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ORIGINAL RESEARCH

Clinical Impact of Intraprocedural Stent Thrombosis During Percutaneous Coronary Intervention in Patients Treated With Potent P2Y12 inhibitors - a VALIDATE-SWEDEHEART Substudy

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BACKGROUND: The clinical importance of intraprocedural stent thrombosis (IPST) during percutaneous coronary intervention in the contemporary era of potent oral P2Y12 inhibitors is not established. The aim of this study was to assess IPST and its association with clinical outcome in patients with myocardial infarction undergoing percutaneous coronary intervention with contemporary antithrombotic medications.

METHODS AND RESULTS: The VALIDATE-SWEDEHEART study (Bivalirudin Versus Heparin in ST-Segment and Non–ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry Trial) included 6006 patients with myocardial infarction, treated with potent P2Y12 inhibitors during percutaneous coronary intervention. IPST, defined as a new or worsening thrombus related to a stent deployed during the procedure, was reported by the interventional cardiologist in 55 patients (0.9%) and was significantly associated with ST-segment elevation myocardial infarction presentation, longer stents, bailout glycoprotein IIb/IIIa inhibitors, and final Thrombolysis in Myocardial Infarction flow <3. The primary composite end point included cardiovascular death, myocardial infarction, out-of-laboratory definite stent thrombosis and target vessel revascularization within 30 days. Secondary end points were major bleeding and the individual components of the primary composite end point. Patients with versus without IPST had significantly higher rates of the primary composite end point (20.0% versus 4.4%), including higher rates of cardiovascular death, target vessel revascularization, and definite stent thrombosis, but not myocardial infarction or major bleeding. By multivariable analysis, IPST was independently associated with the primary composite end point (hazard ratio, 3.82; 95% CI, 2.05–7.12; $P<0.001$).

CONCLUSIONS: IPST is a rare but dangerous complication during percutaneous coronary intervention, independently associated with poor prognosis, even in the current era of potent antiplatelet agents. Future treatment studies are needed to reduce the rate of IPST and to improve the poor outcome among these patients.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02311231.

Key Words: intraprocedural stent thrombosis ■ myocardial infarction ■ oral P2Y12 inhibitors ■ percutaneous coronary intervention ■ stent thrombosis

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CLINICAL PERSPECTIVE

What Is New?

- Intraprocedural stent thrombosis (IPST) was reported in 0.9% of patients with myocardial infarction undergoing percutaneous coronary intervention with potent P2Y12 inhibitors.
- IPST was significantly and independently associated with poor clinical outcome, despite routine use of potent antiplatelet agents and available bailout treatment strategies.

What Are the Clinical Implications?

- IPST should be recognized as a rare but severe complication during contemporary percutaneous coronary intervention.
- The poor prognosis following IPST emphasizes the importance of reporting IPST during percutaneous coronary intervention by routine and supports the inclusion of IPST in future definitions of stent thrombosis.
- As the majority of adverse events among patients with IPST occurred within the first few days following the procedure, prolonged hospital observation after percutaneous coronary intervention complicated by IPST may be considered.

Nonstandard Abbreviations and Acronyms

GPI	glycoprotein IIb/IIIa inhibitor
IPST	intraprocedural stent thrombosis
VALIDATE-SWEDEHEART	Bivalirudin Versus Heparin in ST-Segment and Non–ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry Trial

Stent thrombosis is an uncommon but severe complication after percutaneous coronary intervention (PCI).[1] By definition, the Academic Research Consortium criteria of stent thrombosis defines thrombotic events occurring after PCI, and their relative timing (acute, subacute, late, and very late).[2] However, intraprocedural events, occurring during the procedure, are not encompassed by this definition.

Intraprocedural stent thrombosis (IPST), defined as a new, reappearing, or increasing thrombus, either occlusive or nonocclusive, within or adjacent to a stent implanted during the procedure, was first reported as a relatively rare but potentially serious event during PCI with drug-eluting stents.[3,4] Large-scale studies thereafter reported rates of core laboratory-verified IPST varying from 0.3% to 1.2%, most commonly occurring in patients with myocardial infarction (MI), especially ST-segment–elevation myocardial infarction (STEMI). A strong association between IPST and adverse clinical outcome, including mortality and out-of-laboratory definite stent thrombosis, was moreover demonstrated.[5,6] These studies were performed before the introduction of potent oral P2Y12 inhibitors, known to reduce the occurrence of out-of-laboratory stent thrombosis compared with previous routine use of clopidogrel.[7,8] A reduced risk of IPST in patients treated with the rapid-onset parenteral P2Y12 inhibitor cangrelor during PCI, compared with clopidogrel, has furthermore been reported.[9]However, the clinical importance of IPST in the contemporary era of potent oral P2Y12 inhibitors is not known. The aim of this study was to assess the occurrence and prognosis of IPST in patients with MI treated with contemporary antiplatelet agents, undergoing mainly radial artery PCI, using data from the large-scale registry-based randomized VALIDATE-SWEDEHEART study (Bivalirudin Versus Heparin in ST-Segment and Non–ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry Trial).[10]

METHODS

The authors had full access to the data and the corresponding author takes responsibility for the analyses performed. Upon reasonable request, data that support the findings of this study can be made available after approval by the VALIDATE-SWEDEHEART steering committee.

