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Prognostic Value of Access Site and Nonaccess Site Bleeding After Percutaneous Coronary Intervention

A Cohort Study in ST-Segment Elevation Myocardial Infarction and Comprehensive Meta-analysis

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Objectives This study sought to investigate the prognostic value of access site bleeding (ASB) and non-ASB for recurrent ischemic outcomes and mortality in patients with ST-segment elevation myocardial infarction (STEMI).

Background The prognostic value of ASB-related complications after STEMI is subject to debate.

Methods The prognostic value of ASB and non-ASB for 1-year mortality, recurrent myocardial infarction (MI), stent thrombosis, and stroke was investigated in 2,002 STEMI patients undergoing primary percutaneous coronary intervention. In addition, we performed a meta-analysis of studies investigating the prognostic value of ASB and non-ASB in patients undergoing percutaneous coronary intervention.

Results Seventy-four patients (3.7%) were treated by radial access. ASB developed in 124 patients (6.3%) and non-ASB developed in 102 (5.2%). By multivariable analysis, ASB was not associated with a higher risk of 1-year mortality (hazard ratio [HR]: 1.03; $p = 0.89$), recurrent MI (HR: 1.16; $p = 0.64$), stent thrombosis (HR: 0.55; $p = 0.42$), or stroke (HR: 0.47; $p = 0.31$). Non-ASB was independently associated with 1-year mortality (HR: 2.77; $p < 0.001$) and stent thrombosis (HR: 3.10; $p = 0.021$), but not with recurrent MI and stroke. In a meta-analysis including 495,630 patients, non-ASB was associated with a greater adjusted risk of subsequent 1-year mortality than ASB (HR: 1.66; 95% CI: 1.56 to 1.76 and HR: 1.21; 95% CI: 1.11 to 1.31).

Conclusions In STEMI, ASB was not significantly associated with 1-year clinical outcomes, whereas non-ASB was significantly associated with 1-year mortality and stent thrombosis. These results taken together with those of previous studies indicate a greater risk of subsequent mortality in patients with non-ASB. (J Am Coll Cardiol Intv 2014;7:622–30) © 2014 by the American College of Cardiology Foundation

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Bleeding complications after percutaneous coronary intervention (PCI) are associated with an increased risk of mortality and morbidity (1–4). Therefore, considerable effort has been made to develop novel treatment strategies directed at minimizing bleeding complications. One such strategy, performing PCI via the radial artery, has been shown in prospective, randomized trials to result in a reduction in bleeding complications arising at the arterial puncture site (5,6). Unfortunately, although access site bleeding (ASB) represents a common source of bleeding in patients undergoing PCI, as many as 50% to 60% of major or minor bleeding complications originate at a site not related to the arterial access site (non-ASB) (7–10). Furthermore, ASB was shown in some studies to be associated with increased mortality after PCI, whereas others have failed to confirm these findings (7–9,11,12). Moreover, in the RIVAL (RadIal Vs femorAL access for coronary intervention) trial, the reduction in ASB did not translate into a reduction in mortality (5). Therefore, it is of paramount interest to investigate whether ASB significantly affects the prognosis of patients undergoing PCI because a reduction in ASB may or may not affect long-term prognosis. In this study, we investigate the impact of ASB and non-ASB on discontinuation of antiplatelet therapy and subsequent 1-year clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI (PPCI). In addition, we perform a meta-analysis of current literature to assess the prognostic impact of ASB and non-ASB on 1-year mortality in patients undergoing PCI.

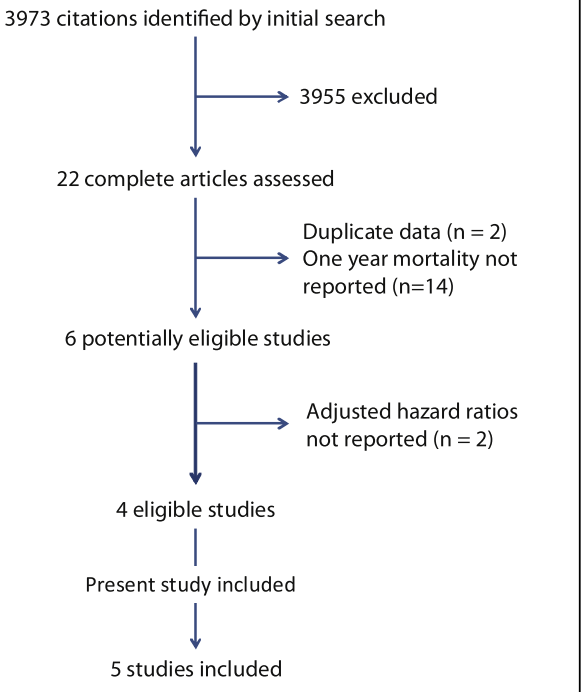

Figure 1. Flow Chart of Search Strategy

Flow chart demonstrating the search strategy and selection of eligible studies for the meta-analysis.

