Clinical consequences of bleeding among individuals with a recent acute coronary syndrome: Insights from the APPRAISE-2 trial

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Background Patients with a recent acute coronary syndrome (ACS) receiving oral antiplatelets and anticoagulants are at risk for bleeding and subsequent adverse non–bleeding-related events.

Methods In this post hoc analysis, we evaluated 7,392 high-risk patients (median follow-up 241 days) with a recent ACS randomized to apixaban or placebo in APPRAISE-2. Clinical events during a 30-day period after Thrombolysis in Myocardial Infarction (TIMI) major/minor bleeding were analyzed using unadjusted and adjusted Cox proportional-hazards models.

Results In total, 153 (2.1%) patients experienced TIMI major/minor bleeding during follow-up. Bleeding risk for patients on triple therapy (apixaban, thienopyridine, and aspirin) was increased compared with those on dual therapy (apixaban plus aspirin: hazard ratio [HR] 2.02, 95% CI 1.08-3.79; thienopyridine plus aspirin: HR 1.99, 95% CI 1.41-2.83). Those receiving apixaban/aspirin had similar bleeding risk compared with those receiving thienopyridine/aspirin (HR 1.01, 95% CI 0.53-1.95). Patients who experienced TIMI major/minor bleeding had an increased risk of 30-day all-cause mortality (HR 24.7, 95% CI 15.34-39.66) and ischemic events (HR 6.7, 95% CI 3.14-14.14).

Conclusions In a contemporary cohort of high-risk patients after ACS, bleeding was associated with a significantly increased risk of subsequent ischemic events and mortality regardless of antithrombotic or anticoagulant strategy. Patients receiving apixaban plus aspirin had a similar bleeding risk compared with those receiving thienopyridine plus aspirin. Interventions to improve outcomes in patients after ACS should include strategies to optimize the reduction in ischemic events while minimizing the risk of bleeding. (Am Heart J 2019;215:106-13.)

In patients with acute coronary syndromes (ACS), there remains a significant residual risk of subsequent ischemic events and death despite treatment with antithrombotic drugs and revascularization.[1-4] Vitamin K antagonists, when combined with aspirin in patients with ACS, reduce the risk of subsequent ischemic events; however, widespread use has been limited by increased bleeding.[5,6] The use of direct-acting oral anticoagulants (DOAC) in addition to guidelines-based antiplatelet therapy in patients after an ACS (who do not have another reason for anticoagulation) have been evaluated in an attempt to reduce the burden of subsequent ischemic events.[7-9] Only rivaroxaban reduced adverse cardiovascular outcomes and ischemic events; neither apixaban nor dabigatran demonstrated a reduction in cardiovascular events[7-9]; furthermore, all studies demonstrated the same increase in risk of bleeding.[7-9]

Analyses of older ACS studies suggest that bleeding in patients after an ACS increases the risk of subsequent ischemic events and death.[10] However, this risk has not been extensively evaluated in a cohort of contemporary and high-risk patients with ACS. Furthermore, the risk of bleeding for patients receiving triple therapy (DOAC with aspirin and a thienopyridine) after an ACS is less well defined. In addition, the response of physicians to a bleeding episode with regard to stopping or continuing antithrombotic agents has not been well described. Using data from the contemporary cohort of high-risk patients with ACS in the

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Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) study, we aimed to evaluate[1] characteristics and management of patients who have experienced a bleeding episode[2]; risk of bleeding in patients who are receiving triple therapy compared with other antithrombotic combinations[3]; risk of subsequent ischemic events or death in patients who have experienced a bleeding episode; and[4] physician response with regard to antithrombotic agents among patients who experience a bleeding episode.

Methods

Study design

The trial design and main results of APPRAISE-2 have been reported.[8] In brief, APPRAISE-2 was a double-blind, placebo-controlled randomized clinical trial of 7,392 patients with ACS (symptoms of myocardial ischemia at rest, elevated cardiac biomarkers, or dynamic ST-segment changes on electrocardiogram) within the previous 7 days receiving aspirin or aspirin plus a P2Y12 receptor inhibitor. Patients were also required to have ≥2 of the following risk factors: age ≥ 65 years, diabetes mellitus, myocardial infarction (MI) within the previous 5 years, cerebrovascular disease, peripheral artery disease, clinical heart failure or left ventricular ejection fraction (LVEF) <40% associated with the index event, creatinine clearance <60 mL/min, or no revascularization after the index event.