Design and Study Population

The VALIDATE-SWEDEHEART study was a multicenter, registry-based, randomized, open-label

clinical trial performed at 25 PCI centers in Sweden between 2014 and 2016. In summary, the study randomized patients with MI (STEMI or non-STEMI) planned for urgent PCI to receive anticoagulation with bivalirudin or heparin during the procedure. Further specifics on patient enrollment, randomization, data collection, and follow-up has previously been described in detail, together with full inclusion and exclusion criteria.[10,11] The current substudy assessing the clinical importance of IPST was a retrospective post hoc analysis.

Antithrombotic Treatment

All patients received a potent P2Y12 inhibitor (ticagrelor, prasugrel, or cangrelor) before PCI, together with aspirin pretreatment in accordance with local protocols. Pretreatment with up to 5000 U of intravenous heparin was allowed in patients with STEMI. Intra-arterial administration of up to 3000 U of heparin was permitted for all patients, before angiography, if no prior heparin pretreatment had been given. Only bailout use of glycoprotein IIb/IIIa inhibitors (GPIs) was allowed. At discharge, dual antiplatelet therapy was recommended for 12 months after PCI.

Intraprocedural Thrombotic Events

The occurrence of IPST, defined as a new or worsening thrombus, either occlusive or nonocclusive, within or adjacent to a stent implanted during the procedure, was reported by the interventional cardiologist performing the procedure, as defined by the prespecified study protocol. Additionally, the initial thrombus burden grade in accordance with Sianos et al[12] and the Thrombolysis in Myocardial Infarction (TIMI) flow[13] before and after PCI were reported. An initial thrombus burden ≥4 was categorized as large thrombus burden and final TIMI flow <3 as impaired final TIMI flow.

Primary and Secondary End Points

The primary composite end point included cardiovascular death, MI, out-of-laboratory definite stent thrombosis and target vessel revascularization within 30 days. Secondary end points were the individual components of the primary composite end point and major bleeding within 30 days. The composite primary end point was additionally assessed after 180 days of follow-up. Cardiovascular death, MI according to the third universal definition, definite stent thrombosis according to Academic Research Consortium criteria, and major bleeding events (type 2, 3 or 5 according to the Bleeding Academic Research Consortium scale)[14] were adjudicated by a blinded central adjudication committee. Revascularization events were captured by the nationwide SWEDEHEART registry.

Statistical Analysis

Continuous variables are expressed as medians with interquartile range and categorical variables as counts and percentages. Differences in baseline and procedural characteristics in patients with versus without IPST were assessed with the Mann-Whitney *U* test, chi-square test, or Fisher exact test, as appropriate. Unadjusted event rates are visually presented in Kaplan-Meier plots; with the log-rank test for significance testing. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox regression models. The independent association between IPST and the primary composite end point was assessed in a multivariable Cox regression model, adjusted for age, sex, hypertension, diabetes, hyperlipidemia, current smoking, renal failure, prior MI, STEMI presentation, Killip class at admission, initial thrombus burden before PCI, initial TIMI flow before PCI, maximum stent length, maximum stent diameter, and randomization to bivalirudin versus heparin during PCI, based on prior knowledge of the association with clinical outcome. The proportional hazards assumption was assessed by Schoenfeld residuals. The association between IPST and clinical outcome within 30 days was analyzed in the following subgroups: age ≥65 versus <65, male versus female, diabetes versus no diabetes, hypertension versus no hypertension, Killip class ≥2 versus Killip class 1, initial large thrombus versus no large thrombus, final TIMI flow <3 versus final TIMI 3 flow after PCI, and STEMI versus non-STEMI. The associations between an initial large thrombus burden, final TIMI flow <3 and the primary end point were additionally assessed. Finally, a sensitivity analysis excluding patients treated with parenteral cangrelor during PCI was performed to evaluate the importance of IPST in patients strictly treated with potent oral P2Y12 inhibitors. Statistical analyses were performed in STATA (version 14.1, StataCorp, College Station, Texas) and a 2-sided *P*-value <0.05 was considered to indicate statistical significance.

Ethics

The VALIDATE SWEDEHEART (ClinicalTrials.gov number, NCT02311231) was approved by the Swedish Medical Products Agency and by the Lund University ethics committee. All patients provided oral and written consent. The current substudy was approved by the VALIDATE-SWEDEHEART steering group.

RESULTS

Baseline characteristics of the 6006 included patients are presented in Table 1. In summary, IPST was reported in 55 patients (0.9%) and there were no significant differences in baseline characteristics among

Table 1. Baseline and Procedural Characteristics in Patients With Versus Without Intraprocedural Stent Thrombosis

