CLINICAL RESEARCH　　　　　　　　　　　　　　　　　　　**Interventional Cardiology**

Impact of Intraprocedural Stent Thrombosis During Percutaneous Coronary Intervention

Insights From the CHAMPION PHOENIX Trial
(Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention)

Philippe Généreux, MD,*†‡ Gregg W. Stone, MD,*† Robert A. Harrington, MD,§
C. Michael Gibson, MD,‖ Ph. Gabriel Steg, MD,¶ Sorin J. Brener, MD,†#
Dominick J. Angiolillo, MD, PHD,** Matthew J. Price, MD,†† Jayne Prats, PHD,‡‡
Laura LaSalle, MPH,† Tiepu Liu, MD, PHD,†† Meredith Todd, BSC,†† Simona Skerjanec, PHARMD,††
Christian W. Hamm, MD,§§ Kenneth W. Mahaffey, MD,§ Harvey D. White, DSC,‖‖
Deepak L. Bhatt, MD, MPH,¶¶ for the CHAMPION PHOENIX Investigators

*New York, New York; Montréal, Quebec, Canada; Stanford, California; Boston, Massachusetts; Paris, France;
London, United Kingdom; Jacksonville, Florida; La Jolla, California; Parsippany, New Jersey;
Bad Nauheim, Germany; and Auckland, New Zealand*

Objectives	This study sought to evaluate the clinical impact of intraprocedural stent thrombosis (IPST), a relatively new endpoint.
Background	In the prospective, double-blind, active-controlled CHAMPION PHOENIX (Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention) trial, cangrelor significantly reduced periprocedural and 30-day ischemic events in patients undergoing percutaneous coronary intervention (PCI), including IPST.
Methods	An independent core laboratory blinded to treatment assignment performed a frame-by-frame angiographic analysis in 10,939 patients for the development of IPST, defined as new or worsening thrombus related to stent deployment at any time during the procedure. Adverse events were adjudicated by an independent, blinded clinical events committee.
Results	IPST developed in 89 patients (0.8%), including 35 of 5,470 (0.6%) and 54 of 5,469 (1.0%) patients in the cangrelor and clopidogrel arms, respectively (odds ratio: 0.65; 95% confidence interval: 0.42 to 0.99; p = 0.04). Compared to patients without IPST, IPST was associated with a marked increase in composite ischemia (death, myocardial infarction [MI], ischemia-driven revascularization, or new-onset out-of-laboratory stent thrombosis [Academic Research Consortium]) at 48 h and at 30 days (29.2% vs. 4.5% and 31.5% vs. 5.7%, respectively; p < 0.0001 for both). After controlling for potential confounders, IPST remained a strong predictor of all adverse ischemic events at both time points.
Conclusions	In the large-scale CHAMPION PHOENIX trial, the occurrence of IPST was strongly predictive of subsequent adverse cardiovascular events. The potent intravenous adenosine diphosphate antagonist cangrelor substantially reduced IPST, contributing to its beneficial effects at 48 h and 30 days. (Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention [PCI] [CHAMPION PHOENIX]; NCT01156571)　(J Am Coll Cardiol 2014;63:619–29) © 2014 by the American College of Cardiology Foundation

From the *Columbia University Medical Center, New York, New York; †Cardiovascular Research Foundation, New York, New York; ‡Hôpital du Sacré-Coeur de Montréal, Université de Montréal, Montréal, Quebec, Canada; §Stanford University, Stanford, California; ‖Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ¶Institut National de la Santé et de la Recherche Médicale–Unité 698, Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, and Université Paris-Diderot, Sorbonne-Paris Cité, Paris, France, and Royal Brompton Hospital, London, United Kingdom; #New York Methodist Hospital, Brooklyn, New York; **University of Florida College of Medicine-Jacksonville, Jacksonville, Florida; ††Scripps Clinic and Scripps Translational Science Institute, La Jolla, California; ‡‡The Medicines Company, Parsippany, New Jersey; §§University of Giessen and Kerckhoff Heart Center, Bad Nauheim, Germany; ‖‖Auckland City Hospital, Auckland, New Zealand; and the ¶¶Brigham and Women's Hospital, and Harvard Medical School,

The prospective, double-blind, active-controlled CHAMPION PHOENIX (Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention) has demonstrated the superiority of cangrelor, a novel, intravenous, rapidly acting, and potent $P2Y_{12}$ platelet receptor inhibitor, compared with clopidogrel in patients undergoing percutaneous coronary intervention (PCI) for various clinical indications (1). Cangrelor was shown at 48 h after PCI to significantly reduce the rate of ischemic events, a composite endpoint that included stent thrombosis (ST). ST was defined in CHAMPION PHOENIX as the occurrence of events occurring after the PCI procedure, as classified by the Academic Research Consortium (ARC) definition (2), as well as intraprocedural ST (IPST), the development of new or increasing thrombus in or adjacent to an implanted stent during the PCI procedure. Although previous reports have linked IPST to future ischemic events (3–5), its recognition and inclusion as a stand-alone angiographic endpoint in randomized trials is not yet universally accepted, and not all prior studies employed an independent blinded angiographic core laboratory to assess IPST events. We therefore sought to determine the incidence, predictors, and clinical impact of IPST from the CHAMPION PHOENIX trial, which incorporated the largest independent angiographic core laboratory analysis to date.

Methods

Study population. The CHAMPION PHOENIX trial rationale and results have been described in detail (1,6). In brief, 11,145 patients presenting with either stable angina, non–ST-segment elevation acute coronary syndromes (NSTE-ACS), or ST-segment elevation myocardial infarction (STEMI) were randomized 1:1 in a double dummy, double-blind design, after angiography, to intravenous cangrelor or oral clopidogrel administered at the time of PCI. Cangrelor (or matching placebo) was administered as a bolus of 30 μg/kg followed by an infusion of 4 μg/kg/min for at least 2 h or the duration of the procedure, whichever was longer. A clopidogrel loading dose (300 to 600 mg, at the discretion of the operator) or matching placebo and aspirin (75 to 325 mg) were administered to all patients. The protocol required clopidogrel (75 mg) to be administered during the first 48 hours; thereafter, clopidogrel or another $P2Y_{12}$ inhibitor could be administered at the discretion of the investigator. The choice of access

site, procedural anticoagulant (bivalirudin, unfractionated heparin, low-molecular-weight heparin, or fondaparinux) and sheath management were per-site routine. Glycoprotein IIb/IIIa inhibitors were allowed only as rescue therapy during PCI to treat thrombotic complications.

