopidogrel; however, the increase was not statistically significant (8.1% versus 7.6%; *P*=0.62). Finally, these patients more commonly had disease in > 1 vascular bed (coronary, cerebrovascular, lower extremity).

Table 1. Baseline Characteristics of Patients With and Without TIMI Major or Minor Bleeding Events Post-Procedure (Coronary and/or Peripheral Revascularization and Lower Extremity Amputation)

Characteristic	Patients With TIMI Major or Minor Bleeding Event(s) (N=218)	Patients Without TIMI Major or Minor Bleeding Event(s) (N=2452)	*P* Value of Association of Baseline Characteristics to TIMI Major or Minor Bleeding
Age, median (25th, 75th), y	67.0 (61.0, 73.0)	66.0 (60.0, 72.0)	0.3530
Female sex	76 (36.4%)	660 (26.9%)	0.0035
Geographic region			<0.0001
Europe	75 (35.9%)	1216 (49.6%)	
Asia	14 (6.7%)	220 (9.0%)	
North America	110 (52.6%)	814 (33.2%)	
Central/South America	10 (4.8%)	202 (8.2%)	
History of coronary or carotid revascularization	86 (41.1%)	907 (37.0%)	0.1871
History of coronary stent implantation	43 (20.6%)	491 (20.0%)	0.8369
Prior CABG	41 (19.6%)	387 (15.8%)	0.1407
Prior TIA	21 (10.0%)	110 (4.5%)	0.0004
Dyslipidemia	169 (80.9%)	1978 (80.7%)	0.8938
Medications			
Prior antiplatelet therapy	191 (91.4%)	2197 (89.6%)	0.3781
Statins	163 (78.0%)	1871 (76.3%)	0.5945
Beta-blockers	107 (51.2%)	1140 (46.5%)	0.1426
Clopidogrel	95 (45.5%)	985 (40.2%)	0.1572
PPIs	62 (29.7%)	563 (23.0%)	0.0244
Limb symptoms			0.5952
Asymptomatic	45 (21.5%)	473 (19.3%)	
Mild/moderate claudication	99 (47.4%)	1201 (49.0%)	
Severe claudication	47 (22.5%)	626 (25.5%)	
CLI	18 (8.6%)	151 (6.2%)	
Inclusion criteria for randomization			0.3213
ABI/TBI criterion	51 (24.4%)	687 (28.0%)	
Prior revascularization	158 (75.6%)	1765 (72.0%)	
History of diabetes mellitus	889 (42.1%)	1080 (44.0%)	0.7545
Prior CAD	84 (40.2%)	905 (36.9%)	0.2940
Number of affected vascular beds at enrollment			0.3210
1	88 (42.1%)	1176 (48.0%)	
2	80 (38.3%)	918 (37.4%)	
3	41 (19.6%)	358 (14.6%)	
Smoking status at baseline			0.5562
Current smoker	74 (35.7%)	834 (34.3%)	
Former smoker	95 (45.9%)	1202 (49.4%)	
Never smoked	38 (18.4%)	398 (16.4%)	

ABI indicates ankle-brachial index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CLI, critical limb ischemia; PPI, proton pump inhibitor; TBI, toe-brachial index; TIA, transient ischemic attack; and TIMI, Thrombolysis in Myocardial Infarction.

Procedures Performed

In EUCLID, 770 patients underwent coronary revascularization (626 percutaneous coronary intervention, 176 coronary artery bypass graft). A total of 1738 patients underwent lower extremity revascularization (1347 endovascular, 688 surgical), 203 carotid revascularization procedures, and 38 other revascularization procedures including mesenteric and renal arteries. A total of 387 underwent any amputation during the course of the study (148 above knee, 69 below knee, 170 minor). These numbers are reported in Tables 2, 3, and 4; Table I in the Data Supplement.

Incidence of Bleeding

The overall incidence of TIMI major or minor bleeding following procedures is shown in Table 5. The incidence of bleeding ≤7 days following peripheral revascularization (3.3%; CI, 2.5%–4.1%) was similar to the rates following coronary revascularization (4.0%; CI, 2.6%–5.4%) and lower extremity amputation (2.3%; CI, 0.8%–3.8%). The cumulative incidence of major/minor bleeding within 30 days following peripheral revascularization increased (4.0%; CI, 3.1%–4.9%) but remained similar to rates after coronary revascularization (4.4%; CI, 2.9%–5.9%) and lower extremity amputation (4.0%; CI, 2.0%–6.0%).