Methods

Source population and procedures. The data analyzed in this study were obtained from consecutive STEMI patients who were accepted for PPCI at the Academic Medical Center–University of Amsterdam between January 1, 2003 and July 31, 2008. The study complied with the Declaration of Helsinki, and the local ethics committee approved the study protocol. In general, patients qualified for PPCI if they had typical ischemic chest pain and at least 1-mm ST-segment elevation in ≥2 contiguous leads, a new left bundle-branch block, or a true posterior myocardial infarction (MI). The PPCI and adjunctive pharmacological treatment were performed according to American College of Cardiology/American Heart Association and European Society of Cardiology guidelines. Patients received a standard 300- to 600-mg loading dose of clopidogrel. If a coronary stent was implanted, clopidogrel was prescribed for at least 1 month in patients with a bare-metal stent and for 6 to 12 months in patients with a drug-eluting stent. Patients were routinely pretreated with 300 mg aspirin and 5,000 IU unfractionated heparin. An additional heparin bolus was administered at the catheterization laboratory, if necessary, to achieve a targeted activated clotting time of 300 s followed by an infusion of 12 U/kg/h with titration to achieve a target activated partial thromboplastin time (aPTT) of 1.5 to 2 times the control. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator.

Abbreviations and Acronyms

aPTT = activated partial thromboplastin time
ASB = access site bleeding
HR = hazard ratio
IABP = intra-aortic balloon pump
IQR = interquartile range
MI = myocardial infarction
PCI = percutaneous coronary intervention
PPCI = primary percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

Procedural and angiographic data were prospectively collected in a dedicated database by interventional cardiologists and specialized nurses. Chart review for consecutive STEMI patients with available aPTT measurements was performed in the context of a study designed to investigate the relationship between periprocedural aPTT and clinical outcome in STEMI patients treated with PPCI. A detailed description of the study protocol was previously reported (13). Laboratory measurements (including hemoglobin) that were performed in referring hospitals were added to the study database. We obtained clinical history and detailed information on periprocedural treatment from inpatient records in the PCI center and referring hospitals. We obtained

Table 1. Clinical and Procedural Characteristics of Patients With and Without Access Site Bleeding

Characteristic	Access Site Bleeding (n = 124)*	Nonaccess Site Bleeding (n = 102)*	No Bleeding (n = 1,806)	p Value†	p Value‡
Age, yrs	71.0 ± 13.4	68.3 ± 12.4	61.3 ± 12.8	<0.001	<0.001
Female	86/124 (69.4)	37/102 (36.3)	489/1,806 (27.1)	<0.001	0.043
BMI, kg/m^2	24.2 (22.0–27.1)	24.9 (22.8–27.8)	26.2 (24.2–29.1)	<0.001	0.009
History of					
Diabetes	24/124 (19.4)	18/102 (17.6)	239/1,806 (13.2)	0.055	0.20
Hypertension	56/124 (45.2)	40/102 (39.2)	677/1,806 (37.5)	0.088	0.73
Dyslipidemia	19/124 (15.3)	11/102 (10.8)	435/1,806 (24.1)	0.026	0.002
Peripheral artery disease	19/124 (15.3)	13/102 (12.7)	106/1,806 (5.9)	<0.001	0.005
Ischemic stroke or TIA	14/124 (11.3)	10/102 (9.8)	105/1,806 (5.8)	0.014	0.099
Malignancy	17/124 (13.7)	17/102 (16.7)	124/1,806 (6.9)	0.005	<0.001
Bleeding	10/124 (8.1)	10/102 (9.8)	66/1,806 (3.7)	0.015	0.002
Surgery <10 days	5/124 (4.0)	8/102 (7.8)	11/1,806 (0.6)	<0.001	<0.001
Previous MI	20/124 (16.1)	18/102 (17.6)	216/1,806 (12.0)	0.17	0.088
Previous PCI	10/124 (8.1)	13/102 (12.7)	181/1,806 (10.0)	0.48	0.38
Previous CABG	2/124 (1.6)	5/102 (4.9)	38/1,806 (2.1)	0.71	0.064
Family history of CAD	40/124 (32.3)	24/102 (23.5)	690/1,806 (38.2)	0.19	0.003
Current smoker	41/124 (33.1)	37/102 (36.3)	810/1,806 (44.9)	0.011	0.090