Study endpoints. The primary efficacy endpoint was the composite rate of all-cause mortality, MI, ischemia-driven revascularization (IDR), or ST in the 48 h after randomization. The key secondary endpoint was the incidence of ST at 48 hours. ST was defined as the occurrence of IPST or ARC ST (further classified as definite, probable, or possible ST) (2). IPST was defined as any angiographically new or worsening thrombus related to stent implantation occurring

during the PCI procedure, as assessed in frame-by-frame analysis by a blinded independent core laboratory (Cardiovascular Research Foundation, New York, New York) (5). Thrombus was defined as any discrete, mobile, intraluminal filling defect, with defined borders, with or without associated contrast staining or a total occlusion with convex edges and staining. Thrombus was described as: 1) occlusive (TIMI [Thrombolysis In Myocardial Infarction] flow grade 0, occupying the entire lumen); 2) globular (definite border on 3 edges); 3) filling defect (definite borders on 2 edges); or 4) hazy (irregular contour, smooth convex meniscus or haziness at the site of the lesion). Thrombus area was traced to better characterize the thrombotic burden. In cases of

Table 1	Baseline Clinical Characteristics According to the Occurrence of IPST		
Characteristic	**IPST (n = 89)**	**No IPST (n = 10,850)**	**p Value**
Age (yrs)	63.0 (55–74)	64.0 (56–72)	0.76
Female	31/89 (34.8)	3,019/10,850 (27.8)	0.14
Body mass index (kg/m^2)	28.1 (25.4–31.6)	28.4 (25.6–31.8)	0.43
Medical history			
Diabetes mellitus	26/89 (29.2)	3,028/10,835 (27.9)	0.79
Current smoker	33/86 (38.4)	3,020/10,589 (28.5)	0.04
Hypertension	69/89 (77.5)	8,635/10,821 (79.8)	0.60
Hyperlipidemia	54/78 (69.2)	6,647/9606 (69.2)	0.99
Prior stroke/TIA	4/89 (4.5)	511/10,815 (4.7)	0.92
Prior MI	19/85 (22.4)	2,248/10,784 (20.8)	0.73
Prior PTCA/PCI	15/88 (17.0)	2,586/10,832 (23.9)	0.13
Prior CABG	9/88 (10.2)	1,069/10,839 (9.9)	0.91
History of CHF	8/88 (9.1)	1,128/10,825 (10.4)	0.68
History of peripheral artery disease	11/89 (12.4)	821/10,734 (7.6)	0.10
Region			0.04
United States	24/89 (27.0)	4,073/10,850 (37.5)	
Non-U.S.	65/89 (73.0)	6,777/10,850 (62.5)	
Patient presentation			0.0006
NSTE-ACS	33/89 (37.1)	2,777/10,850 (25.6)	
Stable angina	32/89 (36.0)	6,106/10,850 (56.3)	
STEMI	24/89 (27.0)	1,967/10,850 (18.1)	
Baseline cardiac biomarkers			<0.0001
Normal	38/89 (42.7)	6,912/10,841 (63.8)	
Abnormal	51/89 (57.3)	3,929/10,841 (36.2)	
Periprocedural medications			
Aspirin	87/89 (97.8)	10,022/10,842 (94.3)	0.16
Unfractionated heparin	67/89 (75.3)	7,459/10,849 (68.8)	0.19
Clopidogrel loading dose 600 mg	58/89 (65.2)	8,075/10,850 (74.4)	0.047
Clopidogrel loading dose 300 mg	31/89 (34.8)	2,775/10,850 (25.6)	0.047
Glycoprotein IIb/IIIa inhibitor	31/89 (34.8)	349/10,850 (3.2)	<0.0001
Bivalirudin	18/89 (20.2)	2,463/10,848 (22.7)	0.58
Low molecular weight heparin	4/89 (4.5)	509/10,848 (4.7)	0.93
Fondaparinux	0/89 (0)	31/10,849 (0.3)	0.61
Catheter access site			0.29
Femoral	72/89 (80.9)	7,992/10,850 (73.7)	
Radial	17/89 (19.1)	2,835/10,850 (26.1)	
Brachial	0/89 (0)	23/10,850 (0.2)	
Length of stay (randomization to discharge, h)	45.6 (26.2–136.2)	27.0 (23.0–51.1)	<0.0001

Values are median (interquartile range) or n/N (%).

CABG = coronary artery bypass grafting; IPST = intra-procedural stent thrombosis; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; STEMI = ST-segment elevation myocardial infarction.

complete occlusion, the thrombus area was measured after wire introduction (when possible) and before any device therapy (thromboaspiration, balloon, or stent). Interobserver level of agreement for thrombus detection at baseline and during PCI was 0.95 and 0.8 (kappa statistic), respectively, indicative of an almost perfect level of agreement (7). The primary safety endpoint was severe bleeding not related to coronary artery bypass grafting according to the GUSTO (Global Use of Strategies to Open Occluded Coronary

Arteries) criteria at 48 h. Detailed definitions of the primary and major secondary endpoints have been previously reported (1). The primary efficacy endpoints occurring during the first 30 days after randomization were adjudicated by an independent clinical events committee (Duke Clinical Research Institute, Durham, North Carolina).

Statistical analysis. All of the analyses were performed with data from the modified intention-to-treated (mITT) population, as previously described (1). Continuous variables