	NO IPST (N=5951)	IPST (N=55)	*P* value
Baseline characteristics			
Age, median (interquartile range)	68 (60–75)	69 (62–74)	0.646
Male sex, n (%)	4371 (73.5)	35 (63.6)	0.097
BMI	26.9 (24.5–29.7)	26.2 (24.2–29.0)	0.206
Current smoker, n (%)	1407 (23.6)	19 (34.6)	0.064
Diabetes, n (%)	994 (16.7)	5 (9.1)	0.129
Hypertension, n (%)	3075 (51.7)	30 (54.6)	0.705
Hyperlipidemia, n (%)	1871 (31.4)	18 (32.7)	0.800
Renal failure (eGFR <60), n (%)	920 (15.7)	7 (13.2)	0.622
Previous MI, n (%)	966 (16.2)	8 (14.6)	0.734
Previous PCI, n (%)	873 (14.7)	9 (16.4)	0.726
Previous CABG, n (%)	292 (4.9)	1 (1.8)	0.290
Previous stroke, n (%)	236 (4.0)	4 (7.3)	0.213
Preprocedural characteristics			
CPR before admission, n (%)	46 (0.77)	0 (0.00)	0.513
Killip class at admission ≥ 2, n (%)	188 (3.2)	6 (10.9)	0.001
STEMI presentation, n (%)	2963 (49.8)	42 (76.4)	<0.001
Non-STEMI presentation, n (%)	2988 (50.2)	13 (23.5)	<0.001
Symptom onset to PCI (minutes)*	190 (125–330)	182 (114–353)	0.848
First ECG to PCI (minutes)*	64 (48–88)	63 (51–79)	0.717
Heparin pretreatment,* n (%)	1903 (64.2)	23 (54.8)	0.211
Time from P2Y12 inhibitor to PCI,* n (%)			0.577
<1 h	1759 (59.6)	27 (65.90)	
1–2 h	1019 (34.5)	11 (26.80)	
>2 h	174 (5.9)	3 (7.30)	
Procedural characteristics, n (%)			
Radial access	5376 (90.5)	48 (87.3)	0.703
TIMI flow 0–1 before PCI	2698 (45.3)	36 (65.5)	0.003
Large thrombus before PCI	791 (13.3)	12 (21.8)	0.064
Randomization to bivalirudin	2973 (50.0)	31 (56.4)	0.344
Max ACT <median	2142 (47.2)	22 (50.0)	0.707
Additional heparin because of low ACT	687 (12.0)	14 (25.9)	0.002
Bailout glycoprotein IIb/IIIa inhibitor	126 (2.1)	30 (54.6)	<0.001
Treated vessels			
Left anterior descending	3047 (51.2)	29 (52.7)	0.822
Left circumflex	1743 (29.3)	12 (21.8)	0.225
Right coronary artery	2183 (36.7)	22 (40.0)	0.611
Number of treated vessel >1	1154 (19.5)	11 (20.0)	0.919
Thrombus aspiration	307 (5.2)	15 (27.3)	<0.001
Direct stent during procedure	1400 (23.6)	18 (32.7)	0.113
Maximum stent diameter <median	1648 (28.8)	12 (21.8)	0.254
Maximum stent length >median	2683 (47.8)	39 (72.2)	<0.001
Postdilatation balloon	2379 (40.1)	37 (67.3)	<0.001
TIMI flow <3 after PCI	563 (9.5)	18 (32.7)	<0.001
Antiplatelet medications at discharge,† n (%)			
Aspirin	5542 (96.5)	47 (95.2)	0.905
P2Y12 inihibitor			0.874

(*Continued*)

Table 1. Continued

	NO IPST (N=5951)	IPST (N=55)	*P* value
Ticagrelor	5106 (88.9)	43 (87.8)	
Prasugrel	57 (0.99)	0 (0)	
Clopidogrel	469 (8.2)	4 (8.2)	

ACT indicates activated clotting time; BMI, body mass index; CABG, coronary artery bypass grafting; CPR, cardiopulmonary resuscitation; eGFR, estimated glomerular filtration rate; IPST, intraprocedural stent thrombosis; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*Including 3005 patients with STEMI.

†Including 5794 patients with available records of discharge medications.

patients with versus without IPST. However, patients with IPST more often presented with STEMI, Killip class ≥2 and TIMI flow 0 to 1 before PCI, compared with patients without IPST. They also more often received bailout GPI, additional heparin because of a low activated clotting time, thrombus aspiration, stents >28 mm and postdilatation compared with patients without IPST. The P2Y12 inhibitor used during the procedure was ticagrelor in 94.9%, prasugrel in 2.1%, and cangrelor in 0.3%, and there was no significant difference in time from P2Y12 inhibitor administration to PCI among patients with STEMI with versus without IPST. Post-PCI final TIMI 3 flow was less often restored in patients with versus without IPST.

Clinical Outcome

Primary and secondary end points are presented in Figure 1 and Table 2. IPST was significantly associated with a higher risk of the primary composite end point of cardiovascular death, MI, definite stent thrombosis, and target vessel revascularization within 30 days (HR, 4.87; 95% CI, 2.66–8.90; *P*<0.001). The association remained significant after adjustments in the multivariable analysis (HR, 3.82; 95% CI, 2.05–7.12; *P*<0.001), independent of baseline characteristics, STEMI presentation, Killip class at admission, stent length, stent diameter, initial thrombus burden, and TIMI flow. IPST was also significantly associated with the individual components of the primary composite end point at 30 days, including cardiovascular death (HR, 5.66; 95% CI, 2.31–13.91; *P*<0.001), Academic Research Consortium criteria definite stent thrombosis (HR, 8.48; 95% CI, 2.01–35.73; *P*=0.004) and target vessel revascularization (HR, 4.74; 95% CI, 2.09–10.72, *P*<0.001), but not with MI, nor with major bleeding. Results remained in the multivariable models, although the limited number of definite stent thrombosis during follow-up did not allow for multivariable adjustments (Table 2). The multivariable analyses within 180 days did not meet the proportional hazards assumption of Cox regression, and were instead evaluated by multivariable logistic regressions, adjusted for the same prespecified variables, and with consistent results. The subgroup analyses demonstrated coherent results among all subgroups, with the exception of patients with non-STEMI, where no events were recorded among the 13 patients with non-STEMI and IPST (Figure 2). An initial large thrombus before PCI and final TIMI flow grade <3 after PCI were similarly associated with adverse clinical outcome (Figure 3). Comparing patients with IPST treated with bailout GPI versus patients with IPST not treated with GPI, there was no significant difference in clinical outcome (Figure S1). The sensitivity analysis excluding patients receiving parenteral cangrelor (n=21) did not alter results from the primary or secondary end point analyses (Table S1).