Continued on the next page

follow-up of clinical outcome, including recurrent MI, stroke, stent thrombosis, and bleeding, by reviewing in- and outpatient charts in the tertiary PCI center and referring hospitals between 2011 and 2012. For each patient, we systematically checked inpatient charts of every hospital admission for the occurrence of clinical events, including hemorrhagic events and their location. Follow-up of clinical events was censored at the actual date of chart review. Patients whose whereabouts could not be traced were considered lost to follow-up from the date of last known medical contact. Follow-up information regarding vital status was obtained from computerized long-term mortality records from the National Death Index. If a patient could not be identified in these records (e.g., foreign patients), censoring was at the date of last contact. For the present analysis, patients were censored at the date of death or at 1 year after the index PCI, whichever came first.

Study design. The study cohort consisted of all STEMI patients included in our study database who were alive at the end of the procedure. Bleeding was considered to have occurred when the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) severe or moderate bleeding criteria were met (14). Bleeding was considered access site–related if it originated at the PCI-related arterial puncture site or in the retroperitoneal cavity in case of femoral access. Bleeding originating at arterial puncture sites required for achieving arterial access for an intra-aortic balloon pump (IABP) or other left ventricular assist devices during the index PCI were also defined as ASB. All other bleeding complications were considered nonaccess site-related. As a sensitivity analysis, ASB and non-ASB were defined according to the Thrombolysis In Myocardial Infarction major or minor criteria (15).

Cardiac mortality, recurrent MI, and stent thrombosis (definite) were defined according to the Academic Research Consortium criteria (16). Stroke was defined as an irreversible neurological deficit, as classified by the treating neurologist, on the basis of supporting information, including brain images and neurological evaluation.

Meta-analysis. We performed a computerized literature search for the period 1980 to September 16, 2013, of the PubMed and Embase databases, using search terms that included "bleeding" or "hemorrhage" and "acute coronary syndrome" or "percutaneous coronary intervention." Study selection was done by 2 independent reviewers (W.J.K., R.D.), and disagreement was resolved by a third reviewer (J.P.S.H.). Citations were screened at the title/abstract level and retrieved as full reports. Bibliographies of identified studies and relevant review articles were screened for potentially suitable studies. Non-English articles, case reports, reviews, and studies reporting duplicate data were excluded.

To be included, studies had to include patients treated with PCI and compared 1-year mortality of patients with ASB and non-ASB occurring within 30 days after PCI. We did not include studies that did not report adjusted HRs for 1-year mortality. Studies in which HRs for mortality were not calculated in time-dependent Cox models were also eligible for inclusion.

The flow chart of the search strategy and selection of studies is depicted in Figure 1. We identified 22 studies