Table 2	Baseline Angiographic and Procedural Characteristics According to the Occurrence of IPST		
	IPST (n = 89)	No IPST (n = 10,850)	p Value
Number of vessels with stenosis >50%			
0	0/89 (0.0)	3/10,832 (0.0)	0.39
1	38/89 (42.7)	5,255/10,832 (48.5)	
2	25/89 (28.1)	3,245/10,832 (30.0)	
3	17/89 (19.1)	1,691/10,832 (15.6)	
>3	9/89 (10.1)	638/10,832 (5.9)	
Number of vessels per patient undergoing PCI during the Index procedure			
0	0/89 (0.0)	98/10,850 (0.9)	0.009
1	70/89 (78.7)	9,076/10,850 (83.6)	
2	14/89 (15.7)	1,477/10,850 (13.6)	
3	4/89 (4.5)	188/10,850 (1.7)	
>3	1/89 (1.1)	11/10,850 (0.1)	
Vessels treated			
Right coronary artery	29/89 (32.6)	3,884/10,850 (35.8)	0.53
Left anterior descending artery	51/89 (57.3)	5,368/10,850 (49.5)	0.14
Left circumflex artery	28/89 (31.5)	3,117/10,850 (28.7)	0.57
Left main	6/89 (6.7)	269/10,850 (2.5)	0.011
Drug-eluting stent(s) implanted	47/89 (52.8)	6,033/10,850 (55.6)	0.60
Bare metal stent(s) implanted	50/89 (56.2)	4,601/10,850 (42.4)	0.009
Total stent length implanted (mm)	37.0 (23.0–59.0)	23.0 (16.0–36.0)	<0.0001
Time from study drug administration to start of PCI (min)	4 (2–8)	4 (2–8)	0.99
Duration of PCI (min)	37.0 (21–60)	17.0 (10–30)	<0.0001
Patients with IVUS-guided PCI	6/89 (6.7)	605/10,850 (5.6)	0.63
Pre-TIMI flow grade			0.005
0	18/89 (20.2)	1,694/10,727 (15.8)	
1	8/89 (9.0)	386/10,727 (3.6)	
2	13/89 (14.6)	1,041/10,727 (9.7)	
3	50/89 (56.2)	7,606/10,727 (70.9)	
Post-TIMI flow grade			<0.0001
0	6/88 (6.8)	87/10,542 (0.8)	
1	7/88 (8.0)	92/10,542 (0.9)	
2	6/88 (6.8)	356/10,542 (3.4)	
3	69/88 (78.4)	10,007/10,542 (94.9)	
Lesion length	15.9 (11.4–24.3)	13.1 (9.4–19.3)	0.0007
Thrombus at baseline	38/89 (42.7)	2,562/10,740 (23.9)	<0.0001
Thrombus area (mm^2)	17.7 (10.5–28.6)	13.2 (8.1–21.4)	0.28
Tortuosity Moderate or Severe	6/89 (6.7)	319/10,718 (3.0)	0.04
Calcification			0.99
None/mild	66/89 (74.2)	7,948/10,657 (74.6)	
Moderate	18/89 (20.2)	2,133/10,657 (20.0)	
Severe	5/89 (5.6)	576/10,657 (5.4)	

Values are n/N (%) or median (interquartile range).

IPST = intra-procedural stent thrombosis; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Table 3	Independent Predictors of IPST	
Variable	**Adjusted Odds Ratio (95% CI)**	**p Value**
STEMI (vs. SA)	1.87 (1.04–3.36)	0.04
NSTE-ACS (vs. SA)	2.07 (1.26–3.40)	0.004
Thrombus at baseline	1.79 (1.12–2.84)	0.01
Total stent length (per 1-mm increase)	1.03 (1.02–1.03)	<0.0001
Cangrelor at randomization (vs. clopidogrel)	0.65 (0.42–1.00)	0.048

*Candidate variables included in the model: current smoker, diagnosis at presentation (stable angina vs. NSTE-ACS vs. STEMI), number of PCI vessels, DES versus BMS used, total stent length, TIMI flow at baseline (3 vs. 0-1-2), presence of thrombus at baseline, U.S. versus non-U.S. site, cangrelor infusion.

BMS = bare-metal stent(s); DES = drug-eluting stent(s); SA = stable angina; other abbreviations as in Tables 1 and 2.

are summarized as medians and quartiles or as mean ± SD, as appropriate, and were compared using the Student *t* test or Mann-Whitney rank sum test accordingly. Categorical variables are presented as rate (%) and were compared by the chi-square or Fisher exact test. Time-to-event curves were constructed using Kaplan-Meier methodology and compared with the log-rank test. Logistic regression was performed to identify independent predictors of IPST. The multivariable model was built by selecting variables of clinical interest and/or satisfying the entry criterion of $\alpha < 0.05$ in the univariate analysis. The number of variables included in the model was chosen to avoid overfitting. The final model was derived with a stepwise regression procedure with entry/stay α criteria of 0.10. To assess the association between the occurrence of IPST and subsequent all-cause death, MI, ARC ST, ARC definite ST, and IDR, logistic regression was used to derive a propensity score for IPST, which was then included in a logistic regression model

(along with IPST) for 48-h and 30-day outcomes. Interaction between the occurrence of IPST and different subgroups on major adverse events was tested using the Breslow-Day method. No adjustment was made for multiple comparisons. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Patients and baseline characteristics. Detailed angiographic core laboratory analysis was completed in 10,939 of 10,942 randomized patients (99.9%) in the mITT cohort. Among those, IPST occurred in 89 patients (0.8%), including 35 of 5,470 (0.6%) and 54 of 5,469 (1.0%) patients in the cangrelor and clopidogrel arms, respectively (odds ratio [OR]: 0.65; 95% confidence interval [CI: 0.42 to 0.99; p = 0.04). IPST occurred in 32 of 6,138 patients (0.5%) presenting with stable angina, 33 of 2,810 patients (1.2%) presenting with NSTE-ACS, and 24 of 1,991 patients (1.2%) presenting with STEMI (p = 0.0006). Among IPST patients, 48 of 89 (53.9%) had new evidence of thrombus, and 41 of 89 (46.1%) had worsening or growing thrombus.

Baseline clinical, angiographic, and procedural characteristics of patients with and without IPST are shown in Tables 1 and 2. Patients with versus without IPST were more frequently current smokers, treated outside of the United States, presented with NSTE-ACS or STEMI rather than stable angina, had elevated baseline cardiac biomarkers (troponin and/or creatine kinase-MB), and received a loading dose of 300 mg rather 600 mg of clopidogrel. Patients with IPST more frequently had baseline and final TIMI flow grade <3, had thrombotic lesions, underwent multivessel PCI, were treated with bare-metal stents

Table 4	Relationship Between IPST and Subsequent 48-Hour and 30-Day Adverse Ischemic Events					
Time Point/ Endpoint	**IPST (n = 89)**	**No IPST (n = 10,850)**	**Unadjusted**		**Adjusted**	
			OR (95% CI)	**p Value**	**AOR (95% CI)**	**p Value**
48 h						
Death/MI/IDR/ARC-ST	26 (29.2)	490 (4.5)	8.73 (5.48–13.90)	<0.0001	11.85 (7.08–19.84)	<0.0001
Death	5 (5.6)	31 (0.3)	20.77 (7.89–54.73)	<0.0001	20.82 (7.34–59.02)	<0.0001
ARC definite ST	3 (3.4)	31 (0.3)	12.17 (3.65–40.58)	<0.0001	12.15 (3.46–42.68)	<0.0001
IDR	4 (4.5)	62 (0.6)	8.19 (2.91–23.01)	<0.0001	10.32 (3.50–30.37)	<0.0001
MI	23 (25.8)	439 (4.0)	8.26 (5.09–13.41)	<0.0001	12.00 (6.97–20.64)	<0.0001
30 days*						
Death/MI/IDR/ARC-ST	28 (31.5)	617 (5.7)	7.60 (4.82–11.97)	<0.0001	9.65 (5.86–15.89)	<0.0001
Death	9 (10.1)	106 (1.0)	11.38 (5.57–23.27)	<0.0001	12.25 (5.76–26.05)	<0.0001
ARC ST	5 (5.6)	86 (0.8)	7.44 (2.95–18.79)	<0.0001	7.56 (2.91–19.65)	<0.0001
ARC definite ST	4 (4.5)	61 (0.6)	8.31 (2.95–23.36)	<0.0001	8.17 (2.81–23.77)	<0.0001
IDR	5 (5.6)	117 (1.1)	5.45 (2.17–13.68)	<0.0001	6.36 (2.46–16.40)	<0.0001
MI	24 (27.0)	473 (4.4)	8.08 (5.02–13.03)	<0.0001	11.34 (6.66–19.30)	<0.0001