Timing of Bleeding

TIMI major or minor bleeding events following peripheral revascularization most often occurred periprocedurally (Table 5). Among patients who experienced any bleeding events post-procedure, nearly half of them occurred within the first 7 days (62 versus 147). The cumulative event rate within the first 7 days was 3.3%, CI, 2.5%–4.1% compared with those at 30 days (4.0%; CI, 3.1%–4.9%), 180 days (5.8%; CI, 4.7%–6.9%), and 365 days (7.0%; CI, 5.8%–8.2%; Figure 2 and 3).

Table 2. Severity of Bleeds Within 30 Days of Procedure

ISTH Bleeding Categories	Peripheral Revascularization		Coronary Revascularization		Amputation		*P* Value (Log-Rank Test Comparing 3 Procedures)
	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)	
ISTH major and minor bleeding post-procedure	330/1905 (17.3%)		132/770 (17.1%)		58/387 (15.0%)		0.5448
ISTH major bleeding post-procedure	187/1905 (9.8%)		76/770 (9.9%)		38/387 (9.8%)		0.8837
ISTH minor bleeding post-procedure	175/1905 (9.2%)		71/770 (9.2%)		26/387 (6.7%)		0.2584
ISTH major and minor bleeding within 30 days of procedure	130/1905 (6.8%)	6.9 (5.8–8.0)	61/770 (7.9%)	8.0 (6.1–9.9)	27/387 (7.0%)	7.1 (4.5–9.7)	
Major bleeding ISTH major							
Any	89 (4.6%)	4.7 (3.7–5.7)	40 (5.1%)	5.2 (3.6–6.8)	20 (5.2%)	5.3 (3.0–7.6)	0.8837
Decrease in hemoglobin ≥2 g/dL	75 (3.9%)	4.0 (3.1–4.9)	32 (4.2%)	4.2 (2.8–5.6)	16 (4.1%)	4.2 (2.2–6.2)	0.7758
Transfusion of ≥2 units of PRBCs	8 (0.4%)	0.4 (0.1–0.7)	4 (0.5%)	0.5 (0.0–1.0)	3 (0.8%)	0.8 (0.0–1.7)	0.5946
Symptomatic bleed in a critical location	3 (0.2%)	0.2 (0.0–0.4)	4 (0.5%)	0.5 (0.0–1.0)	0		0.5283
Fatal bleeding	3 (0.2%)	0.3 (0.0–0.8)	0		1	0.3 (0.0–0.8)	0.2306
Access site bleeding	6 (0.3%)	0.3 (0.0–0.6)	3 (0.4%)	0.4 (0.0–0.8)	0		
Bleeding associated with cardiac surgery			28 (3.6%)	3.6 (2.3–4.9)			
Bleeding associated with noncardiac surgery	63 (3.3%)	3.3 (2.5–4.1)			17 (4.4%)	4.5 (2.4–6.6)	
Minor bleeding ISTH minor	42 (2.2%)	2.2 (1.5–2.9)	21 (2.7%)	2.8 (1.6–4.0)	9 (2.3%)	2.4 (0.9–3.9)	
Access site bleeding	8	0.4 (0.1–0.7)	7	0.9 (0.2–1.6)	0		

ISTH indicates International Society on Thrombosis and Haemostasis; KM, Kaplan Meier; and PRBCs, packed red blood cells.

The largest rise in the cumulative event rate occurred almost immediately following revascularization and increased more slowly throughout the study period.