Table 1. Continued

Characteristic	Access Site Bleeding (n = 124)*	Nonaccess Site Bleeding (n = 102)*	No Bleeding (n = 1,806)	p Value†	p Value‡
Laboratory assays					
Baseline WBC count, $\times 10^3/mm^3$	11.7 (9.7–15.7)	13.4 (9.9–17.3)	11.1 (8.8–14.1)	0.005	<0.001
Baseline Hb, mmol/l	8.1 (7.1–8.8)	8.0 (7.0–8.9)	8.9 (8.3–9.5)	<0.001	<0.001
Baseline thrombocyte count, $\times 10^9$/l	254 (207–305)	233 (184–310)	247 (208–291)	0.49	0.21
<150	7/124 (5.6)	10/101 (9.9)	61/1,787 (3.4)		
150–400	111/124 (89.5)	86/101 (85.1)	1,665/1,787 (93.2)	0.29	0.002
>400	6/124 (4.8)	5/101 (5.0)	61/1,787 (3.4)		
Baseline CrCl, ml/min/1.73 m^2	59.1 (41.1–78.1)	63.3 (45.4–87.2)	94.8 (71.6–119.9)	<0.001	<0.001
Mean aPTT, s	121 (94.2–143)	92.8 (66.8–134)	89.9 (71.1–112)	<0.001	0.33
Procedural characteristics					
Puncture site					
Radial only	2/124 (1.6)	1/102 (1.0)	72/1,804 (4.0)		
Femoral only	118/124 (95.2)	100/102 (98.0)	1,721/1,804 (95.4)	0.003	0.28
Other	4/124 (3.2)	1/102 (1.0)	11/1,804 (0.6)		
Tortuous peripheral arteries	8/124 (6.5)	5/102 (4.9)	61/1,806 (3.4)	0.075	0.41
Calcified peripheral arteries	8/124 (6.5)	2/102 (2.0)	31/1,806 (1.7)	<0.001	0.85
Clopidogrel loading dose, mg				0.44	0.001
No loading dose	7/124 (5.6)	11/98 (11.2)	59/1,751 (3.4)		
300	80/124 (64.5)	59/98 (60.2)	1118/1,751 (63.8)		
600	37/124 (29.8)	28/98 (28.6)	563/1,751 (32.2)		
Other	0/124 (0.44)	0/98 (0.0)	11/1,751 (0.6)		
Cardiogenic shock	25/122 (20.5)	25/100 (25.0)	111/1,785 (6.2)	<0.001	<0.001
IABP/LVAD	45/124 (36.3)	39/102 (38.2)	193/1,806 (10.7)	<0.001	<0.001
Total ischemic time, min	240 (158–346)	192 (131–304)	178 (128–260)	<0.001	0.20
Peak CK-MB release, mmol/l	321 (113–488)	175 (77.8–455)	213 (94.6–405)	0.010	0.64
GP IIb/IIIa inhibitor	46/124 (37.1)	32/102 (31.4)	501/1,806 (27.7)	0.025	0.43
Angiographic characteristics					
IRA				0.13	0.85
LM/LAD	59/119 (56.7)	40/93 (43.0)	759/1,753 (43.3)		
LCX/RCA	60/119 (50.4)	53/93 (57.0)	994/1,753 (56.7)		
TIMI flow					
0/1	78/110 (70.9)	65/84 (77.4)	1,183/1,630 (72.6)	0.71	0.34
2/3	32/119 (29.1)	19/84 (22.6)	447/1,630 (27.4)		
CTO in a non-IRA	22/118 (18.6)	18/97 (18.6)	232/1,727 (13.4)	0.11	0.15
MVD	57/118 (48.3)	46/97 (47.4)	623/1,727 (36.1)	0.008	0.024

Values are n (%), mean ± SD, or median (interquartile range). *Patients who experienced both access and nonaccess site bleeding were counted in both access and nonaccess site bleeding groups. †p Value for access site bleeding versus no bleeding. ‡p Value for nonaccess site bleeding versus no bleeding.

aPTT = activated partial thromboplastin time; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CK-MB = creatine kinase-myocardial band; CrCl = creatinine clearance; CTO = chronic total occlusion; GP = glycoprotein; Hb = hemoglobin; IABP = intra-aortic balloon pump; IRA = infarct-related artery; LAD = left anterior descending artery; LM = left main artery; LVAD = left ventricular assist device; MI = myocardial infarction; MVD = multivessel disease; PCI = percutaneous coronary intervention; RCA = right coronary artery; RCx = ramus circumflexus; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; WBC = white blood cell.

potentially suitable for inclusion in our meta-analysis; 2 of these were excluded because they reported duplicate data, and 14 studies were excluded because 1-year mortality after ASB and non-ASB was not reported. Of the 6 studies reporting 1-year mortality after ASB and non-ASB, 2 were removed because adjusted HRs for 1-year mortality were not reported. Finally, we included the results of the present study in our meta-analysis. Therefore, a total of 5 studies were included in our meta-analysis of the prognostic value of ASB and non-ASB.

Statistical analysis. To investigate the occurrence of clinical outcomes (cardiac and noncardiac mortality, recurrent MI, stent thrombosis, and stroke) after ASB and non-ASB, the following analyses were designed. The relationship between the occurrence of ASB and non-ASB within 30 days and subsequent 1-year outcomes compared with patients without bleeding was investigated by inserting these events simultaneously as time-dependent variables in 2 sets of Cox proportional hazards models for each clinical outcome measure: unadjusted models and

models adjusted for relevant predictors of these clinical outcomes. Relevant predictors were identified by performing stepwise backward-selection Cox regression analyses. Entry criterion was set at $p < 0.05$ and exit criterion was set at $p = 0.10$.

Normally distributed continuous variables are reported as the mean with SD and compared with the Student *t* test; skewed distributed variables are presented as the median with interquartile range (IQR) and compared with the Wilcoxon rank sum test. Categorical variables are presented as proportions and compared with the chi-square test. All tests were 2-sided, and a $p < 0.05$ was considered statistically significant.