Values are n (%). *30-day efficacy data were unavailable in 20 patients in the no-IPST group (n = 10,830). Propensity score based upon age, sex, smoking status, U.S. versus non-US region, race, weight, biomarker, previous MI (stable angina vs. NSTE-ACS vs. STEMI), previous PCI, previous CABG, peripheral artery disease, patient presentation, worst pre-procedure TIMI score, stent type, bifurcation treatment, aspirin dose, number of treated vessels, clopidogrel loading received, clopidogrel loading dose (300 vs. 600 mg), cangrelor infusion duration, bivalirudin received. Missing data were excluded from the modeling.

AOR = adjusted odds ratio; ARC = Academic Research Consortium; IDR = ischemia-driven revascularization; OR = odd ratio; ST = stent thrombosis; other abbreviations as in Tables 1 and 2.
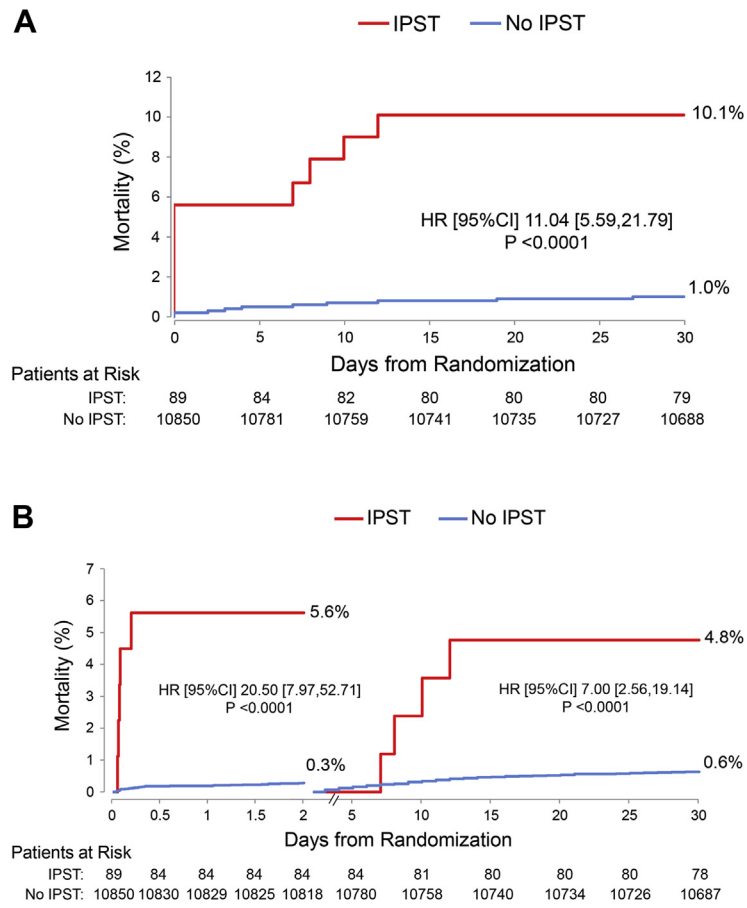
Figure 1 **Time-to-Event Through 30 Days in Patients With and Without IPST**

(A) 30-Day mortality. **(B)** 30-Day mortality with 48-h landmark analysis. **(C)** 30-Day Academic Research Consortium (ARC) (definite or probable) stent thrombosis.
(D) 30-day ARC stent thrombosis with 48-h landmark analysis. HR = hazard ratio; IPST = intraprocedural stent thrombosis. *Continued on the next page*

rather than drug-eluting stents and longer stents, and had a lengthier PCI procedure. Of note, 78.4% of IPST patients had TIMI flow grade 3 after the procedure, suggesting resolution of the thrombotic event in most patients. IPST was also associated with a doubling of the duration of hospitalization (Table 1).

As shown in Table 3, by multivariate analysis, NSTE-ACS and STEMI at presentation, angiographic thrombus prior to PCI, and total stent length were independent predictors of IPST. The use of cangrelor at randomization (compared to clopidogrel) was independently associated with freedom from IPST during PCI.

Clinical outcomes. IPST was associated with a marked increase in mortality, MI, IDR, and ARC ST at 48 h and at 30 days (Table 4, Fig. 1). After controlling for potential confounders, IPST remained a strong predictor of all adverse ischemic events, including mortality and ARC ST (definite and definite or probable) outside the catheterization laboratory, at both time periods. The independent association between IPST and these adverse ischemic events

remained independent, even among patients in whom IPST treatment restored final angiographic TIMI flow grade 3 (Table 5). The impact of IPST on 30-day mortality was consistent among specified subgroups (Fig. 2). The association between the occurrence of IPST and ARC definite ST (at 48 h and 30 days) and subsequent mortality is shown in Figure 3. Among patients experiencing definite ST by 48 h and 30 days, 3 of 34 (8.8%) and 4 of 65 (6.2%) patients, respectively, had an earlier IPST. Similarly, 84 of 89 patients with IPST did not experience ARC ST at 30 days, and 86 of 91 ARC ST did not have IPST, indicating little overlap between both outcomes. IPST was also associated with an increase in bleeding events (moderate and mild GUSTO bleeding, minor TIMI bleeding, Bleeding Academic Research Consortium [BARC] 3a, and ACUITY [Acute Catheterization and Urgent Intervention Triage Strategy] major bleeding [excluding hematoma ≥5 cm]) at 48 h (Table 6).