Outcomes and definitions

The primary efficacy end point for APPRAISE-2 was a composite of cardiovascular death, MI, and ischemic stroke. The primary safety end point was Thrombolysis in Myocardial Infarction (TIMI) major bleeding,[11] with TIMI major or minor bleeding assessed as a secondary safety outcome. Additional safety outcomes were major/clinically relevant nonmajor (CRNM) bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH).[12] All efficacy outcomes and the main safety outcome were adjudicated by a clinical events committee whose members were blinded to treatment assignment. For this study, the primary end points include all-cause mortality, ischemic events (MI or stroke), and the composite of all-cause mortality or ischemic events. We used a composite of major and minor bleeding to ascertain the totality of bleeding events. Anticoagulant and antiplatelet use was assessed at randomization.

To assess the impact of anticoagulant and antiplatelet use on bleeding, patients were divided into the following groups: triple therapy (apixaban, thienopyridine, and aspirin), dual therapy (apixaban plus aspirin or thienopyridine plus aspirin), and monotherapy (aspirin only). Because of small numbers of patients on nonaspirin single antiplatelet regimens (n = 181), these patients were excluded. Physician response to bleeding was determined by evaluating antiplatelet and anticoagulant therapy the day before and after a bleeding event.

Statistical analysis

Baseline characteristics among those patients who experienced TIMI major/minor bleeding and those who did not were compared using descriptive statistics and displayed using medians and 25th, 75th percentiles or proportions. TIMI major/minor bleeding was used to ascertain the impact of all bleeding events on subsequent cardiovascular events. The frequency and timing of interventions and treatment changes following a TIMI major/minor bleeding event were described. The association between antiplatelet and anticoagulant combination at randomization and the risk of bleeding was analyzed using Cox proportional-hazards models.

The risk of ischemic events or death 30 days after a TIMI major/minor bleeding event was analyzed using Cox proportional-hazards models with the bleeding events considered as time-dependent variables. Unadjusted and adjusted results are presented. Adjustment variables were selected from factors known and presumed to be associated with bleeding: age, $CHADS_2$ (Congestive heart failure history, Hypertension history, Ages ≥ 75 years, Diabetes mellitus history, Stroke or TIA symptoms) core, history of cerebrovascular disease, heart failure or LVEF <40% associated with index ACS, renal impairment, statins at randomization, diabetes, sex, history of MI (in previous 5 years), peripheral vascular disease, prior coronary revascularization, type of index ACS, elevated cardiac biomarkers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and proton-pump inhibitors at randomization. The adjustment variables used for each outcome of interest are summarized in Supplemental Table I. Type of antithrombotic therapy received was added to the adjusted models to assess the association of bleeding with other end points. The numbers of patients included in the models not adjusting and adjusting for antithrombotic therapy at baseline were 7,392 and 7,206, respectively. Analyses were repeated using ISTH major/CRNM bleeding definitions as a sensitivity analysis. The analyses presented were designed by the authors and performed at the Duke Clinical Research Institute using SAS version 9.3 (SAS Institute, Cary, NC).

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Results

Baseline characteristics and management of bleeding

Overall, of the 7,392 patients enrolled in APPRAISE-2, 153 (2.1%) experienced a TIMI major/minor bleeding