DISCUSSION

This study evaluated the clinical impact of IPST during PCI with modern antiplatelet agents. The primary findings were that IPST during contemporary PCI is rare but still significantly and independently associated with adverse clinical events, including a higher risk of cardiovascular death, target vessel revascularization, and out-of-laboratory definite stent thrombosis. The poor prognosis following IPST, despite routine use of potent antiplatelet agents and available bailout treatment strategies, substantiates the clinical importance of IPST. Thus, although rare, IPST should be recognized as an important and dangerous event during PCI, even in the contemporary era of potent antithrombotic medications.

Why IPST is associated with a higher risk of adverse outcome, despite the immediate detection and possibility of treatment, is not entirely known. The higher rate of STEMI presentation and Killip class ≥2 among patients with IPST are possible contributors to both the development of IPST and the poor outcome. Nevertheless, the association with clinical events was independent of both STEMI presentation and Killip class in the multivariable analysis. Impaired final TIMI flow after PCI was similarly more frequent in patients with IPST, which also may have mediated adverse outcome. That IPST was associated with adverse outcome also in the subgroup of patients who did receive final TIMI 3 flow after PCI, however, emphasizes the importance in recognizing and reporting intraprocedural

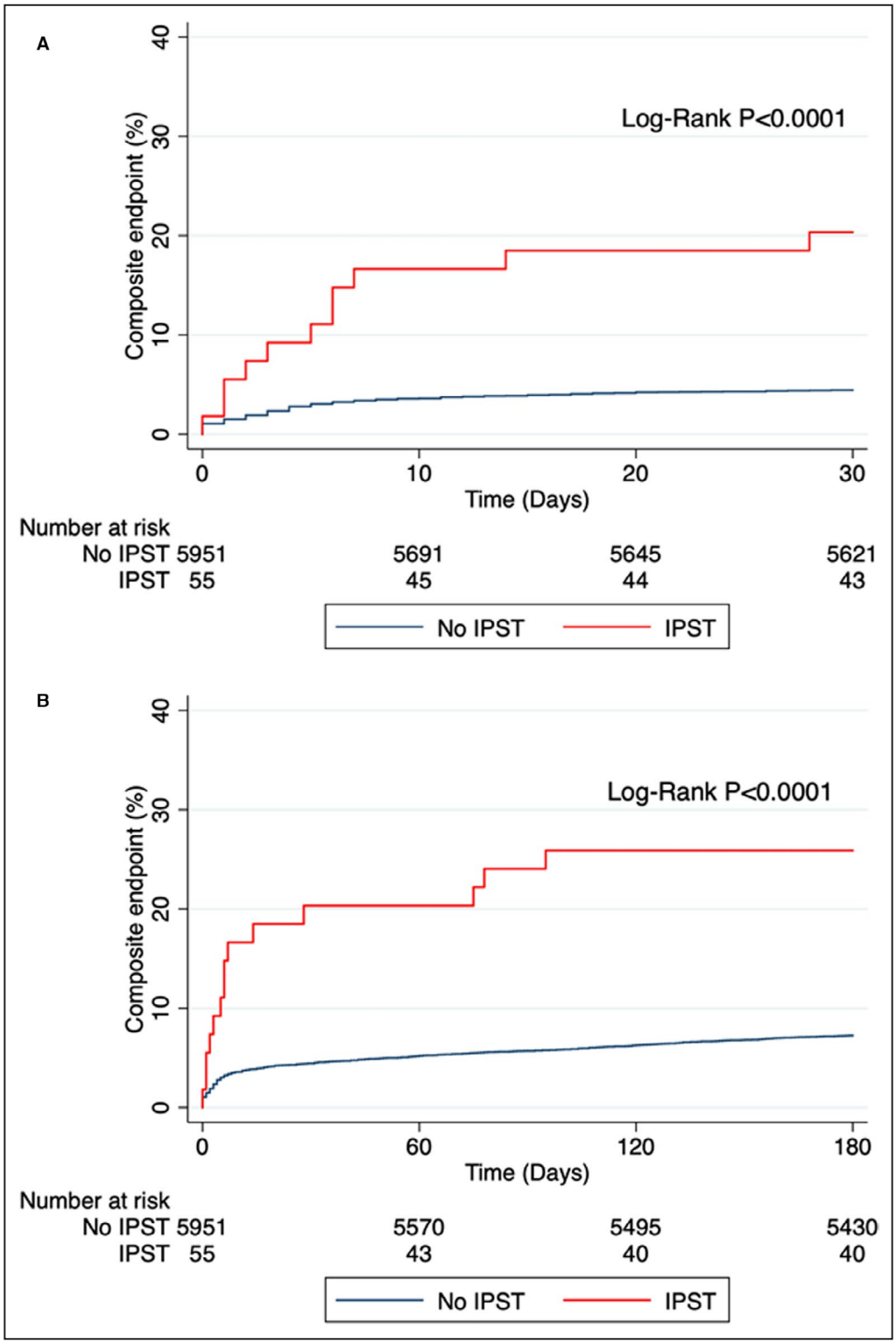

Figure 1. Clinical impact of intraprocedural stent thrombosis.
Kaplan-Meier failure functions for the composite primary end point (cardiovascular death, myocardial infarction, target vessel revascularization, and definite stent thrombosis) within 30 days (**A**) and 180 days (**B**) in patients with versus without IPST. IPST indicates intraprocedural stent thrombosis.