Use of cangrelor resulted in a significant reduction in the rate of IPST compared with clopidogrel in the entire study

Figure 1   Continued
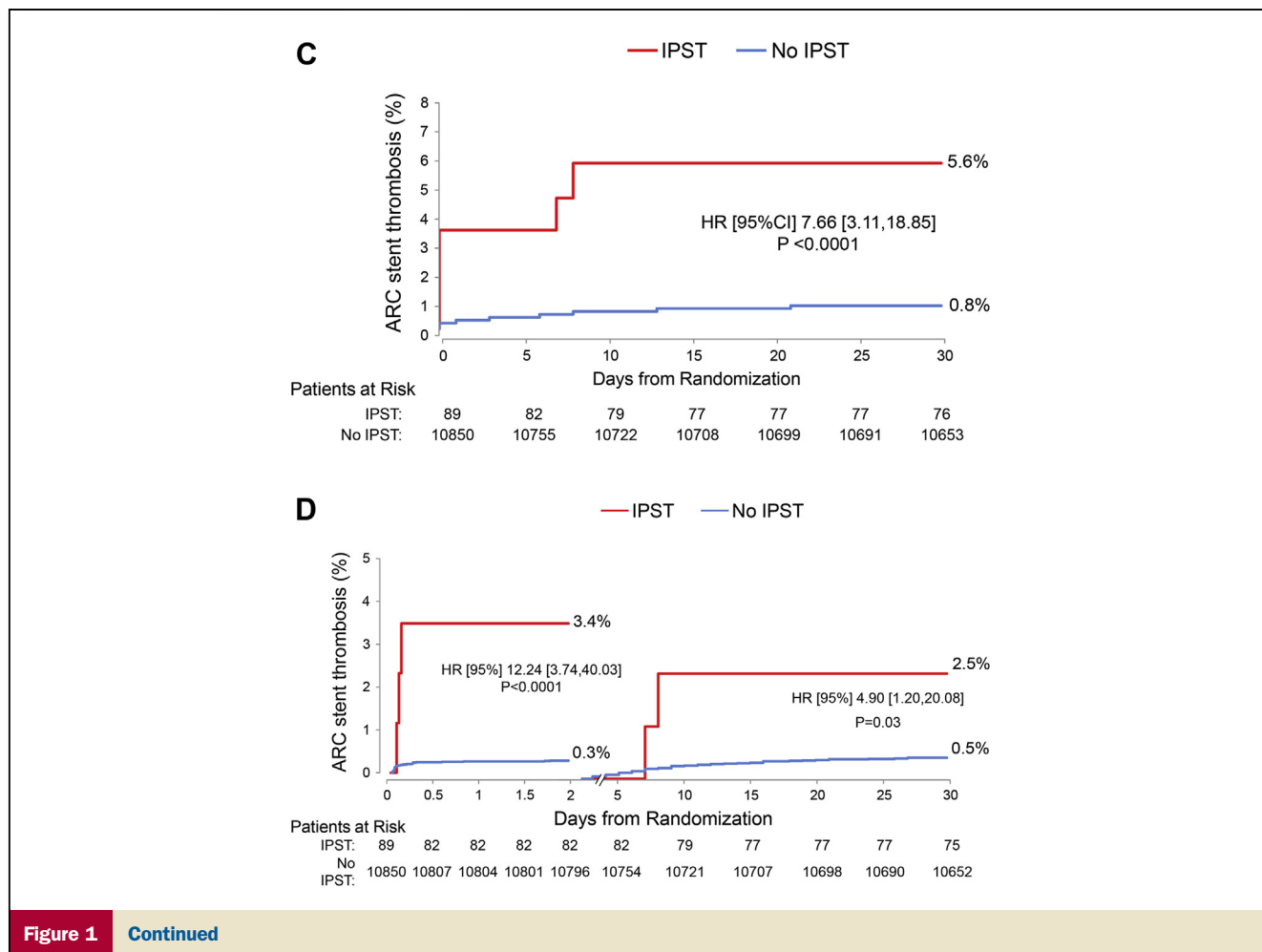
population and separately in the patient cohorts presenting with stable angina, NSTE-ACS, and STEMI (Fig. 4).

Discussion

The current analysis from 10,939 patients enrolled in the multinational, prospective, double-blind randomized CHAMPION PHOENIX trial is the largest study to specifically evaluate the incidence, predictors, and impact of IPST on the early prognosis of patients undergoing elective, urgent, and emergent PCI. The main results of the present study are as follows: 1) IPST occurred in approximately 1% of patients undergoing PCI; 2) NSTE-ACS or STEMI at presentation, the presence of angiographic thrombus, and the total stent length implanted were independently associated with the occurrence of IPST, and cangrelor use independently associated with freedom of IPST; 3) IPST was associated with a significant increase in mortality, MI, IDR, and ARC definite or probable ST at 48 h and at 30 days; and 4) treatment with cangrelor compared to clopidogrel at the time of the PCI procedure significantly decreased the occurrence of IPST and adverse events through 30 days.

IPST was an infrequent event during PCI, occurring in 0.8% of PCI patients in the CHAMPION PHOENIX trial. Similar results have been reported by previous groups, with an incidence varying from 0.5% to 0.7% (3–5). From a pooled analysis of the ACUITY (8) and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials (9), IPST occurred in 47 (0.7%) of the 6,591 analyzed patients, with a higher incidence in STEMI compared to NSTE-ACS (1.2% vs. 0.3%, respectively) (5). The rate of IPST in CHAMPION PHOENIX was similar to that in HORIZONS-AMI (1.2%), although IPST occurred more frequently in NSTE-ACS patients in the present study than in ACUITY (1.2% vs. 0.3%, respectively) (5). As the angiographic core laboratory and methodology to assess IPST were the same in both studies, this difference is likely explained by underlying differences in the patient populations and adjunct pharmacology between the 2 studies. In the present study, IPST was notably less common in patients with stable coronary artery disease (incidence 0.5%), consistent with the lower rate of out-of-laboratory ST in these patients compared to NSTE-ACS and STEMI.

Table 5	Relationship Between IPST and Subsequent 48-H and 30-Day Adverse Ischemic Events in Patients With Post–PCI TIMI Flow Grade 3					
Time Point/ Endpoint	**IPST (n = 69)**	**No IPST (n = 10,007)**	**Unadjusted**		**Adjusted**	
			OR (95% CI)	**p Value**	**AOR (95% CI)**	**p Value**
48 h						
Death/MI/IDR/ARC-ST	18 (26.1)	429 (4.3)	7.88 (4.56–13.60)	<0.0001	10.24 (5.64–18.60)	<0.0001
Death	2 (2.9)	20 (0.2)	14.91 (3.42–65.04)	<0.0001	15.95 (3.38–75.35)	0.0005
ARC Definite ST	3 (4.3)	23 (0.2)	19.73 (5.78–67.32)	<0.0001	20.58 (5.64–75.08)	<0.0001
IDR	4 (5.8)	43 (0.4)	14.26 (4.97–40.88)	<0.0001	15.50 (5.15–46.62)	<0.0001
MI	16 (23.2)	397 (4.0)	7.31 (4.14–12.90)	<0.0001	9.74 (5.21–18.19)	<0.0001
30 days*						
Death/MI/IDR/ARC-ST	20 (29.0)	535 (5.4)	7.21 (4.26–12.22)	<0.0001	8.85 (5.00–15.65)	<0.0001
Death	4 (5.8)	79 (0.8)	7.72 (2.75–21.70)	<0.0001	8.55 (2.94–24.84)	<0.0001
ARC ST	5 (7.2)	67 (0.7)	11.57 (4.51–29.66)	<0.0001	12.28 (4.64–32.55)	<0.0001
ARC Definite ST	4 (5.8)	48 (0.5)	12.74 (4.47–36.37)	<0.0001	12.94 (4.36–38.39)	<0.0001
IDR	5 (7.2)	91 (0.9)	8.50 (3.34–21.61)	<0.0001	8.87 (3.39–23.17)	<0.0001
MI	17 (24.6)	424 (4.2)	7.38 (4.23–12.86)	<0.0001	9.66 (5.25–17.76)	<0.0001