Table I. Baseline characteristics by TIMI major/minor bleeding

Characteristic	TIMI major/minor bleeding: Yes (n = 153)	TIMI major/minor bleeding: No (n = 7239)	*P* value*
Female sex	51 (33.3%)	2327 (32.1%)	.5476
≥65 y of age	106 (69.3%)	4248 (58.7%)	.0010
Age, median (25th, 75th), y	70 (63, 75)	67 (58, 73)	<.0001
Diabetes	85 (55.6%)	3451 (47.7%)	.0247
History of MI (5 y)	33 (21.6%)	1903 (26.3%)	.1314
History of cerebrovascular disease	18 (11.8%)	724 (10.0%)	.3957
History of PVD	32 (20.9%)	1306 (18.0%)	.2184
HF or LVEF <40% associated with index ACS	67 (43.8%)	2902 (40.1%)	.4549
HF	42 (27.5%)	2034 (28.1%)	0.4379
Prior coronary revascularization	48 (31.4%)	2042 (28.2%)	0.2581
Type of index ACS event			0.8765
STEMI	57 (37.3%)	2870 (39.6%)	
NSTEMI	68 (44.4%)	3006 (41.5%)	
UA	28 (18.3%)	1312 (18.1%)	
Undetermined	0 (0.0%)	51 (0.7%)	
Elevated cardiac markers	125 (81.7%)	5876 (81.7%)	0.7865
Medications at randomization			
Aspirin	149 (97.4%)	7048 (97.4%)	0.9506
Thienopyridines	138 (90.2%)	6024 (83.2%)	0.0029
Parenteral antithrombotics	128 (83.7%)	5836 (80.7%)	0.3273
ACE inhibitors	98 (64.1%)	4742 (65.6%)	0.6174
ARBs	22 (14.4%)	1008 (13.9%)	0.5945
β-Blockers	114 (74.5%)	5555 (76.8%)	0.4573
Statins	131 (85.6%)	6050 (83.6%)	0.2036
PPIs	38 (24.8%)	1762 (24.4%)	0.5385
$CHADS_2$ score, mean (SD)	2.24 (1.19)	1.99 (1.18)	0.0037
$CHADS_2$ score			0.0033
0-1	43 (28.1%)	2436 (33.7%)	
2	49 (32.0%)	2789 (38.5%)	
>2	61 (39.9%)	2013 (27.8%)	

Data presented as n (%), unless otherwise indicated.
PVD, peripheral vascular disease; *HF*, heart failure; *STEMI*, ST-segment elevation myocardial infarction; *NSTEMI*, non–ST-segment elevation myocardial infarction; *UA*, unstable angina; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *PPI*, proton-pump inhibitor.
* *P* value comparing patients with versus without TIMI major bleeding derived using a univariate Cox model.

event. Patients who experienced bleeds were older and had a higher incidence of diabetes mellitus (Table I). However, other cardiovascular comorbidities were equally represented in patients who did and did not have bleeding events. There was no difference in the index ACS type (ST elevation MI, non–ST elevation MI, unstable angina) between the 2 groups. Besides higher thienopyridine use in patients who bled compared with those who did not, there were no differences in other drug therapies.

Details of the management of patients who experienced a TIMI major/minor bleed were available from the case report forms in 85 of the 153 patients (Table II). In patients who were randomized to receive apixaban, compared with placebo, there was no difference in the number of transfusions, medical or surgical treatments of bleeding, or procedure-related bleeding. The need for hospitalization or the length of hospitalization stay was statistically increased in those randomized to receive apixaban. Baseline characteristics by bleeding and randomization stratification are presented in Supplementary Table I.

Association between antithrombotic drug therapies and bleeding

Patients on triple therapy had a significantly increased risk of TIMI major/minor bleeding compared with patients on dual therapy, both with apixaban plus aspirin (hazard ratio [HR] 2.02, 95% CI 1.08-3.79) and thienopyridine plus aspirin (hazard ratio [HR] 1.99, 95% confidence interval [CI] 1.41-2.83), and monotherapy with aspirin alone (HR 5.8, 95% CI 2.12-15.82) (Table III and Figure 1). Patients receiving apixaban plus aspirin, as compared with thienopyridine plus aspirin, did not have an increased risk of bleeding (HR 1.01, 95% CI 0.53-1.95). Patients receiving thienopyridine plus aspirin also had an increased risk of bleeding events compared with those receiving aspirin alone (HR 2.91, 95% CI 1.05-8.06).