We performed a meta-analysis of adjusted HRs for 1-year mortality according to ASB and non-ASB, using the generic inverse variance method (17). The heterogeneity across studies was assessed using the I^2 statistic. Analyses were performed with Statistical Package for Social Sciences software (SPSS version 18.0, Chicago, Illinois) and Review Manager (RevMan) (Version 5.2., The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Of the 3,472 STEMI patients treated with primary PCI in our institution between January 1, 2003 and July 31, 2008, we collected follow-up for 2,009 patients. Of these 2,009 patients, 2,002 were alive at the end of the procedure. Baseline, procedural, and angiographic characteristics for patients included and excluded in the analysis are given in Online Table 1. Patients included in the analysis more often presented in cardiogenic shock and were more often treated with an IABP. One-year mortality was complete in 99.8% (1997/2002) of patients included in the analysis and 99.1% (1,457/1,470) of patients excluded from the analysis. One-year mortality was 11.8% in patients included in the analysis, whereas mortality was 10.3% in patients excluded ($p = 0.22$).

Seventy-four patients underwent PCI via radial access, 1,910 patients underwent PCI via the femoral artery, and the remaining 16 patients underwent PCI via a combination of femoral or radial access or an access site other than the femoral or radial access site. One-year clinical follow-up was complete for 99% of patients (1981/2002). In total, 196 patients (9.9%) experienced GUSTO severe or moderate bleeding within 30 days of follow-up. The distribution of the location of bleeding events is shown in Online Table 2. Of the 196 patients who experienced GUSTO severe or moderate bleeding within 30 days, 52% (n = 102) of patients experienced non-ASB, 63.2% (n = 124) of patients experienced bleeding originating at an arterial puncture site (30 patients experienced both). In the first 30 days after PPCI, 7 patients experienced a fatal bleeding event. Five of these events had a hemopericardial origin, 1 was coronary artery bypass graft related, and 1 was located in the retroperitoneal cavity. Baseline clinical and procedural characteristics of patients with ASB or non-ASB compared with patients without bleeding are given in Table 1. Patients with ASB and non-ASB had a higher baseline risk profile. Compared with patients without bleeding, they typically had more severe atherosclerosis, a higher leukocyte count, and lower creatinine clearance on presentation; more often had cardiogenic shock; and more often required IABP treatment for hemodynamic support.

Prognostic value of ASB and non-ASB. Figure 2 displays Kaplan-Meier curves for 1-year mortality of patients with ASB and non-ASB. Table 2 displays the unadjusted and adjusted associations between ASB and non-ASB that met the GUSTO severe or moderate bleeding criteria and 1-year outcomes. On multivariable analysis, ASB was not associated with a higher risk of recurrent MI, stroke, stent thrombosis, and cardiac and all-cause mortality. Conversely, non-ASB was associated with a 3-fold higher risk of stent thrombosis and cardiac and all-cause mortality after adjustment for confounders. Online Table 3 provides the unadjusted and adjusted relationships between ASB and non-ASB that met the Thrombolysis In Myocardial Infarction major or minor bleeding criteria and 1-year outcomes.

Impact of ASB and non-ASB on antithrombotic therapy. Patients who experienced non-ASB during the index hospital admission were admitted for a median duration of 18 days (interquartile range [IQR]: 11 to 24 days) compared

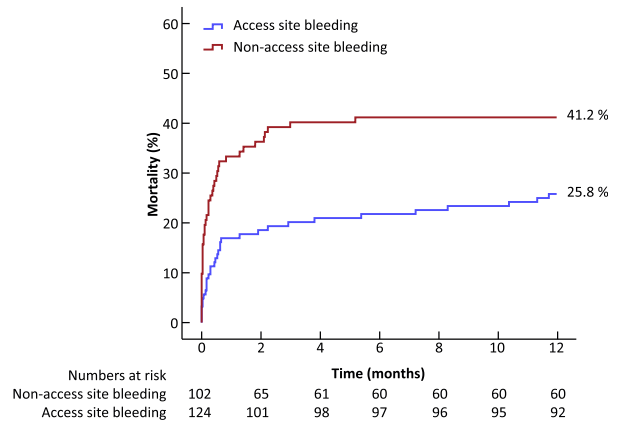

Figure 2. Cumulative Mortality According to Access Site–Related and Nonaccess Site–Related Bleeding

Shown are Kaplan-Meier curves for mortality after the occurrence of access site–related bleeding or nonaccess site–related bleeding within 30 days after primary percutaneous coronary intervention. Zero time point is time of the bleeding event. Patients who experienced both access and nonaccess site bleeding were counted in both access and nonaccess site bleeding groups.

