Efficacy and Safety of Vorapaxar in Non–ST-Segment Elevation Acute Coronary Syndrome Patients Undergoing Noncardiac Surgery

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Background—Perioperative antiplatelet agents potentially increase bleeding after non–ST-segment elevation (NSTE) acute coronary syndromes (ACS). The protease-activated receptor 1 antagonist vorapaxar reduced cardiovascular events and was associated with increased bleeding versus placebo in NSTE ACS, but its efficacy and safety in noncardiac surgery (NCS) remain unknown. We aimed to evaluate ischemic, bleeding, and long-term outcomes of vorapaxar in NCS after NSTE ACS.

Methods and Results—In the TRACER trial, 2202 (17.0%) patients underwent major or minor NCS after NSTE ACS over 1.5 years (median); continuing study treatment perioperatively was recommended. The primary ischemic end point for this analysis was cardiovascular death, myocardial infarction, stent thrombosis, or urgent revascularization within 30 days of NCS. Safety outcomes included 30-day NCS bleeding and GUSTO moderate/severe bleeding. Overall, 1171 vorapaxar and 1031 placebo patients underwent NCS. Preoperative aspirin and thienopyridine use was 96.8% versus 97.7% (*P*=0.235) and 89.1% versus 86.1% (*P*=0.036) for vorapaxar versus placebo, respectively. Within 30 days of NCS, no differences were observed in the primary ischemic end point between vorapaxar and placebo groups (3.4% versus 3.9%; adjusted odds ratio 0.81, 95% CI 0.50 to 1.33, *P*=0.41). Similarly, no differences in NCS bleeding (3.9% versus 3.4%; adjusted odds ratio 1.41, 95% CI 0.87 to 2.31, *P*=0.17) or GUSTO moderate/severe bleeding (4.2% versus 3.7%; adjusted odds ratio 1.15, 95% CI, 0.72 to 1.83, *P*=0.55) were observed. In a 30-day landmarked analysis, NCS patients had a higher long-term risk of the ischemic end point (adjusted hazard ratio 1.62, 95% CI 1.33 to 1.97, *P*<0.001) and GUSTO moderate/severe bleeding (adjusted hazard ratio 5.63, 95% CI 3.98 to 7.97, *P*<0.001) versus patients who did not undergo NCS, independent of study treatment.

Conclusion—NCS after NSTE ACS is common and associated with more ischemic outcomes and bleeding. Vorapaxar after NSTE ACS was not associated with increased perioperative ischemic or bleeding events in patients undergoing NCS. (***J Am Heart Assoc***. 2015;4:e002546 doi: 10.1161/JAHA.115.002546)

Key Words: coronary disease • hemorrhage • noncardiac surgery • non–ST-segment elevation acute coronary syndromes • surgery • vorapaxar

A fter an acute coronary syndromes (ACS) or percutaneous coronary interventions, up to one-third of patients require noncardiac surgery (NCS).[1–3] Importantly, a previous ACS is an important risk factor for perioperative major adverse cardiac events.[4–6] Although the perioperative use of antiplatelet therapies has been reported to reduce major adverse cardiac events in high-risk NCS patients, it may also increase bleeding complications.[7–10] In the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, the protease-activated receptor 1

antagonist vorapaxar reduced the secondary end point of cardiovascular death, myocardial infarction, or stroke but increased the risk of bleeding in patients with non–ST-segment elevation (NSTE) ACS.[11] The long biologic half-life of vorapaxar coupled with its recent US Food and Drug Administration regulatory approval for use in patients with a previous myocardial infarction without a previous stroke, transient ischemic attack, or intracranial bleeding creates unique questions regarding its optimal perioperative use. The efficacy and safety of vorapaxar in patients undergoing NCS after NSTE ACS have not been explored.[12]

Although the 30-day perioperative risks and clinical outcomes in NCS have been described in the percutaneous coronary intervention era, the long-term outcomes associated with major and minor NCS after NSTE ACS remain unclear.[1,3,13,14] Accordingly, in the TRACER trial, we evaluated (1) the 30-day perioperative and long-term efficacy and safety of vorapaxar in patients undergoing major and minor NCS as they relate to the type and timing of surgery and (2) the long-term prognosis associated with NCS after NSTE ACS.

Methods

The TRACER trial (ClinicalTrials.gov identifier NCT00527943) was a multicenter, double-blind, randomized placebo-controlled study that evaluated vorapaxar in 12 944 NSTE ACS patients in 37 countries. The methods and results of this study have been previously described.[11,12] Briefly, patients were enrolled if they presented to a hospital within 24 hours of coronary ischemia symptoms with ≥1 of the following: creatinine kinase-MB or troponin level higher than the upper limit of normal; new ST-segment depression >0.1 mV; or transient (<30 minutes) ST-segment elevation >0.1 mV in 2 contiguous leads. Patients also required ≥1 of the following additional risk factors: age ≥55 years; prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting; diabetes mellitus; or peripheral arterial disease. Randomized patients received vorapaxar or a matching placebo, and the intention to use a glycoprotein IIb/IIIa inhibitor and a parenteral direct thrombin inhibitor was stratified. The study was approved by the appropriate national and institutional regulatory and ethics committees, and all participants provided informed consent.