events, also in patients where adequate final TIMI flow is restored. The longer stents used in patients with IPST and the trend of greater thrombus burden at baseline observed in this study are in alignment with previously reported risk factors of both out-of-laboratory stent thrombosis and IPST,[9,15,16] although the association

Table 2. IPST and the Association With Clinical Outcome

30 days	No IPST, n (%)	IPST, n (%)	Unadjusted hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Composite end point	263 (4.42)	11 (20.0)	4.87 (2.66–8.90)	<0.001	3.82 (2.05–7.12)	<0.001
Cardiovascular death	98 (1.65)	5 (9.09)	5.66 (2.31–13.91)	<0.001	3.33 (1.32–8.41)	0.011
MI	56 (0.94)	0 (0)	NA	NA	NA	NA
Definite ST*	26 (0.44)	2 (3.64)	8.48 (2.01–35.73)	0.004	NA	NA
TVR	147 (2.47)	6 (10.91)	4.74 (2.09–10.72)	<0.001	4.86 (2.09–11.3)	<0.001
Major bleeding	318 (5.34)	3 (5.45)	1.04 (0.33–3.25)	0.944	1.1 (0.35–3.44)	0.875
180 days	**No IPST, n (%)**	**IPST, n (%)**	**Unadjusted hazard ratio (95% CI)**	***P* value**	**Adjusted odds ratio (95% CI) †**	***P* value**
Composite end point	428 (7.19)	14 (25.45)	4.01 (2.35–6.82)	<0.001	4.75 (2.43–9.26)	<0.001
Cardiovascular death	138 (2.32)	5 (9.09)	4.08 (1.67–9.96)	0.002	3.02 (1.05–8.63)	0.040
MI	129 (2.17)	2 (3.64)	1.78 (0.44–7.21)	0.417	1.82 (0.42–7.88)	0.422
Definite ST*	31 (0.5231)	3 (5.45)	10.79 (3.30–35.29)	<0.001	NA	NA
TVR	232 (3.9)	8 (14.55)	4.20 (2.08–8.50)	<0.001	4.76 (2.16–10.5)	<0.001
Major bleeding	513 (8.62)	3 (5.45)	0.66 (0.21–2.05)	0.471	0.65 (0.20–2.12)	0.477

The composite end point includes cardiovascular death, myocardial infarction, definite stent thrombosis, and target vessel revascularization. Multivariable models were adjusted for age, sex, hypertension, diabetes, hyperlipidemia, current smoking, renal failure, prior MI, STEMI presentation, Killip class at admission, initial thrombus burden before PCI, initial TIMI flow before PCI, maximum stent length, maximum stent diameter, and randomization to bivalirudin versus heparin during PCI. IPST indicates intraprocedural stent thrombosis; MI, myocardial infarction; NA, not applicable; ST, stent thrombosis; and TVR, target vessel revascularization.

*The multivariable model was not applied for definite stent thrombosis due to the small number of events.

†Adjusted odds ratio (95% CI) attributable to violation of proportional hazards assumption of Cox regression.

with longer total stent length also could represent the need for an additional stent following IPST. Similarly, the more frequent use of postdilatation balloons could represent both a higher risk of IPST after postdilatation or a more frequent use of postdilatation balloons to treat an acute IPST. The causality of these associations could, however, not be discriminated in this observational study. Finally, the acute event of IPST may have influenced operators to change treatment strategy to avoid the situation from deteriorating, subsequently affecting outcome after PCI.

Despite the use of potent P2Y12 inhibitors in this study, the rates of both IPST and its associated adverse outcome, were comparable to those reported in prior studies of patients treated with clopidogrel.[4,5] Insufficient platelet inhibition at the time of the procedure may partially explain these comparable rates, especially in patients with STEMI, where time to PCI is short and where full onset of platelet inhibition after oral administration may be further prolonged because of morphine administration.[17] Indeed, shorter time (<1 hour) from P2Y12 inhibitor administration to PCI was numerically more common among STEMI patients with versus without IPST. This finding furthermore indicates that IPST may be a valuable trial end point to analyze when evaluating antithrombotic medications during PCI, including the potential importance of antiplatelet pretreatment, a question under continuous debate.

While previous studies have demonstrated an independent association between IPST and poor prognosis, IPST is still not widely recognized or routinely reported during PCI. We speculate that this could be attributable to concerns about IPST being mainly a core laboratory diagnosis. Certainly, the operator-reported detection of IPST in this study possesses both strengths and limitations. Despite the lack of standardized core laboratory verification, it represents the clinical manifestation of IPST, as experienced and managed by the interventional cardiologist at the time of the procedure. The strong association with adverse outcome, despite routine use of potent antiplatelet agents and the possibility of prompt pharmacological and/or mechanical bailout treatment strategies, furthermore extends the clinical importance of IPST into contemporary clinical practices. Thus, our findings encourage previous suggestions to include IPST in future classifications of stent thrombosis,[5] allowing IPST to be routinely reported and preventive measures to be systematically evaluated. Interestingly, the rate of final TIMI 3 flow in patients with IPST was generally higher in our study (67%) compared with pooled data from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarctions) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) studies (40%–50%).[5] Whether this discrepancy represents a possible benefit with improved TIMI flow following IPST in patients treated with more potent