Table 2. Unadjusted and Adjusted Hazard Ratios for 1-Year Clinical Outcome According to Bleeding Status

		Unadjusted*			Adjusted†		
	No. of Patients	HR	95% CI	p Value	HR	95% CI	p Value
All-cause mortality							
No ASB	203	1.00	—	—	1.00	—	—
After ASB	32/124	1.73	1.16–2.58	0.008	1.03	0.69–1.53	0.89
No non-ASB	193	1.00	—	—	1.00	—	—
After non-ASB	42/102	5.77	4.03–8.26	<0.001	2.77	1.92–3.99	<0.001
Cardiac mortality							
No ASB	173	1.00	—	—	1.00	—	—
After ASB	28/124	1.73	1.13–2.67	0.012	0.97	0.64–1.49	0.90
No non-ASB	164	1.00	—	—	1.00	—	—
After non-ASB	37/102	6.02	4.09–8.84	<0.001	3.15	2.14–4.66	<0.001
Noncardiac mortality							
No ASB	30	1.00	—	—	1.00	—	—
After ASB	4/124	1.65	0.55–4.94	0.38	1.04	0.32–3.37	0.95
No non-ASB	29	1.00	—	—	1.00	—	—
After non-ASB	5/102	4.44	1.63–12.1	0.003	2.57	0.92–7.22	0.072
Recurrent myocardial infarction							
No ASB	134	1.00	—	—	1.00	—	—
After ASB	15/124	1.71	0.99–2.97	0.057	1.16	0.66–2.02	0.64
No non-ASB	139	1.00	—	—	1.00	—	—
After non-ASB	10/102	2.08	1.10–3.93	0.024	1.46	0.77–2.76	0.24
Stent thrombosis							
No ASB	64	1.00	—	—	1.00	—	—
After ASB	2/124	0.43	0.10–1.83	0.25	0.55	0.13–2.36	0.42
No non-ASB	61	1.00	—	—	1.00	—	—
After non-ASB	5/102	3.17	1.25–8.09	0.016	3.10	1.19–8.11	0.021
Stroke							
No ASB	35	1.00	—	—	1.00	—	—
After ASB	2/124	1.22	0.29–5.06	0.79	0.47	0.11–2.01	0.31
No non-ASB	37	1.00	—	—	1.00	—	—
After non-ASB	0/102	—	—	—	—	—	—

The HR for all-cause mortality was adjusted for age, history of hypertension, family history of coronary artery disease, current smoking, history of bleeding, history of malignant disease, creatinine clearance, thrombocyte count, leukocyte count, baseline hemoglobin, percutaneous coronary intervention access site, cardiogenic shock, intra-aortic balloon pump, multivessel disease, the presence of a chronic total occlusion, infarct-related artery, and total ischemic time. A list of the variables included in the remaining multivariable models can be found in the Online Appendix.
*Unadjusted HRs and corresponding CIs were calculated using Cox proportional hazard models using bleeding status as a time-dependent covariate. †Adjusted HRs and corresponding CIs were calculated using Cox proportional hazard models using bleeding status as a time-dependent covariate.

ASB = access site bleeding; CI = confidence interval; HR = hazard ratio.

with 13 days (IQR: 7 to 21 days) in patients who experienced ASB and 5 days (IQR: 3 to 8 days) in those who did not experience any bleeding during the index admission ($p < 0.001$). Other treatment aspects associated with ASB and non-ASB are given in Table 3. Figure 3 displays the rates of discontinuation of antiplatelet therapy according to bleeding source. Antiplatelet agents were most often discontinued indefinitely in patients with non-ASB. Of the 124 patients with ASB, 3 experienced a stent thrombosis within the following year. Conversely, of the 104 patients with non-ASB, 5 experienced a stent thrombosis within the following year. In 1 of these patients, antiplatelet therapy was discontinued indefinitely after the preceding bleeding event.

Meta-analysis. Including the present study, there are 5 studies reporting adjusted HRs for mortality after ASB and non-ASB, including a total of 495,630 patients (7–10). Two studies included patients undergoing elective PCI or PCI for acute coronary syndrome (7,9). The study by Rao et al. (9) excluded patients younger than 65 years of age. Two studies including the present study were conducted in STEMI (8). Finally, 1 study was performed in elective PCI and non–ST-segment elevation acute coronary syndrome only (10). A forest plot of the adjusted HRs for 1-year

Table 3. Characteristics of Bleeding Episodes by Access and Nonaccess Site Bleeding

Characteristics	Access Site Bleeding (n = 124)	Nonaccess Site Bleeding (n = 102)	p Value
Blood transfusions, U	3 (2–4)	3 (2–7)	0.048
Hemoglobin decrease, mmol/l	2.9 (2.2–3.9)	2.6 (1.7–3.9)	0.076
Immediate discontinuation of antithrombotic therapy because of bleeding event	35/124 (28.2)	44/102 (43.1)	0.019
Diagnostic radiological procedure related to bleeding	65/124 (52.4)	36/102 (35.3)	0.010
Surgery related to bleeding	10/124 (8.1)	21/102 (20.6)	0.006

Values are median (interquartile range) or n (%). Patients who experienced both access and nonaccess site bleeding were counted in both access and nonaccess site bleeding groups.