Severity of Bleeding

The ISTH bleeding definition was used to analyze severity of bleeding because we were unable to subcategorize major and minor bleeds using the TIMI definition. Important differences in the ISTH and TIMI definitions for major bleeding include drop in hemoglobin (≥2 versus ≥5 g/dL) and the transfusion criteria included in the ISTH definition. Minor bleeding according to the TIMI definition includes a hemoglobin drop of 3 to 5 g/dL while the definition for ISTH includes hospital or surgical intervention, or change in antithrombotic therapy. Major and minor bleeding events according to ISTH definitions occurred in 130 patients in the peripheral revascularization group (6.8%; 95% CI, 5.8%–8.0%) within 30 days of the procedure, 61 patients in the coronary revascularization group (8.0%; 95% CI, 6.1%–9.9%), and 27 patients in the amputation group (7.1%; 95% CI, 4.5%–9.7%; Table 2). A drop in hemoglobin levels ≥2 g/dL was the most frequently adjudicated reason for major bleeding and was similar across all procedural groups. The rates of blood transfusion (≥2 units), symptomatic bleeding in a critical location, and fatal bleeding after procedure were similar between peripheral revascularization, coronary revascularization, and lower extremity amputation.

Source of Bleeding

The source of bleeding is reported in Table 2. Access site bleeding occurred in 24 patients (14 peripheral revascularization, 10 coronary revascularization, 0 amputation).

DISCUSSION

This post hoc analysis from the EUCLID trial provides important insights into postprocedural bleeding in patients with PAD. The incidence of major or minor bleeding after peripheral revascularization was 3.3% within 7 days following the procedure and was comparable with bleeding rates after coronary revascularization and lower extremity amputation. The severity of major and minor bleeding events within 30 days

Table 3. Severity of Bleeds Within 30 Days of Procedure: Further Breakdown of Peripheral Revascularization

ISTH Bleeding Categories	Peripheral Revascularization (N=1905)							
	Endovascular (N=1347)		Surgical (N=688)		Carotid (N=203)		Other (MESENTERIC", "RENAL; N=38)	
	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)
ISTH major and minor bleeding post-procedure	211/1347		159/688		27/203		8/38	
ISTH major bleeding post-procedure	105/1347		121/688		11/203		5/38	
ISTH minor bleeding post-procedure	127/1347		56/688		21/203		4/38	
ISTH major and minor bleeding within 30 days of procedure	66	4.9 (3.7–6.1)	27	4.4 (2.8, 6.0)	13	6.4 (3.0–9.8)	2	5.3 (0–12.5)
Major bleeding ISTH major								
Any	36	2.7 (1.8–3.6)	84	12.3 (9.8–14.8)	6	3.0 (0.7–5.3)	2	5.3 (0–12.5)
Decrease in hemoglobin ≥2 g/dl	30	2.2 (1.4–3.0)	74	10.8 (8.5–13.1)	2	1.0 (0–2.4)	2	5.3 (0–12.5)
Transfusion of ≥2 units of PRBCs	2	0.1 (0–0.3)	8	1.2 (0.4–2.0)	1	0.5 (0–1.5)	0	
Symptomatic bleed in a critical location	1	0.1 (0–0.2)	0		3	1.5 (0–3.2)	0	
Fatal bleeding	3	0.2 (0–0.5)	2	0.3 (0–0.7)	0		0	
Access site bleeding	6	0.4 (0–0.8)	1	0.1 (0–0.4)	0		0	
Bleeding associated with noncardiac surgery	14	1.0 (0.5–1.5)	75	11.0 (8.7–13.3)	2	1.0 (0–2.4)	1	2.6 (0–7.7)
Minor bleeding ISTH minor	32	2.4 (1.6–3.2)	13	1.9 (0.9–2.9)	7	3.5 (1.0–6.0)	0	

ISTH indicates International Society on Thrombosis and Haemostasis; KM, Kaplan Meier; and PRBCs, packed red blood cells.

post-procedure was comparable in patients undergoing peripheral revascularization, coronary revascularization, and lower extremity amputation. Finally, bleeding events occurred more commonly in patients randomized to ticagrelor compared with clopidogrel, but the increase was not statistically significant.