Values are n (%). *Thirty-day efficacy data were unavailable in 18 patients in the no-IPST group. Propensity score based upon age, sex, smoking status, U.S. versus non-U.S. region, race, weight, biomarker, previous MI (stable angina vs. NSTE-ACS vs. STEMI), previous PCI, previous CABG, peripheral artery disease, patient presentation, worst pre-procedure TIMI score, stent type, bifurcation treatment, aspirin dose, number of treated vessels, clopidogrel loading dose (300 vs. 600 mg), infusion duration, bivalirudin received. Missing data were excluded from the modeling.

Abbreviations as in Tables 1, 2, and 4.

The current study demonstrates a strong independent relationship between IPST and short-term mortality. After propensity-score–adjusted multivariable analysis, IPST was associated with increases of >20- and >12-fold in 48-h and 30-day mortality, respectively. Brener et al. (5) reported similar results in ACS patients, with IPST associated with a 10-fold increase in 30-day mortality. IPST was also a strong independent predictor of MI and IDR. Of note,

while 5.6% of patients with IPST died within 48 h, an additional ~5% died between 48 h and 30 days. This finding underscores the importance of preventing IPST, as well as close monitoring and optimal treatments should IPST occur. Additionally, in approximately one-third of the cases, IPST was associated with use of bailout glycoprotein IIb/IIIa inhibitors, with attendant bleeding hazards and financial implications. Furthermore, prevention of IPST

	IPST	No IPST	OR [95%CI]	P [Int]
Age ≥75	4/19 (21.1)	38/1989 (1.9)	13.69 [4.34, 43.18]	0.67
Age <75	5/70 (7.1)	68/8841 (0.8)	9.92 [3.88, 25.42]	
Male	6/58 (10.3)	61/7816 (0.8)	14.67 [6.07, 35.43]	0.34
Female	3/31 (9.7)	45/3104 (1.5)	7.07 [2.07, 24.10]	
STEMI	4/24 (16.7)	49/1963 (2.5)	7.81 [2.57, 23.71]	0.93
NSTE-ACS	4/33 (12.1)	36/2772 (1.3)	10.48 [3.50, 31.36]	
SA	1/32 (3.1)	21/6095 (0.3)	9.33 [1.22, 71.53]	
Diabetic Yes	3/26 (11.5)	33/3021 (1.1)	11.81 [3.38, 41.27]	0.94
Diabetic No	6/63 (9.5)	73/7794 (0.9)	11.13 [4.65, 26.63]	
Drug-Eluting Stent	3/47 (6.4)	36/6019 (0.6)	11.33 [3.36, 38.17]	0.99
Bare Metal Stent	6/42 (14.3)	70/4811 (1.5)	11.29 [4.61, 27.65]	
LM Bifurcation Treated	1/4 (25.0)	2/127 (1.6)	20.83 [1.46, 297.72]	0.64
LM Bifurcation Not Treated	8/85 (9.4)	104/10703 (1.0)	10.59 [4.99, 22.49]	
Single vessel PCI	6/70 (8.6)	81/9058 (0.9)	10.39 [4.38, 24.67]	0.66
≥2 vessel PCI	3/19 (15.8)	21/1674 (1.3)	14.76 [4.00, 54.48]	
600 mg clopidogrel load	2/58 (3.4)	66/8055 (0.8)	4.32 [1.03, 18.08]	0.06
300 mg clopidogrel load	7/31 (22.6)	40/2775 (1.4)	19.94 [8.12, 48.95]	
Bivalirudin Only	1/15 (6.7)	12/2036 (0.6)	12.05 [1.47, 99.04]	0.96
Heparin Only	8/68 (11.8)	77/7486 (1.0)	12.83 [5.93, 27.74]	
Cangrelor	4/35 (11.4)	56/5427 (1.0)	12.38 [4.23, 36.23]	0.87
Clopidogrel	5/54 (9.3)	50/5403 (0.9)	10.92 [4.18, 28.57]	