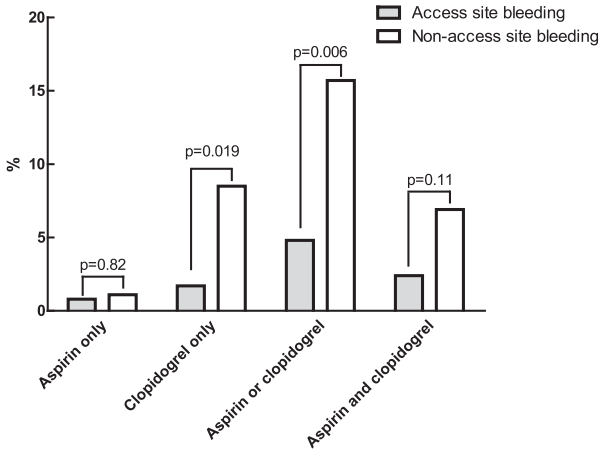

Figure 3. Discontinuation of Antiplatelet Therapy Related to Bleeding

The **bars** indicate the percentage of patients with bleeding in whom antiplatelet therapy was discontinued indefinitely after a bleeding event. Patients who experienced both access and nonaccess site bleeding were counted in both access and nonaccess site bleeding groups.

mortality is shown after ASB (Fig. 4A) and non-ASB (Fig. 4B). Both ASB and non-ASB are significantly associated with 1-year mortality. The degree of risk, however, is dependent on the source of bleeding; the adjusted risk of 1-year mortality is higher in patients with non-ASB compared with patients with ASB (combined HRs of 1.66 and 1.21, respectively).

Discussion

The main findings of our study are that in 2,002 STEMI patients, bleeding complications arising at the arterial puncture site, regardless of the bleeding definition applied, were not associated with an increased risk of mortality, recurrent MI, stent thrombosis, or stroke. By contrast, non-ASB was associated with a 3-fold higher risk of cardiac and all-cause mortality within 1 year after PPCI. A novel finding that provides further insight into the difference in prognostic value was that non-ASB was associated with higher rates of discontinuation of antiplatelet therapy and stent thrombosis. In a meta-analysis including 5 studies investigating the risk of 1-year mortality in patients with ASB and non-ASB, we found that both ASB and non-ASB were significantly associated with 1-year mortality. Non-ASB was associated with the strongest risk of 1-year mortality.

Difference in prognostic value. On univariate analysis, ASB and non-ASB were associated with a higher risk of 1-year mortality. After multivariable adjustment, ASB was no longer associated with a higher risk of mortality, whereas non-ASB was associated with a 3-fold higher risk of mortality. This suggests that the higher mortality in patients with ASB can be explained by factors associated with high mortality, such as cardiogenic shock, acute renal insufficiency, and multivessel disease. Our observation that non-ASB is associated with a worse prognosis than ASB is consistent with previous studies. In our meta-analysis, we found that non-ASB was associated with a greater risk of 1-year mortality than ASB.

Several factors may have contributed to the difference in prognostic value between ASB and non-ASB. First, ASB was less often associated with a discontinuation in antithrombotic therapy, which is known to increase the risk of stent thrombosis and recurrent MI (18). Indeed, we observed a greater risk of stent thrombosis within 1 year in patients with a non-ASB. Second, compared with ASB, non-ASB occurs in anatomically more remote areas of the body, resulting in a greater delay between the moment of onset of bleeding and diagnosis. Moreover, non-ASB is less easily accessible to interventions directed at gaining immediate control of the bleeding. Third, non-ASB may unveil previously concealed ominous comorbidities, which are by themselves correlates of a worse outcome, such as an unknown malignancy. Finally, we hypothesize that non-ASB, more than ASB, may be a marker of unmeasured confounders or frailty.