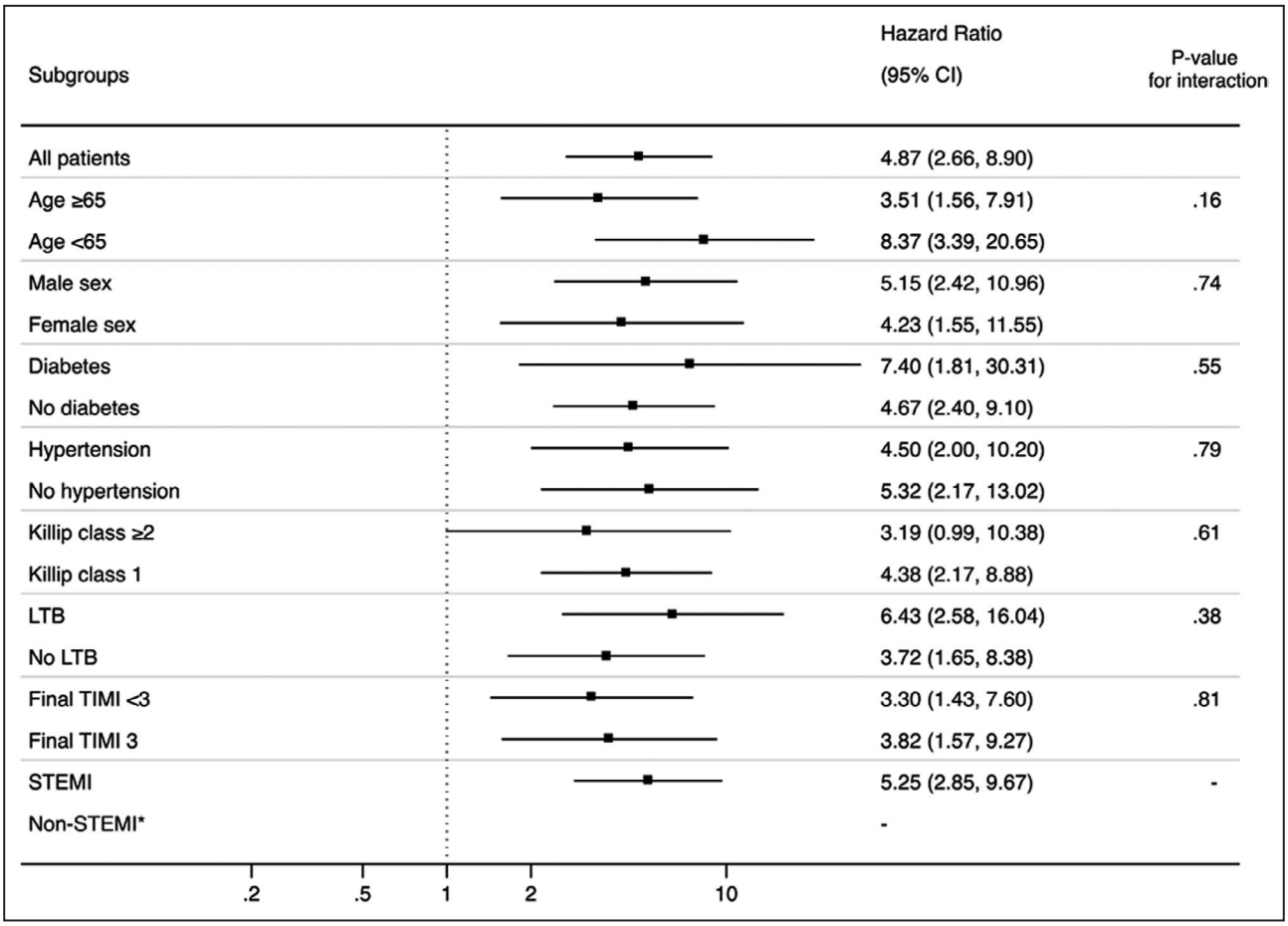

Figure 2. Clinical impact of intraprocedural stent thrombosis in different subgroups of patients.
The association between IPST and the composite primary end point (cardiovascular death, myocardial infarction, target vessel revascularization, and definite stent thrombosis) within 30 days was consistent among subgroups, with the exception of non-STEMI. Black lines with boxes represents hazard ratios with 95% CI. IPST indicates intraprocedural stent thrombosis; LTB, large thrombus burden; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction. *There were no adverse events among the group of patients with IPST and non-STEMI.

antiplatelet medications, or if this represent a potential mismatch in TIMI flow classifications by the interventional cardiologist performing the procedure versus independent core laboratory analysis is, however, not known. The similar rates of operator-reported versus core laboratory-reported final TIMI 3 flow in the complete study populations in VALIDATE-SWEDEHEART versus pooled data from the ACUITY and HORIZONS-AMI studies are, however, reassuring (90.3% versus 91.6%, respectively).