Association between bleeding, ischemia, and all-cause mortality

Following a TIMI major/minor bleeding event, the risk of subsequent adverse events was significantly increased (Table IV). In the 30 days after a bleed, compared with those who did not bleed, there was an increased risk of all-cause mortality (adjusted HR 24.7, 95% CI 15.34-39.66), ischemic events (adjusted HR 6.7, 95% CI 3.14-14.14), and ischemic events or all-cause mortality (adjusted HR 11.4, 95% CI 7.52-17.30). This association persisted after extensive multivariable adjustments (Supplemental Table II), including antithrombotic therapy regimen at randomization.

Physician response to bleeding

The day before a TIMI major/minor bleed, 53/153 patients were taking apixaban, thienopyridine, and aspirin, and 49/153 patients were on thienopyridine plus aspirin (Table V). The day after the bleeding event, among patients on triple therapy, 18/53 (34%) remained on triple therapy, 21/53 (39.6%) were continued on dual therapy with thienopyridine plus aspirin, and 8/53 (15%) received no antithrombotic therapy (Table V). Of the patients initially on thienopyridine plus aspirin, on the day after the TIMI major/minor bleed, 37/49 (75.5%) remained on dual therapy and 6/49 (12%) received no antithrombotic therapy.

Sensitivity analysis

A sensitivity analysis using the ISTH bleeding definitions was also conducted. There were 214 patients who experienced an ISTH major/CRNM bleed. The characteristics and clinical management of these patients were similar to those observed based on TIMI major/minor definitions (data not shown). Using the ISTH bleeding definition, the magnitude of bleeding risk when comparing various

Table II. Characteristics and management of bleeding

	TIMI major/minor	Apixaban	Placebo	*P* value
Bleeding events	153	108	45	
Bleeding events with details available (CRF)	85 (55.6%)	60 (55.6%)	25 (55.6%)	1.0000
Was hemoglobin checked?	83 (97.7%)	59 (98.3%)	24 (96.0%)	.5179
Amount fall				.0922
<1 g/dL	4 (4.8%)	4 (6.8%)	0 (0.0%)	
1-<2 g/dL	3 (3.6%)	2 (3.4%)	1 (4.2%)	
2-<3 g/dL	13 (15.7%)	7 (11.9%)	6 (25.0%)	
3-<4 g/dL	13 (15.7%)	13 (22.0%)	0 (0.0%)	
4-<5 g/dL	15 (18.0%)	10 (16.9%)	5 (20.8%)	
≥5 g/dL	35 (42.2%)	23 (39.0%)	12 (50.0%)	
Required treatment to stop bleeding?	55 (64.7%)	39 (65.0%)	16 (64.0%)	.9300
Type of treatment				.1235
Medical only	38 (69.1%)	30 (76.9%)	8 (50.0%)	
Surgical only	14 (25.5%)	7 (18.0%)	7 (43.8%)	
Medical and surgical	3 (5.4%)	2 (5.1)	1 (6.2%)	
Bleeding associated with hemodynamic compromise?	26 (30.6%)	18 (30.0%)	8 (32.0%)	.8553
Transfusion given due to bleeding?	63 (74.1%)	46 (76.7%)	17 (68.0%)	.4058
Led to hospitalization or prolongation of hospitalization	56 (65.9%)	45 (75.0%)	11 (44.0%)	.0060
Related to procedure	22 (25.9%)	12 (20.0%)	10 (40.0%)	.0551

Data presented as n (%).
CRF, case report form.

Table III. Association between oral antithrombotics at randomization and TIMI major/minor bleeding

	Patients	Events (rate)	HR (95% CI)
Triple therapy	2762	84 (6.19)	
HR vs dual therapy (thienopyridine + ASA)			1.99 (1.41-2.83)
HR vs dual therapy (apixaban +ASA)			2.02 (1.08-3.79)
HR vs monotherapy (aspirin)			5.79 (2.12-15.82)
Dual therapy (thienopyridine + ASA)	3243	50 (3.09)	
HR vs dual therapy (apixaban + ASA)			1.01 (0.53-1.95)
HR vs monotherapy (aspirin)			2.91 (1.05-8.06)
Dual therapy (apixaban + ASA)	595	11 (2.83)	
HR vs monotherapy (aspirin)			2.87 (0.91-9.01)
Monotherapy (aspirin)	604	4 (0.98)	

Rates per 100 patient-years of follow-up.
ASA, acetylsalicylic acid.