Study Population and Covariates

The present analysis included all patients in the TRACER trial who were admitted with an NSTE ACS and treated either with a coronary stent or with medical therapy alone and subsequently underwent either major or minor NCS. Patients who underwent coronary artery bypass grafting were specifically

excluded: vorapaxar outcomes in this patient population have been previously described.[15] The TRACER case report form contained the type, date, and reasons for NCS procedure as entered by local study personnel. The study authors examined all NCS data entries and classified them as either major or minor surgery. Major surgical procedures were defined using the American Heart Association/American College of Cardiology definitions of intermediate- and high-risk procedures.[16] Major procedures were further classified by surgical site according to prior categorization as follows: abdominal, thoracic, orthopedic and spinal, vascular, pelvic (urological and gynecological), intracranial neurologic, and head and neck surgeries.[17–19] Minor surgical procedures were similarly identified using guideline definitions of low-risk procedures and included endoscopic, superficial, cataract, breast, ambulatory, percutaneous, or dental procedures.[16] Repeat coronary angiograms, percutaneous coronary interventions, and cardiac surgical procedures were excluded. If a patient underwent a major and minor surgical procedure within 30 days, the major procedure was hierarchically selected as the index procedure to avoid an excess attributable risk to minor procedures (eg, a bronchoscopy preceding a lobectomy).

The timing of NCS after NSTE ACS events was a priori categorized as follows: ≤30, >30 to 180, >180 days to 1 year, and >1 year. The TRACER case report form coded for the preoperative use of all cardiac medications. Given the long biologic half-life of vorapaxar, the study protocol recommended study drug continuation through NCS procedures.[12] The timing and reasons for interruptions were recorded in the case report form by local study personnel. The primary analysis of this study compared clinical end points in vorapaxar- versus placebo-treated patients who underwent NCS. A secondary analysis evaluated the long-term clinical outcomes in NSTE ACS patients who underwent NCS regardless of treatment assignment. A sensitivity analysis limited to participants who were receiving perioperative treatment was also performed.

Outcomes

The primary ischemic end point for this analysis was the incidence of 30-day perioperative cardiovascular death, nonfatal myocardial infarction, stent thrombosis, or urgent revascularization. The secondary ischemic end points of interest included the TRACER trial primary end point (cardiovascular death, myocardial infarction, recurrent ischemia with rehospitalisation, or stroke), the individual components of the primary ischemic end point, all-cause mortality, stroke, and the incidence of the composite primary outcome among 30-day NCS survivors through study follow-up. The primary bleeding end point was the 30-day incidence of perioperative NCS bleeding defined as any GUSTO (Global Utilization of

Strategies to Open Occluded Arteries) or TIMI (Thrombolysis In Myocardial Infarction) bleeding associated with the NCS. For example, a surgical incision site hematoma would qualify as NCS bleeding but spontaneous epistaxis would not. The secondary bleeding end points included all 30-day perioperative GUSTO moderate or severe bleeding, TIMI major or minor bleeding, and TIMI clinical significant bleeding. All clinical end points were adjudicated by a clinical events committee.

Statistical Methods

Patient and procedural characteristics, concomitant treatment, and in-hospital procedures are reported as medians (25th, 75th percentiles) for continuous variables and as percentages for discrete variables. The Wilcoxon rank sum test and χ^2 test were applied, respectively, to test differences between groups, including 30-day outcomes. Kaplan–Meier estimates were reported for 2-year follow-up, and differences among groups were tested by using the log-rank test (when proportional hazard assumptions were met).

The associations of vorapaxar versus placebo with the 30-day NCS primary end point and safety end points for the NCS patients (intent-to-treat) were examined through multivariable logistic regression. These associations were examined in patients who were event free at the time of surgery. Study treatment–related analyses were based on the intention-to-treat assumption, unless otherwise stated. Associations with 30-day events were reported as odds ratios (ORs) with 95% CIs. Sensitivity analyses were also carried out on patients who were receiving treatment during surgery, including 901 vorapaxar- and 819 placebo-treated patients.

To compare long-term prognosis between NSTE ACS patients who did not undergo NCS with those who did undergo NCS and survived 30 days postrandomization and postoperatively, respectively, time-to-event analyses were performed. Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazards regression, including NCS as a time-dependent covariate and with the adjustment of baseline covariates and randomized stratification factors (Table S1).

SAS software version 9.4 (SAS Institute) was used to perform statistical analyses. P-values were not adjusted for multiple comparisons.

Results

In the TRACER trial, 2202 (17.0%) of 12 944 patients underwent NCS after randomization during a median follow-up of 1.5 years. A total of 1312 (10.1%) patients underwent cardiac surgery after randomization and were excluded from the study. Baseline characteristics of patients who did and did not undergo NCS are provided in Table S2. Briefly, patients who underwent NCS were more likely to be older, have a higher body mass index, have more comorbidities, and have a lower creatinine clearance and were more frequently in the vorapaxar treatment group. There were no differences between the 2 groups in revascularization strategies after the index NSTE ACS. The incidence of NCS varied by study region as follows: North America 25.8%, South America 12.6%, Western Europe 16.8%, Eastern Europe 12.8%, Asia 19.6%, and Australia/New Zealand 30.4%.