Prognostic value of non-ASB. In accordance with previous studies, the risk of 1-year mortality was greatest in patients with non-ASB. This is a significant finding given the fact that half of all bleeding events originated at a location other than the access site. A number of mechanisms may be responsible for the relationship between non-ASB and 1-year mortality. First, non-ASB was associated with a discontinuation of aspirin or clopidogrel in 13.5% of cases. Discontinuation of antiplatelet therapy is associated with a greater risk of stent thrombosis and recurrent MI (18). Second, bleeding may result in anemia and impaired oxygen delivery to vital end organs such as the brain, kidneys, and

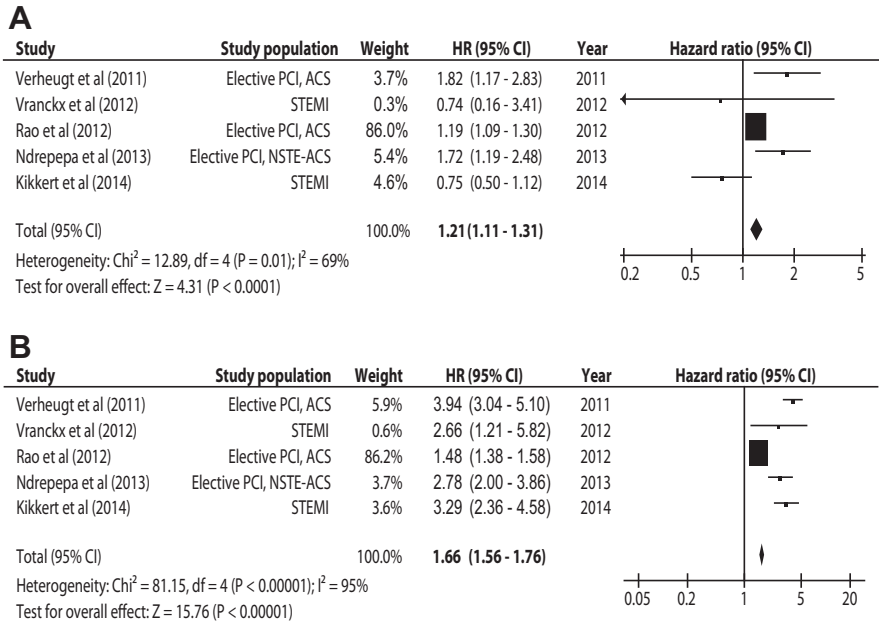

Figure 4. Meta-analysis of Hazard Ratios for Mortality Stratified by Bleeding Source

(A) The meta-analysis of adjusted hazard ratios (HRs) for 1-year mortality of access site–related bleeding. **(B)** The meta-analysis of adjusted hazard ratios for 1-year mortality of nonaccess site–related bleeding. ACS = acute coronary syndrome; CI = confidence interval; NSTE-ACS = non–ST-segment elevation–acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

myocardium. In patients with multivessel coronary artery disease and/or a poor systolic function, impaired oxygen delivery to the myocardium may deteriorate myocardial function and result in hemodynamic compromise and cardiac death. Third, erythropoietin synthesis in response to anemia may induce a prothrombotic state by causing platelet activation and increased production of plasminogen activator inhibitor 1 (19,20). Fourth, non-ASB required blood transfusions, which have been associated with mortality (21). Finally, non-ASB may merely be a marker of unmeasured comorbidities and frailty.

Study limitations. The patients included in the present analysis were selected from a series of consecutive STEMI patients on the basis of the availability of an aPTT measurement. We did not collect information on bleeding and ischemic outcomes in patients without aPTT measurements. This might have introduced selection bias. Although patients included in our analysis more often presented in cardiogenic shock and were more often treated with IABP, there was no difference in 1-year mortality between patients included and excluded in the analysis. Moreover, the primary analyses of this study are based on HRs, which is a proportional effect measure. Therefore, we believe it is unlikely that the selection of patients has influenced the estimates of the HRs provided in Table 2. The data presented in the present analysis pertain to selected STEMI patients undergoing PPCI at a single center. Therefore, our results might not be applicable to a general STEMI population. However, the baseline and procedural characteristics of patients included in the study were representative of a typical European STEMI cohort.

Conclusions

In a contemporary cohort of STEMI patients, ASB was not associated with an increased risk of mortality and recurrent ischemic events, whereas non-ASB was associated with an increased risk of mortality and stent thrombosis. These results taken together with the results of 4 previous studies in almost 500,000 patients indicate a greater hazard of subsequent mortality in patients with non-ASB. Our study supports the need to develop treatment strategies that diminish non-ASB.

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Key Words: major bleeding ■ percutaneous coronary intervention ■ primary percutaneous coronary intervention ■ ST-segment elevation myocardial infarction ■ vascular access site.

APPENDIX

For supplemental tables, please see the online version of this article.