Further studies to assess different treatment strategies to treat or even prevent IPST are warranted to improve the poor outcome among these patients. In this study, there was no difference in the rate of IPST between patients randomized to bivalirudin versus heparin during the procedure. Heparin pretreatment before PCI was numerically more common in patients with STEMI that did not develop an IPST, in line with previous data demonstrating heparin pre-treatment in STEMI patients to be associated with lower thrombus burden and better TIMI flow prior to PCI, compared with patients not receiving heparin pretreatment.[18] As "additional heparin because of a low activated clotting time" was more often reported in patients with IPST, low activated clotting time -values during PCI could represent a risk marker of IPST. If closer monitoring and correction of activated clotting time -values can prevent IPST remains to be evaluated. Bailout GPI is another possible treatment strategy, frequently used in this study. Although without clinical benefit in this observational study, the value of rescue GPI in patients with IPST need proper evaluation in a prospective setting. Finally, this study demonstrated an association between initial large thrombus before PCI, IPST during PCI, and impaired TIMI flow after PCI, which all represent different angiographic aspects of thrombotic burden, assessed at different times during the procedure, and which all may be targeted to improve

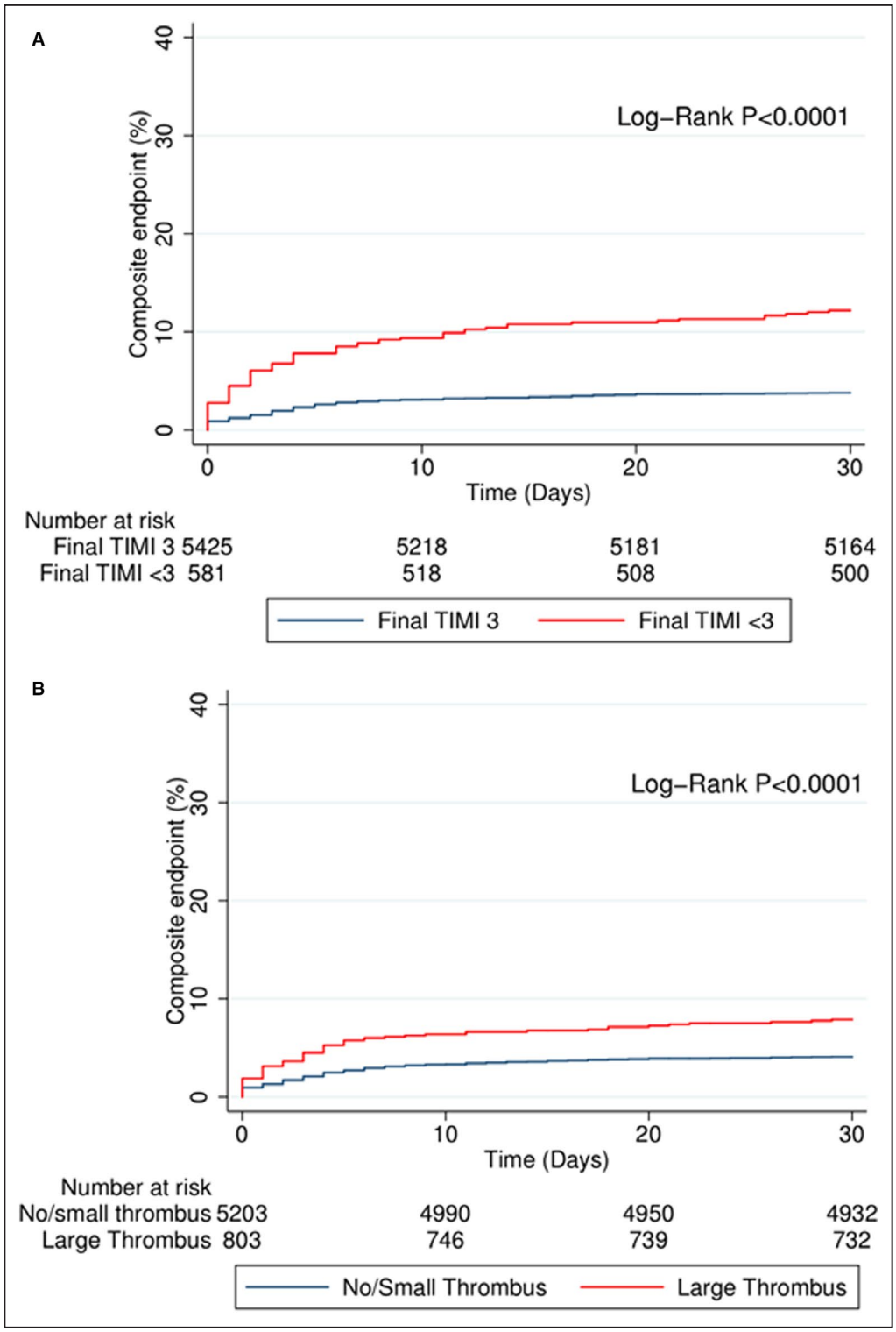

Figure 3. Clinical impact of final TIMI flow and large thrombus burden.
Kaplan-Meier failure functions for the composite primary end point (cardiovascular death, myocardial infarction, target vessel revascularization, and definite stent thrombosis) in patients with versus without final TIMI 3 flow (**A**) and in patients with versus without an initial large thrombus burden (**B**). TIMI indicates Thrombolysis in Myocardial Infarction.

the poor outcome observed in these patients.[19,20] Intriguingly, the vast majority of adverse events in patients with IPST occurred within the first few days after the procedure. Possibly, prolonged hospital observation following interventions complicated by IPST could be one strategy to minimize the poor outcome observed among these patients. Of note, there was no increase in bleeding rates among patients with IPST versus without IPST, despite the more frequent use of additive antithrombotic medications. Ultimately, the ideal treatment strategy during PCI, balancing the risk of thrombotic and bleeding complications, warrants further investigation.