Study participants who underwent NCS were followed for a median of 565 days. Among the 2202 NCS procedures, 474 (21.5%) patients had major and 1728 (78.5%) had minor surgical procedures. The proportion of NCS procedures relative to the timing after the index NSTE ACS was categorized as ≤30, >30 to 180, >180 days to 1 year, and >1 year and distributes as 18.5%, 30.9%, 27.2%, and 23.5%, respectively.[1,16,20] The preoperative use of aspirin and thienopyridines was 97.2% and 87.7%, respectively, and 21.7% of patients stopped the study drug a median of 14.0 (3.0, 62.0) days preoperatively.

The baseline characteristics of NCS patients by treatment assignment are provided in Table 1. Vorapaxar- and placebo-treated patients were well balanced by age, sex, medical history, index NSTE ACS revascularization, major versus minor surgery, and surgical timing. There were no differences in either the number of vorapaxar- and placebo-treated patients in whom the study drug was held preoperatively (23.1% versus 20.2%, P=0.102) or in the median times between the last study drug dose and surgery (13 versus 15 days, P=0.431). Vorapaxar-treated patients were more likely to receive thienopyridines preoperatively (89.1% versus 86.1%, P=0.036). Preoperative aspirin and β-blocker utilization was similar between groups. The incidences of NCS preoperative GUSTO moderate or severe (7.3% versus 4.8%, P=0.011) and TIMI clinically significant (25.4% versus 17.7%, P<0.001) bleeding were higher among vorapaxar-treated NCS patients, but no treatment-related differences were observed in the time between bleeding events and NCS.

Outcomes of NCS Patients by Treatment Assignment

The 30-day incidence of the primary ischemic outcome of cardiovascular mortality, nonfatal myocardial infarction, stent thrombosis, or urgent revascularization was similar in vorapaxar- and placebo-treated NCS patients (3.4% versus 3.9%, P=0.562). Additionally, no differences in the individual components of the 30-day ischemic end point (Figure 1; P>0.05 for all) or the TRACER end point (4.4% versus 4.3%, P=0.843) were observed. The primary bleeding end point of

Table 1. Baseline Characteristics of NCS Patients by Treatment Assignment

Characteristics	Vorapaxar (n=1171)	Placebo (n=1031)	*P* Value
Age, y, median (IQR)	66.0 (60.0–74.0)	65 (59.0–73.0)	0.073
Female, n (%)	335 (28.6)	96 (28.7)	0.958
Racial or ethics group, n (%)			
White	1007 (86.3)	891 (86.7)	0.701
Black	29 (2.5)	25 (2.4)	
Asian	100 (8.6)	86 (8.4)	
Other	31 (2.7)	26 (2.5)	
Body weight, kg, median (IQR)	81.0 (70.0–94.1)	82.0 (70.5–95.0)	0.125
Medical history, n (%)			
Hypertension	846 (72.2)	766 (74.3)	0.278
Dyslipidemia	797 (68.1)	693 (67.2)	0.651
Diabetes mellitus	428 (36.6)	371 (36.0)	0.783
Current tobacco use	264 (22.5)	256 (24.8)	0.208
Myocardial infarction	382 (32.6)	348 (33.8)	0.573
Percutaneous coronary intervention	331 (28.3)	294 (28.5)	0.886
Coronary artery bypass grafting	200 (17.1)	190 (18.4)	0.408
Heart failure	157 (13.4)	168 (16.3)	0.055
Atrial fibrillation	71 (6.1)	65 (6.3)	0.814
Stroke or transient ischemic attack	93 (7.9)	93 (9.0)	0.364
Peripheral arterial disease	120 (10.2)	114 (11.1)	0.539
Variables at NSTE ACS presentation			
Heart rate, bpm, median (IQR)	70 (61–80)	69 (61–79)	0.824
Systolic blood pressure, mm Hg, median (IQR)	131 (118–146)	130 (118–146)	0.759
Diastolic blood pressure, mm Hg, median (IQR)	72 (65–81)	74 (65–83)	0.235
Hemoglobin, g/L, median (IQR)	138 (126–149)	140 (126–150)	0.143
Creatinine clearance, μmol/L, median (IQR)	87.8 (67.1–112.2)	89.1 (66.3–118.0)	0.115
Positive troponin or CK-MB, n (%)	1101 (94.4)	978 (95.2)	0.398
Electrocardiographic findings, n (%)			
ST-segment depression	353 (30.1)	296 (28.7)	0.461
ST-segment elevation	60 (5.1)	44 (4.3)	0.345
TIMI risk score, n (%)			0.520
0–2	6 (0.5)	5 (0.5)	
3–4	515 (44.0)	474 (46.0)	
5–7	650 (55.5)	552 (53.5)	
Killip class, n/N (%)			0.442
I	1090/1166 (93.5)	951 (92.5)	
II	55/1166 (4.7)	60/1028 (5.8)	
III/IV	21/1166 (1.8)	17/1028 (1.7)	
Region of enrollment, n (%)			0.750
North America	399 (34.1)	355 (34.4)	
South America	50 (4.3)	38 (3.7)	