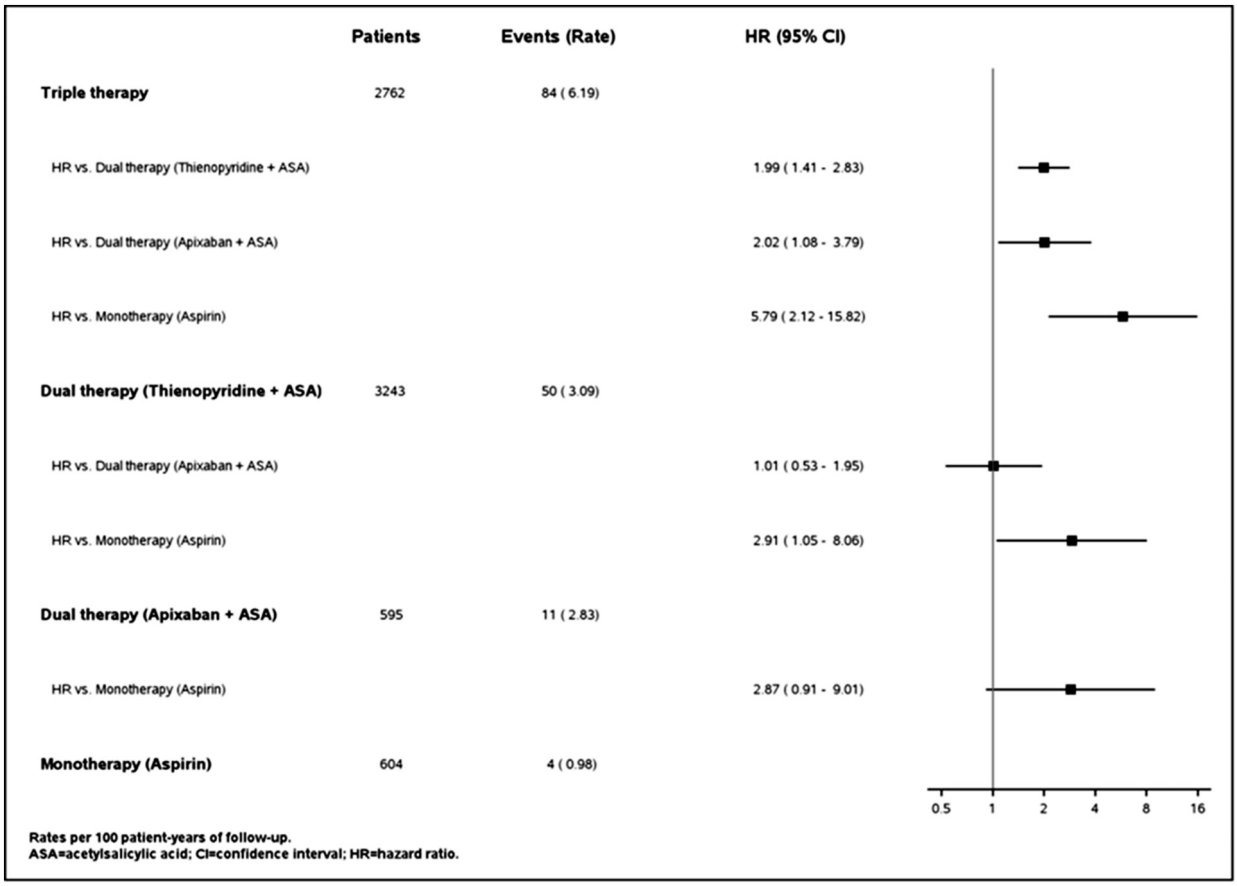
antithrombotic regimens was similar to the results observed with the TIMI major/minor definitions (Supplemental Table III). Similar results were seen with ischemic or mortality risk after bleeding events (Supplemental Table IV).