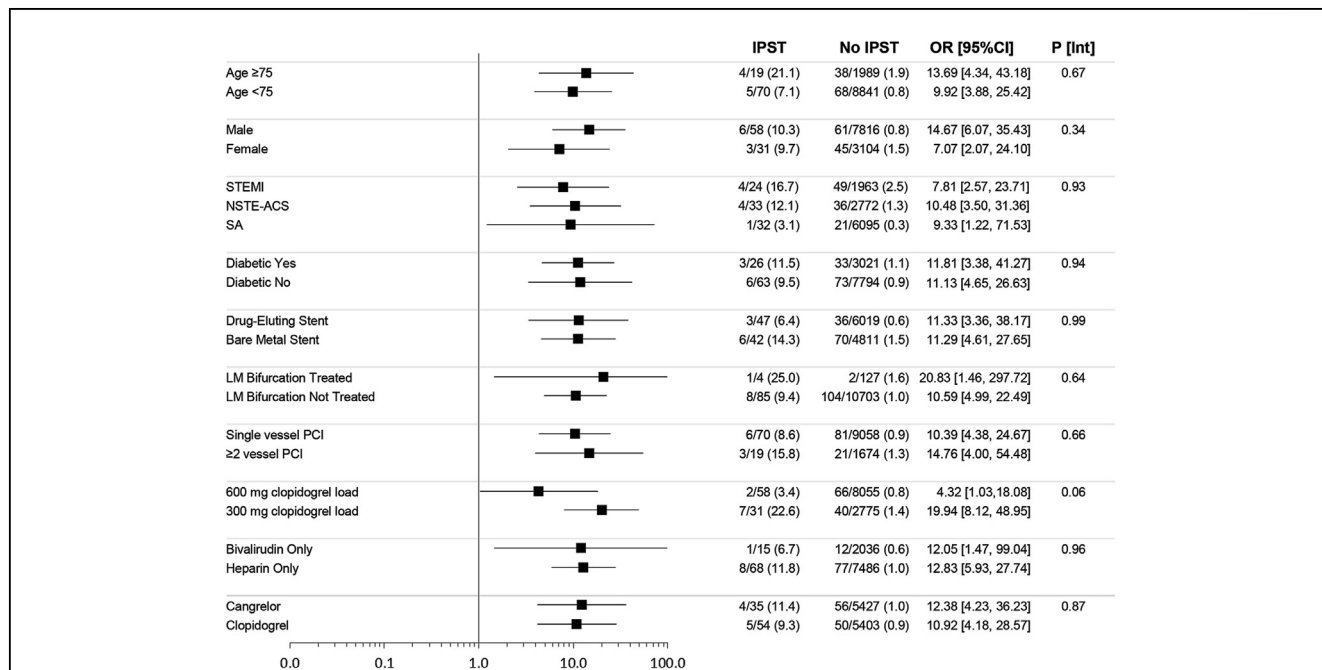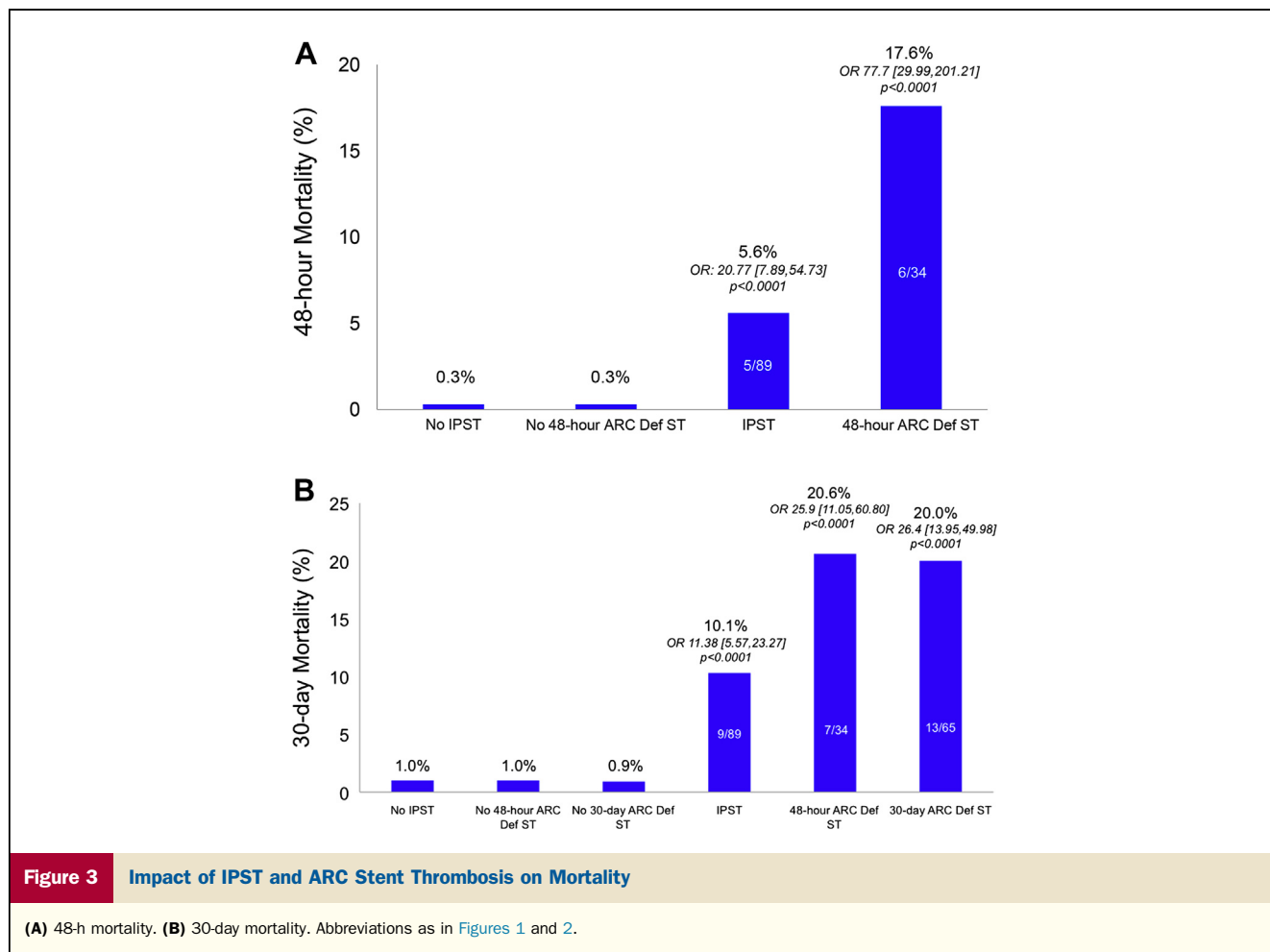| Figure 2	Subgroup Analysis on the Impact of IPST on 30-Day Mortality

The negative impact of intraprocedural stent thrombosis (IPST) on 30-day mortality was consistent among specified subgroups. LM = left main; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; OR = odds ratio; PCI = percutaneous coronary intervention; SA = stable angina; STEMI = ST-segment elevation myocardial infarction.

Figure 3 **Impact of IPST and ARC Stent Thrombosis on Mortality**

(A) 48-h mortality. **(B)** 30-day mortality. Abbreviations as in Figures 1 and 2.

may reduce costs because IPST was associated with a doubling in the length of stay.

In addition, IPST was independently predictive of ARC-ST and ARC definite ST outside the catheterization laboratory. Indeed, IPST was associated with increases of approximately 12-fold and 8-fold in (angiographically confirmed) newly symptomatic ARC definite ST at 48 h and 30 days, respectively. Moreover, while IPST was a relatively rare intraprocedural event, in the CHAMPION PHOENIX trial, its incidence (0.8%) was higher than that of ARC definite ST at 48 h (0.3%) and 30 days (0.6%), and was associated with a similar detrimental impact on short-term prognosis (1). Bleeding rates were also higher in patients experiencing IPST, likely due to the more frequent use of aggressive bailout antithrombotic strategies (such as glycoprotein IIb/IIIa inhibitors) to treat IPST. Moreover, the deleterious impact of IPST persisted even in patients in whom TIMI flow grade 3 was present at the end of the PCI procedure. The present study thus clearly establishes the prognostic utility of IPST, justifying its assessment in future clinical trials in which intraprocedural antithrombotic efficacy is being evaluated. These findings also suggest that future iterations of ST classifications should incorporate IPST as a discrete category.