Continued

Table 1. Continued

Characteristics	Vorapaxar (n=1171)	Placebo (n=1031)	P Value
Western Europe	467 (39.9)	427 (41.4)	
Eastern Europe	93 (7.9)	83 (8.0)	
Asia	93 (7.9)	81 (7.9)	
Australia or New Zealand	69 (5.9)	47 (4.6)	
Drugs at time of NSTE ACS, n (%)			
Thienopyridine	1043 (89.1)	888 (86.1)	0.036
Aspirin	1134 (96.8)	1007 (97.7)	0.235
β-Blocker	889 (75.9)	805 (78.1)	0.230
NSTE ACS revascularization, n (%)			
Medical therapy	418 (35.7)	402 (39.0)	0.186
Bare-metal stent	298 (25.4)	234 (22.7)	
Drug-eluting stent	455 (38.9)	395 (38.3)	
Type of surgery, n (%)			
Major	247 (21.1)	227 (22.0)	0.599
Minor	924 (78.9)	804 (78.0)	
Timing of surgery after randomization, d median (IQR)	180 (51–341)	195 (61–370)	0.053
≤30 d	226 (19.3)	181 (17.6)	0.165
>30 d to 6 mo	362 (30.9)	318 (30.8)	
>6 mo to 1 y	330 (28.2)	270 (26.2)	
>1 y	253 (21.6)	262 (25.4)	
Timing of surgery relative to study drug, n (%)			
Surgery before last dose	901 (76.9)	819 (79.8)	0.102
Surgery after last dose	270 (23.1)	207 (20.2)	
Time between surgery and last dose, d median (IQR)	13.0 (3.0–52.0)	15.0 (3.0–92.0)	0.431

CK-MB indicates creatinine kinase-MB; NCS, noncardiac surgery; NSTE ACS, non–ST-segment elevation acute coronary syndrome; TIMI, Thrombolysis In Myocardial Infarction.

30-day NCS bleeding was similar for vorapaxar- and placebo-treated patients (3.9% versus 3.4%, $P=0.507$). Similarly, no differences in the incidence of all GUSTO moderate/severe, TIMI major/minor, or TIMI clinically significant bleeding were observed ($P>0.05$ for all).

After multivariable adjustment, the 30-day associations between treatment assignment and the primary ischemic end point (adjusted OR 0.81, 95% CI, 0.50 to 1.33, $P=0.412$) (Figure 1), TRACER end point (adjusted OR 1.01, 95% CI, 0.64 to 1.60, $P=0.953$), NCS bleeding (adjusted OR 1.41, 95% CI, 0.87 to 2.31, $P=0.165$), GUSTO moderate or severe bleeding (adjusted OR 1.15, 95% CI, 0.72 to 1.83, $P=0.551$), TIMI clinically significant bleeding (adjusted OR 1.17, 95% CI, 0.84 to 1.65, $P=0.355$), and TIMI major or minor bleeding (adjusted OR 1.07, 95% CI, 0.67 to 1.70, $P=0.768$) remained nonsignificant. In a sensitivity analysis, no differences between treatment groups in the adjusted study outcomes were observed among on-treatment study patients (Table 2). No

differences in the adjusted end points were observed between vorapaxar- versus placebo-treated NCS patients between postoperative day 30 through the end of study follow-up (Table S3).

Clinical Outcomes by Surgical Timing, Surgical Type, and Revascularization Strategy