Discussion

In this cohort of high-risk patients after an ACS without a formal indication for oral anticoagulation, we demonstrated that (1) patients on triple therapy had a 2-fold increased risk of bleeding compared with those receiving dual therapy with apixaban plus aspirin or thienopyridine plus aspirin; (2) there was no increased risk of bleeding for patients on apixaban plus aspirin compared with those receiving thienopyridine plus aspirin; (3) even after adjustment for antithrombotic therapy regimen used, there was an 11-fold increase in the risk of ischemic events or all-cause mortality 30 days after a TIMI major/minor bleed; and (4) a significant number of patients were removed from all antithrombotic agents in response to a TIMI major/minor bleed.

Studies in patients after an ACS have consistently shown that bleeding complications are associated with adverse clinical outcomes, such as MI, stroke, and death.[10,13-15] Furthermore, increasing severity of bleeding is associated with an increased risk of adverse cardiovascular events and death.[13,14,16] Major bleeding is one of the strongest predictors of subsequent mortality in patients after an ACS, and this increased risk extends into the early (<30 days) and late (up to 1 year) periods after a major bleed.[13,15-17] Our study extends these findings by demonstrating that, in a cohort of high-risk

Figure 1



Forest plot of bleeding risk based on antithrombotic therapy.*ASA*, aspirin.

patients after an ACS, the risk for ischemic events and death was significantly higher in the 30 days following a TIMI major/minor bleed when compared with those who did not experience a bleed.

Current standard of care for patients after an ACS without a formal indication for oral anticoagulant therapy (eg, atrial fibrillation [AF]) includes dual antiplatelet therapy, typically with aspirin and a P2Y12 receptor antagonist[2,3]; however, despite aggressive use of dual antiplatelet therapies, patients remain at increased risk for recurrent ischemic events. A meta-analysis of 7 placebo-controlled randomized trials (including APPRAISE-2), although limited by the inclusion of phase 2 dose-finding studies and not using patient-level data, demonstrated that triple therapy with a DOAC, aspirin, and clopidogrel compared with aspirin plus clopidogrel reduced the incidence of cardiovascular events (HR 0.87, 95% CI 0.80-0.95) but more than doubled the risk of bleeding (HR 2.34, 95% CI 2.06-2.66).[18] Another recent meta-analysis suggests that DOAC on top of antiplatelet therapy may significantly reduce the risk of cardiovascular outcomes in patients with ST elevation MI.[19] These results raise the question of whether an oral anticoagulant could be used instead of clopidogrel in patients after an ACS to reduce recurrent ischemic events, especially in patients who are being medically managed for ACS.

The GEMINI-ACS-1 trial demonstrated that a dual pathway antithrombotic therapy strategy (combining low-dose rivaroxaban with a P2Y12 inhibitor) had similar risk of TIMI non–coronary artery bypass graft-related significant bleeding compared with aspirin and a P2Y12 inhibitor (HR 1.09; 95% CI 0.80-1.50).[21] Similarly, our observations suggest that patients receiving apixaban plus aspirin, compared with thienopyridine plus aspirin, do not have an increased risk for significant bleeding. Adjustment for baseline anticoagulation/antiplatelet strategy does not significantly impact on the risk of ischemic events or mortality following a major bleed. This may be in part due to modifications of the anticoagulation/antiplatelet strategy following a bleed. Although an adequately powered cardiovascular outcomes trial would be required to determine if differences

Table IV. Association between bleeding and all-cause mortality and ischemic events (30 days postbleeding)