Limitations

As in all observational studies, there is an inherent risk of residual and unmeasured confounders, despite adjustments in multivariable models. The limited number of IPST, despite a study including over 6000 patients, may also add some uncertainty to the statistical models. The lack of MIs reported during follow-up among patients with IPST is thus most likely attributable to play of chance in a rather small group of patients. Moreover, adjusted multivariable analyses to assess independent predictors of IPST was not feasible in only 55 patients. The occurrence of IPST was furthermore solely based on the reports from the interventional cardiologist performing the procedure, and the angiographic images were not available for retrospective review by an independent core laboratory.

CONCLUSIONS

IPST is a rare but severe complication during PCI, associated with poor prognosis, also in the current era of potent antiplatelet agents. Our findings emphasize the importance of reporting IPST during PCI by routine, regardless of final TIMI flow, and encourage further studies to investigate potential treatment strategies to treat or even prevent IPST.

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ARTICLE INFORMATION

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Supplementary Material

Table S1
Figure S1

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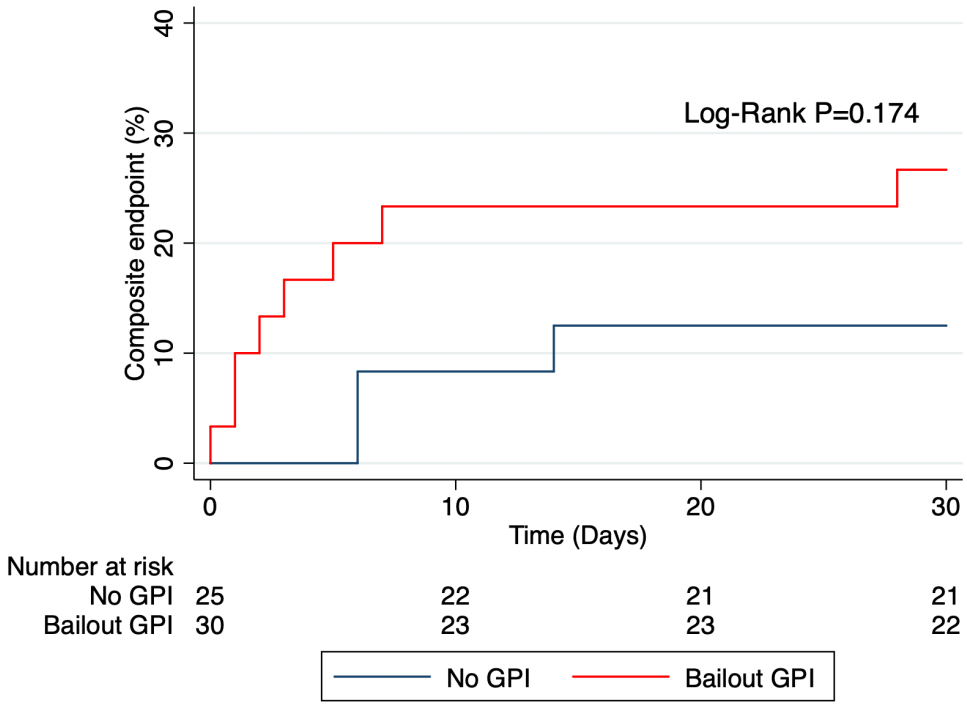
SUPPLEMENTAL MATERIAL

Table S1. Sensitivity analysis excluding n=21 patients treated with parenteral cangrelor during the procedure.

30 days	**No IPST %(n)**	**IPST %(n)**	**HR (95% CI)**	**P-value**
Composite endpoint	4.40% (261)	20.0% (11)	4.89 (2.67-8.94)	<0.001
Cardiovascular Death	1.64% (97)	9.09% (5)	5.70 (2.30-14.01)	<0.001
MI	0.94% (56)	0% (0)	-	-
Definite ST	0.44% (26)	3.64% (2)	8.46 (2.01-35.63)	0.004
TVR	2.46% (146)	10.91% (6)	4.76 (2.10-10.77)	<0.001
Major bleeding	5.35% (317)	5.45% (3)	1.04 (0.33-3.24)	0.947
180 days	**No IPST %(n)**	**IPST %(n)**	**HR (95% CI)**	**P-value**
Composite endpoint	7.17% (425)	25.45% (14)	4.02 (2.36-6.85)	<0.001
Cardiovascular Death	2.31% (137)	9.09% (5)	4.10 (1.68-10.00)	0.002
MI	2.18% (129)	3.64% (2)	1.78 (0.44-7.19)	0.419
Definite ST	0.52% (31)	5.45% (3)	10.76 (3.29-35.19)	<0.001
TVR	3.88% (230)	14.55% (8)	4.23 (2.08-8.55)	<0.001
Major bleeding	8.63% (512)	5.45% (3)	0.66 (0.21-2.04)	0.468

IPST – intra-procedural stent thrombosis, MI - myocardial infarction, Definite ST - definite stent thrombosis, TVR - target vessel revascularization

Figure S1. Kaplan Meier failure functions in 55 patients with IPST treated with vs without GPI.



There was no significant difference in the composite endpoint (cardiovascular death, myocardial infarction, stent thrombosis and target vessel revascularization) in patients with IPST who received bailout GPI compared with patients with IPST that did not receive GPI.

GPI = glycoprotein IIb/IIIa inhibitor, IPST = intra-procedural stent thrombosis