The timing of surgery after NSTE ACS ≤30, >30 to 180, >180 days to 1 year, and >1 year was 20.9%, 32.2%, 26.4%, and 20.5% for minor procedures and 9.7%, 26.2%, 30.2%, and 34.0% for major procedures, respectively. No significant interactions between study treatment and clinical outcomes were observed for surgical timing, revascularization strategies after the index NSTE ACS, or major versus minor surgery; thus, study treatment groups were pooled (Figure 2, Table S4). The adjusted 30-day post-NCS risk of cardiovascular mortality, nonfatal myocardial infarction, stent
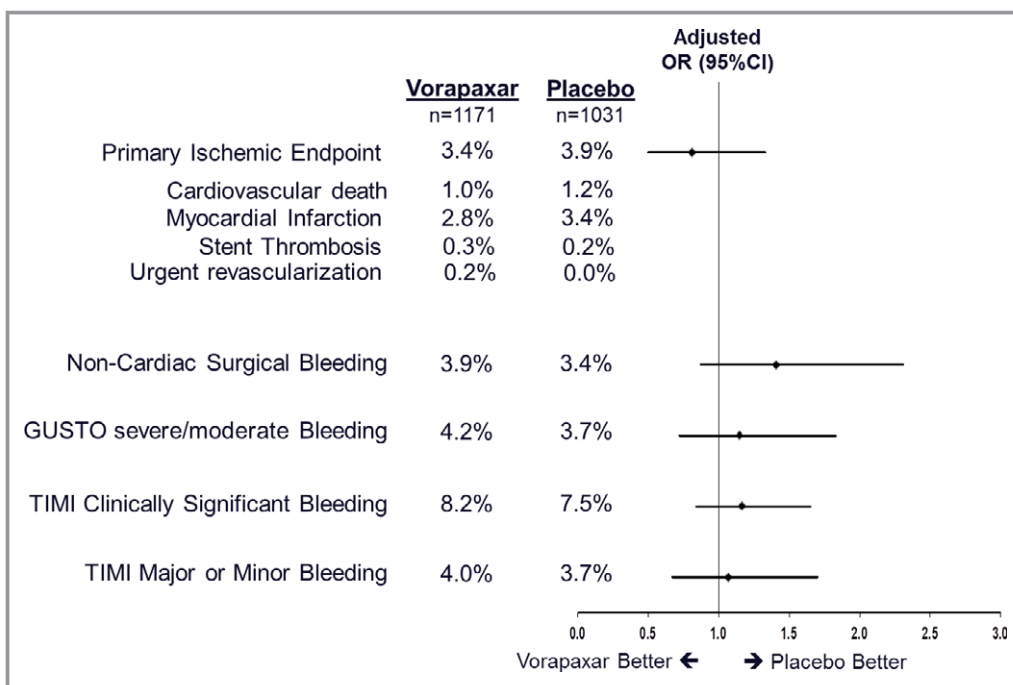
Figure 1. Adjusted associations between study treatment and 30-day clinical outcomes in NCS patients. No treatment-related ischemic or bleeding differences were observed. GUSTO indicates Global Utilization of Strategies to Open Occluded Arteries; NCS, noncardiac surgery; OR, odds ratio; TIMI, Thrombolysis In Myocardial Infarction.

thrombosis, or urgent revascularization was highest among patients undergoing surgery within 30 days of the index NSTE ACS. Perioperative 30-day NCS bleeding was numerically lower than GUSTO moderate/severe, TIMI clinically significant, or TIMI major/minor bleeding. Compared with patients undergoing NCS within 30 days of the index NSTE ACS, the adjusted risk of perioperative NCS bleeding was higher between >30 and 180 days, but no significant difference was observed beyond 180 days. The risk of TIMI clinically significant and major or minor bleeding was significantly lower in patients undergoing NCS after 30 days. There were no observed differences in the adjusted 30-day risk of the primary ischemic outcome between major and minor surgeries, but the risk of 30-day NCS-related bleeding and GUSTO moderate or severe bleeding was higher for major surgical procedures. The risk-adjusted 30-day ischemic outcomes for

Table 2. Unadjusted and Adjusted Vorapaxar Versus Placebo 30-Day Perioperative Outcomes in the On-Treatment Population

Endpoints	Observed Events*		Adjusted OR (95% CI)	P Value
	Vorapaxar	Placebo		
Primary ischemic end point	24/804 (3.0)	26/726 (3.6)	0.80 (0.44–1.48)	0.485
TRACER end point	26/786 (3.3)	27/699 (3.9)	0.85 (0.47–1.54)	0.591
Noncardiac surgical bleeding	30/901 (3.3)	25/819 (3.1)	1.37 (0.76–2.45)	0.291
GUSTO moderate or severe bleeding	35/858 (4.1)	31/784 (4.0)	1.14 (0.66–1.97)	0.646
Severe bleeding	17/1146 (1.5)	12/1018 (1.2)	1.74 (0.55–5.55)	0.350
Moderate bleeding	34/1109 (0.7)	28/995 (2.8)	1.10 (0.59–2.05)	0.763
TIMI clinically significant bleeding	80/698 (11.5)	64/679 (9.4)	1.22 (0.84–1.78)	0.294
TIMI major or minor bleeding	39/850 (4.6)	28/784 (3.6)	1.22 (0.72–2.09)	0.458
Intracranial haemorrhage	4/1165 (0.3)	1/1029 (0.1)	—	—