	Unadjusted			Adjusted		
	HR (95% CI)	χ^2	*P* value	HR (95% CI)	χ^2	*P* value
All-cause mortality*						
TIMI major/minor (yes vs no)						
Not adjusting by antithrombotics at randomization	27.14 (16.97-43.42)	189.74	0.0001	22.57 (14.07-36.19)	167.31	<.0001
Adjusting by antithrombotics at randomization	29.90 (18.62-48.01)	197.78	<.0001	24.67 (15.34-39.66)	175.05	<.0001
Ischemic event (MI/stroke)†						
TIMI major/minor (yes vs no)						
Not adjusting by antithrombotics at randomization	7.88 (3.90-15.92)	33.15	<.0001	7.10 (3.51-14.36)	29.74	<.0001
Adjusting by antithrombotics at randomization	7.29 (3.44-15.45)	26.87	<.0001	6.66 (3.14-14.14)	24.36	<.0001
All-cause mortality or ischemic event (MI/Stroke) ‡						
TIMI major/minor (yes vs no)						
Not adjusting by antithrombotics at randomization	14.14 (9.46-21.12)	167.38	<.0001	11.74 (7.82-17.62)	141.20	<.0001
Adjusting by antithrombotics at randomization	13.86 (9.18-20.94)	156.23	<.0001	11.40 (7.52-17.30)	131.07	<.0001

Event rates (per 100 patients/mo of follow-up) and number of events during bleeding and nonbleeding periods of follow-up for each event were 14.51 (17 events) versus 0.53 (279 events) for all-cause mortality, 6.28 (6 events) versus 0.77 (394 events) for ischemic events, and 23.04 (22 events) versus 1.18 (601 events) for all-cause mortality or ischemic event, respectively. Patients who never had a bleeding contribute all their follow-up time to the nonbleeding group. Patients who had a bleeding contribute to the bleeding group during the 30 days postbleeding, but they also contribute to the nonbleeding group (follow-up time before the bleeding and follow-up time 30 days after the bleeding).
Number of patients included in the models not adjusting for antithrombotic therapy is 7,392. The models adjusting for antithrombotic therapy are based on 7,206 patients. Additional patients can be excluded in adjusted results due to missing values in adjustment covariate.
*Adjusted HRs adjusted by age, $CHADS_2$ score, history of cerebrovascular disease, HF or LVEF <40% associated with index ACS, renal impairment, and statins at randomization. Other candidate variables: diabetes, sex, history of MI (5 years), peripheral vascular disease, prior coronary revascularization, type of index ACS, elevated cardiac biomarkers, ACE inhibitors, ARBs, β-blockers, and proton-pump inhibitors at randomization.
†Adjusted HRs adjusted by age, $CHADS_2$ score, history of MI (5 years), peripheral vascular disease, prior coronary revascularization, and type of index ACS. Other candidate variables: diabetes, sex, history of cerebrovascular disease, HF or LVEF <40% associated with index ACS, renal impairment, elevated cardiac biomarkers, ACE inhibitors, ARBs, β-blockers, statins, and proton-pump inhibitors at randomization.
‡Adjusted HRs adjusted by age, $CHADS_2$ score, history of cerebrovascular disease, HF or LVEF <40% associated with index ACS, renal impairment, statins at randomization, history of MI (5 years), peripheral vascular disease, prior coronary revascularization, and type of index ACS. Other candidate variables: diabetes, sex, elevated cardiac biomarkers, ACE inhibitors, ARBs, β-blockers, and proton-pump inhibitors at randomization.

Table V. Antithrombotics received the day before and after a TIMI major/minor bleeding event

Antithrombotic therapies day before bleeding event	Antithrombotic therapies day after bleeding event				
	Triple therapy* (n)	Dual therapy† (n)	Monotherapy‡ (n)	Nothing (n)	Total (n)
Apixaban + thienopyridine + ASA (n = 53)	18	23	5	8	53
Thienopyridine + ASA (n = 49)		37	12	6	49

* Including apixaban + thienopyridine + ASA.
† Including thienopyridine + ASA, apixaban + ASA, and thienopyridine + apixaban.
‡ Including ASA only, thienopyridine only, or apixaban only.

in clinical outcomes exist, the totality of the data suggests that a dual pathway antithrombotic therapy strategy with DOAC and aspirin may not increase the risk of bleeding compared with a thienopyridine and aspirin in a post-ACS population.