Independent predictors of IPST in the current report were NSTE-ACS and STEMI at presentation, angiographic thrombus at baseline, and total stent length used during the index PCI. Previous studies have similarly identified ACS and thrombus to be predictors of out-of-laboratory ST (10–14). The fact that stent length was predictive of IPST is also consistent with prior reports of post-PCI ST (12,14). The use of cangrelor was also identified as an independent predictor of freedom from IPST. Because none of the novel oral P2Y$_{12}$ receptor blockers (prasugrel, ticagrelor) showed efficacy in reducing acute ST per se (15–17), this finding may have major implications when selecting the most potent antithrombotic treatment during PCI.

Importantly, use of the potent, rapid-acting ADP receptor antagonist cangrelor compared with clopidogrel (begun at the time of PCI) resulted in a 35% reduction in the rate of IPST, with efficacy in this regard evident in patients with stable angina, NSTE-ACS, and STEMI. Cangrelor may be particularly advantageous to prevent IPST in patients in whom potent oral agents have not been started prior to PCI or in situations in which their absorption is delayed, such as in STEMI (18,19). Thus, the present and prior findings emphasize the interplay between the patient/

Table 6	Association Between IPST and Subsequent 48-Hour Bleeding Events			
Endpoint	IPST (n = 89)	No IPST (n = 10,850)	OR (95% CI)	p Value
GUSTO bleeding				
Non–CABG-related	17 (19.1)	1,424 (13.1)	1.56 (0.92–2.66)	0.10
Any	6 (6.7)	277 (2.6)	2.76 (1.19–6.37)	0.01
Severe/life threatening	0 (0)	15 (0.1)	–	0.73
Moderate	1 (1.1)	34 (0.3)	3.61 (0.49–26.70)	0.18
Mild	5 (5.6)	231 (2.1)	2.74 (1.10–6.81)	0.02
TIMI bleeding				
Any	1 (1.1)	21 (0.2)	5.86 (0.78–44.04)	0.051
Major	0 (0)	10 (0.1)	–	0.77
Minor	1 (1.1)	11 (0.1)	11.20 (1.43–87.66)	0.004
BARC bleeding				
Any	17 (19.1)	1,424 (13.1)	1.56 (0.92–2.66)	0.10
BARC type 3	1 (1.1)	34 (0.3)	3.61 (0.49–26.70)	0.18
BARC type 3a	1 (1.1)	14 (0.1)	8.80 (1.14–67.61)	0.01
BARC type 3b	0 (0)	17 (0.2)	–	0.71
BARC type 3c	0 (0)	3 (0)	–	0.88
ACUITY major without hematoma ≥5 cm	2 (2.2)	52 (0.5)	4.77 (1.14–19.91)	0.02

Values are n (%).
ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; BARC = Bleeding Academic Research Consortium; GUSTO = Global Use of Strategies to Open Occluded Arteries; other abbreviations as in Tables 1 and 4.

lesion thrombotic environment, stent platform, and antithrombotic therapy on the occurrence of intraprocedural and early ST. Optimization of each of these components is crucial if PCI outcomes are to be improved.

Study limitations. Although rigorous angiographic assessment was performed by an experienced, independent, angiographic core laboratory, IPST could be diagnosed only if appropriate angiographic documentation was provided by each site investigator. Thus, brief occurrences of abrupt

| Figure 4 | Incidence of IPST, Stratified by Initial Presentation and Antiplatelet Therapy Strategy |

Cangrelor was associated with a significant reduction in the rate of IPST compared with clopidogrel. No interaction was demonstrated among clinical presentation modes (stable angina, NSTE-ACS, and STEMI), suggesting a similar beneficial effect of cangrelor among these groups. Abbreviations as in Figures 1 and 2.

vessel closure or treatment of thrombus that were not recorded would have escaped detection in this analysis. Coronary angiography has been shown to have great specificity for thrombus detection but low sensitivity compared with angioscopy, resulting in potential underestimation of thrombus burden at the lesion level (20). Although its clinical role still remains to be established, the use of novel intracoronary imaging techniques, such as optical coherence tomography, could have been useful to better characterize and quantify new or worsening intraprocedural thrombus compared with the conventional angiographic evaluation. The absolute number of IPST events prevented was 0.4%, meaning that many patients would need to be treated to prevent 1 event. However, IPST was 3-fold more common than ARC definite ST and has similar prognostic implications, warranting efforts to prevent its occurrence. IPST had a low positive predictive value for ARC ST after PCI, suggesting that different mechanisms may be responsible for IPST and later ST. Finally, although IPST was strongly related to subsequent adverse ischemic events in a multivariable model after propensity adjustment for those factors related to IPST (and other variables), the presence of residual confounding elements cannot be excluded.
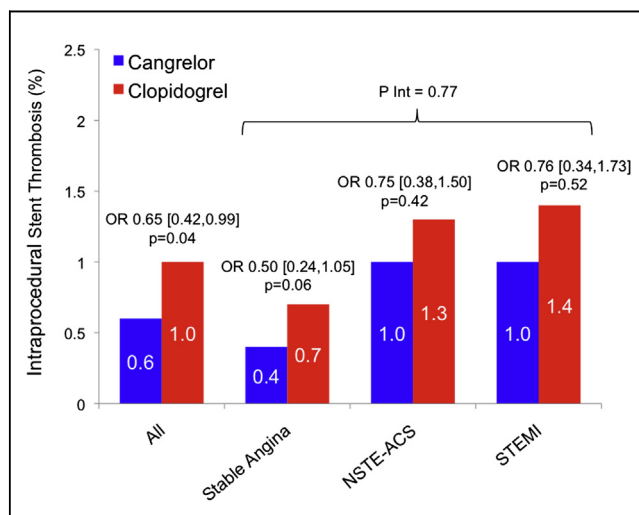
Conclusions

In the large-scale CHAMPION PHOENIX trial, IPST was a relatively infrequent event, occurring in <1% of patients undergoing PCI, but was strongly associated with subsequent ischemic events, including out-of-laboratory ST, MI, and death. The reduction in IPST with cangrelor in CHAMPION PHOENIX contributed to this agent's effectiveness in reducing the rates of ARC-defined stent

thrombosis and MI. These data provide strong evidence for a significant association between IPST and adverse short-term clinical outcomes after PCI and support the inclusion of IPST as an important endpoint in future pharmacological and device trials.

Acknowledgments

Reprint requests and correspondence: Dr. Deepak L. Bhatt, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: DLBHATTMD@post.harvard.edu.

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