GUSTO indicates Global Utilization of Strategies to Open Occluded Arteries; OR, odds ratio; TIMI, Thrombolysis In Myocardial Infarction; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome.
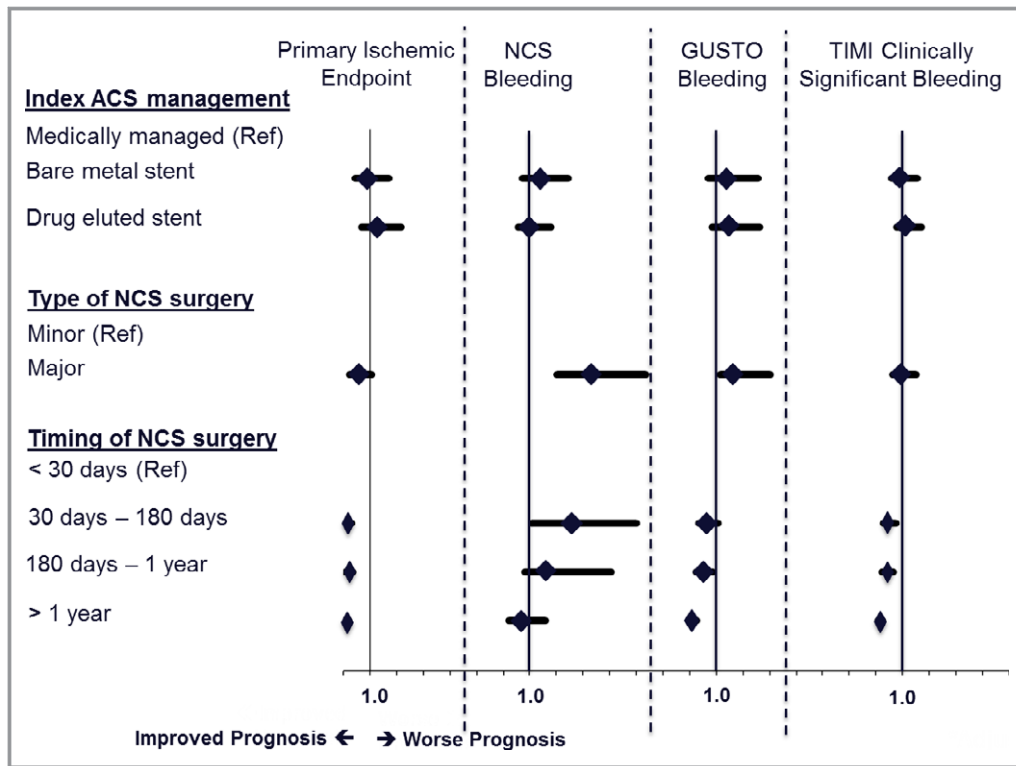*Denominators change with removal of presurgery events.

Figure 2. Adjusted associations of index ACS management, type of NCS, and surgical timing with 30-day clinical outcomes in NCS patients. NCS bleeding was higher in patients who underwent major surgery and in patients who underwent surgery <180 days after NSTE ACS. Ischemic events were higher in patients who underwent NCS <30 days after NSTE ACS. ACS indicates acute coronary syndromes; GUSTO, Global Utilization of Strategies to Open Occluded Arteries; NCS, noncardiac surgery; NSTE, non–ST-segment elevation; TIMI, Thrombolysis In Myocardial Infarction.

patients who underwent revascularization with bare-metal or drug-eluting stents were not significantly different from those for patients who did not undergo revascularization. No relationship between study treatment, surgical site, and bleeding was observed.

Long-term Outcomes in Patients With and Without NCS

Ischemic and bleeding outcomes in NSTE ACS patients who did and did not undergo NCS are presented in Table 3. No significant interactions between treatment assignment and outcomes were observed; thus, treatment groups were pooled. The median follow-up among NCS patients (who survived through 30 days postoperatively) and non-NCS patients (landmarked at 30-day post-NSTE ACS survival) was 1.6 and 1.3 years, respectively. In a 30-day landmark analysis with NCS as a time-dependent covariate, the adjusted ischemic end point (adjusted HR 1.62, 95% CI, 1.33 to 1.97, $P<0.001$) and the TRACER composite end point (adjusted HR 1.92, 95% CI, 1.62 to 2.27) were higher among NCS patients. The incidence of GUSTO moderate or severe

bleeding (adjusted HR 5.63, 95% CI, 3.98 to 7.97, $P<0.001$) (Figure 3), TIMI clinically significant bleeding (adjusted HR 3.54, 95% CI, 2.85 to 4.41, $P<0.001$), and TIMI major or minor bleeding (adjusted HR 5.19, 95% CI, 3.50 to 7.71, $P<0.001$) were all significantly higher in the NCS group. No significant interaction effect was found between the subgroups (major versus minor NCS and type of revascularization) and study treatment assignment with the ischemic and safety end points (results not shown).

Discussion

In this large, contemporary, international cohort of patients undergoing NCS after an NSTE ACS with a rigorously adjudicated clinical end point, several important findings emerge. First, no significant differences were observed in the 30-day incidence of the primary ischemic outcome or NCS bleeding between vorapaxar- and placebo-treated patients. Second, early NCS after an NSTE ACS was associated with a significant increase in adverse perioperative ischemic events. Our findings suggest that surgery should be delayed, where clinically appropriate, ≥30 days to minimize ischemic events