The literature assessing the relationship between bleeding and peripheral revascularization and lower extremity amputation is sparse. We present findings that differ from a few prior studies of bleeding following peripheral revascularization; however, we recognize that it is difficult to compare these studies because of important issues including differences in bleeding definitions and the role of antiplatelet agents. A single-center randomized controlled trial reported an incidence of hematoma following endovascular revascularization of 7.9% (6/76),[11] while an observational single-center study reported an incidence of bleeding within 30 days following endovascular revascularization of 0.2%.[12] Both values are outside the cumulative event rate CIs reported in this study (4.0%; 95% CI, 3.1%–4.9%). A more recent retrospective multicenter analysis also reports similar results. They found that access site complications, including hematomas and pseudoaneurysms, occurred in 3.5% of revascularization procedures and of those, 9.7% required transfusion.[9]

These results build on existing knowledge in a few ways. First, this study is contemporary, as patients were enrolled from 2012 to 2014. Second, a consistent trigger process was used to identify all bleeding events, and all identified events were formally adjudicated using standard bleeding definitions. Strict adjudication processes in this study ensure that (1) events are not overreported, (2) interpretation of events is not biased by clinician interpretation, and (3) influence of external factors (such as reimbursement incentives and quality measures) are minimized.[13] Furthermore, standardized definitions are consistently applied allowing for legitimate comparisons between past and future research using the same definitions.[13] Finally, in addition to describing the incidence of bleeding events, the timing and severity of bleeding events were adjudicated and reported. This is unique and critical because clinicians can use this information to improve management plans by more accurately

Table 4. Severity of Bleeds Within 30 Days of Procedure: Further Breakdown of Coronary Revascularization

ISTH Bleeding Categories	Coronary Revascularization (N=770)			
	CABG (N=176)		PCI (N=626)	
	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)	Patients With Events no. (%)	KM Estimated Rate% at 30 D (95% CI)
ISTH major and minor bleeding post-procedure	51/176		90/626	
ISTH major bleeding post-procedure	38/176		46/626	
ISTH minor bleeding post-procedure	19/176		54 /626	
ISTH major and minor bleeding within 30 d of procedure	41	23.5 (17.2–29.8)	27	4.4 (2.8–6.0)
Major bleeding ISTH major				
Any	32	18.3 (12.6–24.0)	14	2.3 (1.1–3.5)
Decrease in hemoglobin ≥2 g/dL	26	14.9 (9.6–20.2)	12	1.9 (0.8–3.0)
Transfusion of ≥2 units of PRBCs	3	1.7 (0–3.6)	1	0.2 (0–0.5)
Symptomatic bleed in a critical location	3	1.7 (0–3.6)	1	0.2 (0–0.5)
Fatal bleeding	0		0	
Access site bleeding	0		3	0.5 (0–1.0)
Bleeding associated with cardiac surgery	31	17.7 (12.1–23.3)	2	0.3 (0–0.7)
Minor bleeding ISTH minor	9	5.2 (1.9–8.5)	13	2.1 (1.0–3.2)

CABG indicates coronary artery bypass grafting; ISTH, International Society on Thrombosis and Haemostasis; KM, Kaplan Meier; PCI, percutaneous coronary intervention; and PRBCs, packed red blood cells.

risk-stratifying patients before procedures and more precisely calibrating risk post-procedure. Future studies should continue to focus on the factors impacting major and minor bleeding in peripheral revascularization and lower extremity amputation, and the vascular community should make a push to minimize the occurrence and impact of bleeding events in patients with PAD.

There were a few limitations to this study. Every attempt was made to ascertain the occurrence of both invasive procedures and bleeding events; however, it is possible that some patients had procedures and bleeding events not captured in this analysis. Furthermore, the management of medications (including the study medications) surrounding invasive vascular procedures was left to the discretion of the operators, and the impact of these decisions was not accounted for in this analysis. In addition, these were not randomized comparisons, thus limiting the ability to establish any causal relationship. Finally, the patients in this study were highly selected (ie, symptomatic PAD, 50% had prior peripheral revascularization, 30% had concomitant coronary artery disease), and may not reflect a general population of patients with PAD.