The landscape of antithrombotic treatment strategies after an ACS and/or percutaneous coronary intervention among patients with AF is also evolving. The PIONEER AF-PCI trial demonstrated that in patients with AF undergoing stenting (post-ACS or for stable coronary artery disease), a strategy of low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months or very low dose rivaroxaban plus dual antiplatelet agents for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than a vitamin K antagonist plus dual antiplatelet agents for 1, 6, or 12 months.[23] The RE-DUAL PCI trial demonstrated that among patients with AF who had undergone PCI, the bleeding risk of dual therapy with dabigatran and a P2Y12 inhibitor was lower than the risk in those who received triple therapy with warfarin, a P2Y12 inhibitor, and aspirin. Furthermore, dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events.[24] Additional randomized clinical trials such as the ongoing AUGUSTUS (NCT02415400) and ENTRUST-AF (NCT02866175) studies will further clarify optimal strategies of antithrombotic therapies in patients with AF post-PCI and/or post-ACS.

The COMPASS trial randomized 27,395 patients with stable atherosclerotic disease to rivaroxaban 2.5 mg twice daily plus aspirin, rivaroxaban 5 mg twice daily alone, or aspirin alone.[25] Overall, patients randomized to rivaroxaban plus aspirin had improved cardiovascular

outcomes compared with aspirin alone despite an increased risk for major bleeding. Our results, which have suggested that an increased risk for adverse cardiovascular events is associated with major bleeding, contrast with these findings. These differences in results may reflect the higher-risk population enrolled in APPRAISE-2 (patients with a recent ACS) as compared with those enrolled in COMPASS (patients with stable atherosclerotic disease). In addition, although residual confounding in our study population may explain some of the findings of APPRAISE-2, differences in study duration may have also contributed to the varying findings in APPRAISE-2 compared with the COMPASS trial (6-month follow up in APPRAISE-2 vs 23 months in COMPASS).

Regarding management of antithrombotic therapies in the setting of a bleeding event, our study demonstrated that a substantial number of patients had all antithrombotic therapies stopped in response to a major bleed. Cardiovascular events following a bleeding episode may in part be due to the nonresumption of evidence-based antithrombotic therapies after a bleed. Although our study did not evaluate whether antithrombotic therapies were resumed in the long term after the bleeding episode, our results highlight the need for care pathways that will reinforce the need for these antithrombotic therapies and for clinicians to consider the resumption of these therapies once the bleeding episode has been addressed. Future studies assessing the patterns of antithrombotic therapy use after a bleed among patients post-ACS remains warranted. There is little evidence to guide clinicians on how and when to restart antithrombotic therapies after a bleed, and such strategies will have to be evaluated in future studies.

Limitations

The details of the clinical management of patients who experienced a bleed were limited to the subset of patients who had data recorded on the case report form. The comparison of triple and dual therapies was not randomized, and despite extensive multivariable adjustment, residual confounding may exist. We had insufficient sample size to analyze patients on apixaban and clopidogrel alone compared with other triple and dual antiplatelet strategies. Because of the early termination of the trial, the overall event rates were low, and results have to be interpreted with caution; however, the sensitivity analysis using ISTH bleeding definitions (which resulted in a greater number of bleeding events overall compared with the TIMI major/minor bleeding definitions) demonstrated a similar direction of results for all analyses. This study was a subgroup analysis from a randomized clinical trial, and these results might not be applicable to the general population, particularly when specific exclusion criteria related to bleeding risk were used in selecting the APPRAISE-2 trial cohort.

Conclusion

In this cohort of high-risk patients after an ACS, our analysis demonstrated that regardless of the oral antithrombotic strategy used, the risk of death or ischemic events within 30 days of experiencing a bleeding episode was significantly increased. Strategies to minimizing bleeding while reducing the burden of recurrent ischemic events need to be evaluated. These may include assessment of different combinations of antithrombotic agents and consideration of reducing the number used. Indeed, in our study, patients on triple therapy had the highest risk of bleeding. However, the risk of bleeding among those receiving apixaban plus aspirin was not higher than those receiving thienopyridine plus aspirin; further studies on combining apixaban and aspirin compared with dual antiplatelet strategies among high-risk patients after an ACS appear warranted.

Declaration of competing interest

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Appendix. Supplementary data

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