Table 3. Outcomes in Patients With and Without NCS

| | Patients Without NCS (n=9363) | Patients With NCS (n=2202) | | | | |
| | | Events Before NCS | Events After NCS | | | P Value* |
			Total	≤30 Days	>30 Days	
Clinical end points, n (%)						
Primary ischemic end point	1230 (13.1)	255 (11.6)	253 (11.5)	80 (3.6)	173 (7.9)	<0.001
TRACER end point	1348 (14.4)	327 (14.9)	240 (10.9)	96 (4.4)	144 (6.5)	<0.001
All-cause mortality	367 (3.9)	1 (0.04)	201 (9.1)	34 (1.5)	167 (7.6)	<0.001
Cardiovascular mortality	254 (2.7)	1 (0.04)	106 (4.8)	30 (1.4)	76 (3.4)	<0.001
Myocardial infarction	819 (8.8)	237 (10.8)	146 (6.6)	68 (3.1)	78 (3.5)	0.001
Stent thrombosis	77 (0.8)	25 (1.1)	11 (0.5)	6 (0.3)	5 (0.2)	0.117
Urgent revascularization	279 (3.0)	62 (2.8)	25 (1.1)	2 (0.1)	23 (1.0)	<0.001
Stroke	100 (1.1)	31 (1.4)	27 (1.2)	8 (0.4)	19 (0.9)	0.522
Safety end points, n (%)						
GUSTO moderate or severe bleeding	152 (1.6)	135 (6.1)	115 (5.2)	87 (4.0)	28 (1.3)	<0.001
Severe bleeding	71 (0.8)	38 (1.7)	42 (1.9)	29 (1.3)	13 (0.6)	<0.001
Moderate bleeding	83 (0.9)	98 (4.5)	78 (3.5)	62 (2.8)	16 (0.7)	<0.001
TIMI clinically significant bleeding	850 (9.1)	480 (21.8)	236 (10.7)	173 (7.9)	63 (2.9)	0.018
TIMI major or minor bleeding	151 (1.6)	139 (6.3)	106 (4.8)	85 (3.9)	21 (1.0)	<0.001
Intracranial haemorrhage	30 (0.3)	8 (0.4)	9 (0.4)	5 (0.2)	4 (0.2)	0.520

GUSTO indicates Global Utilization of Strategies to Open Occluded Arteries; NCS, non cardiac surgery; TIMI, Thrombolysis In Myocardial Infarction; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome.
*P-value for the comparison of patients with events after NCS vs patients without NCS.

and ≥6 months to minimize bleeding events. Finally, among 30-day survivors, NCS patients had a significantly higher long-term risk of ischemic events and bleeding compared with patients who did not undergo NCS, irrespective of treatment assignment.

The published incidence of NCS after an ACS or stent implantation is 2% to 34%.[1–3,13,14,21–23] This wide reported range in these observational analyses likely reflects differences in NCS surgical procedures (major or minor), revascularization strategies (bare-metal and/or drug-eluting stent), and duration of follow-up. The present analysis, which followed both medically treated and percutaneously revascularized NSTE ACS patients for a median of 1.5 years, found that 17.0% of patients require major or minor NCS procedures. This finding confirms that NCS after an NSTE ACS is common in a relatively unselected population. In addition, the regional variations in the incidence of NCS after an NSTE ACS observed in this study may also provide insight into the wide difference in published NCS estimates. Our observation that Australia/New Zealand and North American had the highest NCS rates is similar to other published estimates in population-based datasets, though this is the first study to describe international geographical differences in NCS after an NSTE ACS.[1–3] Future studies may be

directed at understanding the clinical and environmental reasons underpinning regional variations in the incidence of NCS.

The optimal perioperative antiplatelet management strategies in patients undergoing NCS after ACS remains unresolved. A recent major randomized trial reported that use of aspirin increased the risk of NCS bleeding, but this trial specifically excluded patients with recent coronary stenting or thienopyridine use.[24] Similarly, the perioperative use of thienopyridines has been associated with increased NCS bleeding, but hemorrhagic risks must be weighed against the potential ischemic risks of drug discontinuation early after coronary stenting.[1,7,25–28] The protease-activated receptor 1 antagonist vorapaxar had a higher incidence of bleeding in the overall trial population and, in this analysis, bleeding rates were higher among patients prior to NCS; however, vorapaxar was not associated with differences in 30-day cardiovascular mortality, nonfatal myocardial infarction, stent thrombosis, or urgent revascularization, or 30-day perioperative bleeding. Importantly, 78% of the patients continued vorapaxar through the perioperative period, and the results were similar in an on-treatment sensitivity analysis. In addition, among the 22% of patients who discontinued the study drug a median of 13 days preoperatively, the half-life of up to 311 hours
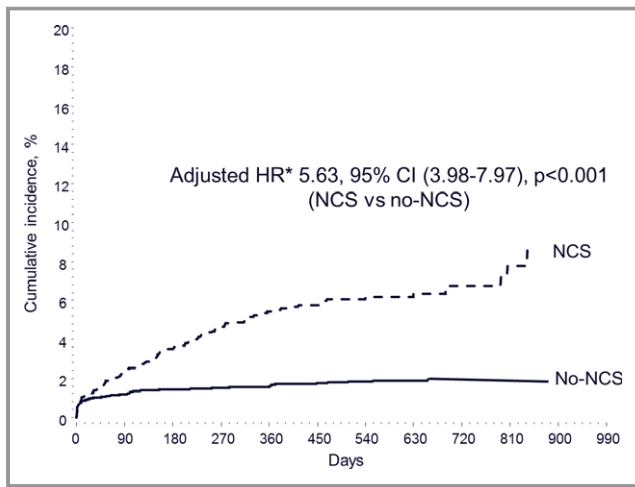
Figure 3. Long-term GUSTO moderate or severe bleeding in NCS and non-NCS patients. Kaplan–Meier survival estimates were obtained in patients landmarked at 30 days postsurgery or NSTE ACS. Among 30-day survivors, there is significant long-term bleeding among NCS patients. GUSTO, Global Utilization of Strategies to Open Occluded Arteries; HR, hazard ratio; NCS, noncardiac surgery; NSTE ACS, non–ST-segment elevation acute coronary syndromes.