CONCLUSIONS

In conclusion, the incidence of major and minor bleeding following peripheral revascularization is comparable with bleeding rates after coronary revascularization and lower extremity amputation. In addition, bleeding events most often occur within 7 days following the procedure. Finally, the severity of periprocedural bleeding events was comparable

Table 5. Kaplan-Meier Estimated Cumulative Event Rate of TIMI Major or Minor Bleeding at Different Time Points Post-Procedure

	No. of Events				
	KM Event Rate (95% CI)				
	≤7 D	≤30 D	≤180 D	≤365 D	All
Peripheral revascularization	62	75	107	124	147
	3.3% (2.5%–4.1%)	4.0% (3.1%–4.9%)	5.8% (4.7%–6.9%)	7.0% (5.8%–8.2%)	
Coronary revascularization	31	34	48	55	66
	4.0% (2.6%–5.4%)	4.4% (2.9%–5.9%)	6.5% (4.7%–8.3%)	7.8% (5.8%–9.8%)	
Amputation	9	15	22	25	31
	2.3% (0.8%–3.8%)	4.0% (2.0%–6.0%)	6.0% (3.6%–8.4%)	7.0% (4.3%–9.7%)	

KM indicates Kaplan-Meier; and TIMI, Thrombolysis in Myocardial Infarction.

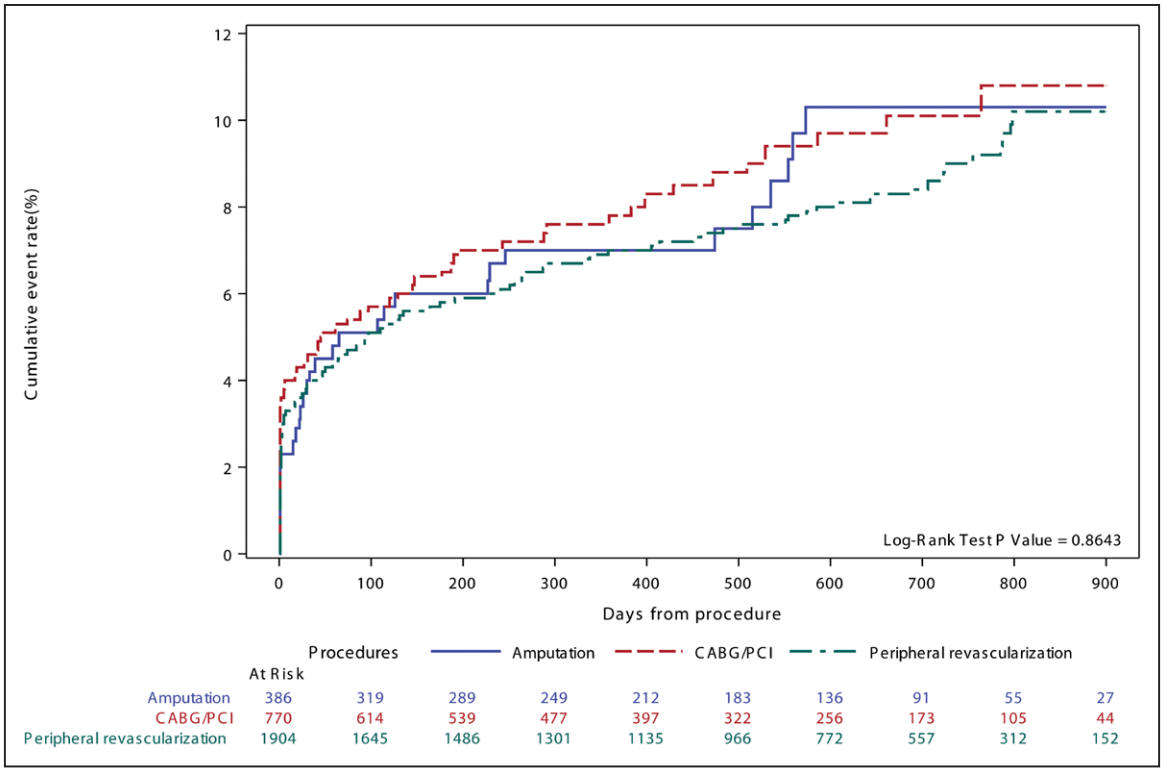

Figure 2. Estimated cumulative event rate of Thrombolysis in Myocardial Infarction major or minor bleeding post-procedure.
CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

across procedures, with the most frequently adjudicated reason being a drop in hemoglobin ≥2 g/dL. Future studies should be performed to enhance our understanding of bleeding risk related to peripheral revascularization and lower extremity amputation in patients with PAD.

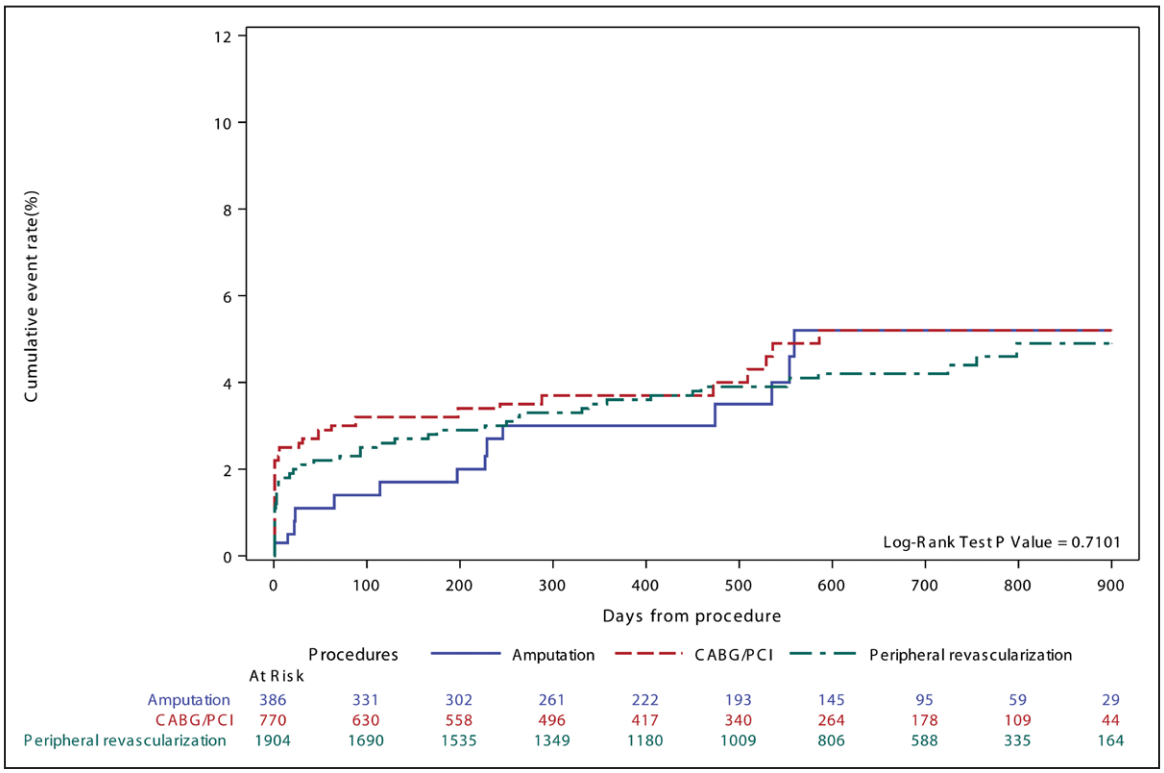

Figure 3. Estimated cumulative event rate of Thrombolysis in Myocardial Infarction major bleeding post-procedure: log-rank test.
CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

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Correspondence

W. Schuyler Jones, MD, Duke University Medical Center, Box 3330, Durham, NC 27710. Email schuyler.jones@duke.edu

Affiliations

Division of Cardiology, Duke Heart Center (A.K., M.R.P., S.J.) and Duke Clinical Research Institute, Duke University School of Medicine (Z.H., F.W.R., M.R.P., W.S.J.), Duke University, Durham, NC. Swiss Cardiovascular Centre, Inselspital, Bern University Hospital, University of Bern, Switzerland (I.B.). Departments of Medicine and Surgery, New York University School of Medicine (J.S.B.). Turku University Hospital, Turku University, Finland (J.I.B.). Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, United Kingdom (F.G.F.). AstraZeneca Gaithersburg, MD (B.K.). Stanford Center for Clinical Research, Stanford University School of Medicine, CA (K.W.M.). Faculty of Medicine and Health, Örebro University, Sweden (L.N.). University of Colorado School of Medicine, Division of Cardiology and CPC Clinical Research, Aurora (W.R.H.).

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