suggests residual pharmacokinetic effect was likely present in many patients. These results are consistent with an animal study that reported no increase in bleeding time or blood loss with vorapaxar in addition to aspirin and thienopyridine treatment, and with the results of a secondary TRACER analysis that reported no increase in coronary artery bypass grafting–related major bleeding.[15,29] The novel composite end point was created to best align with clinically important events in perioperative care; however, the results mirror those of the TRACER end point. Our findings have implications for patients with coronary artery disease on vorapaxar who require NCS. Among patients requiring urgent NCS, preoperative delay for the sole purpose of eliminating the drug effect is likely unnecessary. We acknowledge the need for further clarity regarding the perioperative management of other antiplatelet agents and that preoperative vorapaxar management may need to be individualized for surgical procedures where substantial morbidity with bleeding exists (ie, neurosurgery).

The association between early NCS after an ACS and adverse NCS perioperative outcomes was first described in the prerevascularization era.[4,30] A similar relationship has been well described in patients with percutaneous revascularization and has led to recommendations to delay NCS after an ACS ≥30 days when possible.[1,3,20,22,25,31–34] Our study confirms these findings using a contemporary, international cohort of patients with mixed revascularization strategies, and it suggests that surgery should be delayed ≥30 days when it is clinically appropriate. Moreover, this analysis adds impor-

tant information on perioperative bleeding. Although postoperative bleeding is associated with adverse outcomes across the spectrum of surgical procedures, little is known about its relationship with NCS timing after an NSTE ACS.[24,35–37] A recent major multicenter, randomized controlled trial reported that aspirin before NCS increased major bleeding and, in a post-hoc analysis, major bleeding was an independent predictor of myocardial infarction.[24] This trial did not, however, address the risks and benefits in patients with recent ACS. A prospective cohort of patients in France found that timing of NCS after stenting was independently associated with the risk of hemorrhagic complications.[27] With the use of centrally adjudicated clinical end points, our findings suggest that, if possible, surgery should to be delayed ≥6 months to minimize the risk of both NCS and spontaneous bleeding. Postoperative ischemic events, however, were highest within the first 30 days after NSTE ACS with relatively balanced events thereafter. Our findings suggest that NCS should be delayed >30 days, where clinically appropriate, to minimize the risk of both adverse cardiac events and hemorrhagic complications. Confirmation of this association with other antiplatelet agents requires further investigation.

The cardiovascular and bleeding risks of NCS after an ACS have been well described.[1,38] However, little is known about the long-term outcomes of NCS in this population. In this study we observed a significant risk association between NCS after NSTE ACS and both ischemic events and major bleeding. Importantly, this analysis was landmarked to only include patients who survived through 30 postoperative days to minimize NCS-related events, and the Kaplan–Meier curves for bleeding appeared to continue to separate through the follow-up period, suggesting a long-term risk association between NCS and NSTE ACS that extends well beyond the traditional perioperative period. Although preoperative bleeding rates were higher among vorapaxar-treated patients, no postoperative interaction between treatment and outcomes was observed, suggesting an independent long-term risk association in the NCS population. We acknowledge that the reasons underpinning these findings are beyond the scope of this analysis and a careful evaluation of postoperative care may be merited on the basis of these results. Clinicians ought to carefully consider the individual patient bleeding risks and benefits before resuming antiplatelet therapies in patients with ACS who have undergone NCS.

Study Limitations

The limitations of the study merit consideration. The study case report form coded for the incidence and timing of study drug interruptions, but it did not provide detailed information on the perioperative management of aspirin, thienopyridines, or other cardiac medications. In addition, the current analysis

was neither prespecified nor randomized. Thus, the results of this analysis should be considered hypothesis generating. More patients in the vorapaxar cohort of this study experienced preoperative bleeding, which influences the generalizability of the study. However, no associations between postoperative outcomes or timing of surgery were observed in this analysis. Finally, the number of patients in the major surgery cohort may not be adequately powered to detect a significant result.

Conclusions

Among NSTE ACS patients undergoing NCS, we observed no differences in perioperative ischemic or bleeding events between vorapaxar- and placebo-treated patients. Early NCS (≤30 days) was associated with an increased risk of adverse perioperative ischemic events and bleeding; these findings suggest that NCS should be delayed ≥30 days to minimize ischemic events and delayed ≥6 months to minimize bleeding. Among 30-day NCS survivors, we observed significantly higher long-term ischemic and bleeding risk association in patients with prior NSTE ACS. Future studies should be directed at elucidating the relationships between concurrent antiplatelet agents and revascularization strategies with clinical outcomes.

Sources of Funding

Disclosures

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