Effects of Cangrelor as Adjunct Therapy to Percutaneous Coronary Intervention

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Percutaneous coronary intervention (PCI) in patients with angiographic evidence of intracoronary thrombus is associated with in-hospital and 30-day adverse clinical outcomes. Cangrelor, a direct, rapid-onset acting intravenous $P2Y_{12}$ receptor inhibitor, has been proved to be effective by reducing peri-PCI ischemic complications in subjects who underwent PCI. This study aimed to assess the angiographic and in-hospital clinical outcomes in all-comer patients receiving cangrelor immediately before PCI at a tertiary care center. The study analyzed consecutive unselected subjects treated with cangrelor at the time the decision was made to proceed with PCI. At the end of the procedure, all patients were transitioned to oral antiplatelet therapy. The target lesion angiographic assessment of Thrombolysis in myocardial infarction flow grade (TIMI-Flow), TIMI-thrombus grade (TIMI-Thrombus), myocardial blush grade, and TIMI-myocardial perfusion grade (TMPG) was performed before and post-PCI. Clinical events were recorded during the procedure and at discharge. In total, 223 patients (244 lesions) were included in the analysis (106, 97, and 20 patientswith TIMI-Flow 0/1, TIMI-Flow 2/3, and cardiogenic shock, respectively). The overall mean age was 63 ± 12 years, 70% men and 38% with diabetes mellitus. Acute myocardial infarction was the main presentation (72%). The use of cangrelor improved TIMI-Flow, MGB, TMPG, and TIMI-Thrombus in patients with initial TIMI-Flow 0 to 2. Major bleeding rate was 2.0%. In conclusion, cangrelor was effective and safe in restoring TIMI-Flow 3, reducing thrombus burden and improving myocardial blush grade and TMPG when administered to unselected subjects who underwent PCI. Therefore, cangrelor should be considered in patients presenting with intracoronary thrombus before intervention. © **2019 Published by Elsevier Inc. (Am J Cardiol 2019;123:1228−1238)**

Percutaneous coronary intervention (PCI) in patients with evidence of intracoronary thrombus, in de novo lesions or stent thrombosis (ST), is associated with procedural complications. The presence of intracoronary thrombus when associated with reduction of coronary blood flow,[1,2] perfusion, or myocardial blush[3,4] was associated with adverse clinical outcomes, in-hospital and at 30 days.[5,6] In acute coronary syndrome (ACS), due to the prothrombotic milieu, a $P2Y_{12}$ inhibitor drug with a rapid platelet inhibition is highly desirable.[7] The oral platelet $P2Y_{12}$ inhibitors have delays of at least 60 to 120 minutes before achieving maximal platelet inhibition. Cangrelor is a direct, rapid-onset and -offset intravenous (IV) $P2Y_{12}$ receptor inhibitor that acts immediately upon administration of an IV bolus and infusion.[8,9] Cangrelor has proved to be effective at reducing peri-PCI ischemic complications in patients with stable angina pectoris, ST segment elevation myocardial infarction (STEMI), or non-STEMI (NSTEMI) who were not preloaded with $P2Y_{12}$ receptor inhibitors. In real world- and STEMI-patients on cardiogenic shock, cangrelor demonstrated to be safe and efficacious.[10,11] The aim of this study is: To assess the pre- and postprocedure angiographic and in-hospital clinical outcomes in all-comers patients with and without cardiogenic shock receiving cangrelor before PCI.

Methods

This study is an exploratory registry assessing the utility of cangrelor in all-comers who underwent PCI at a high-volume, tertiary care center (i.e., MedStar Washington Hospital Center), from September 2016 to December 2017. The study was approved by the Institutional Review Board.

The inclusion criteria were >18 years old, all-comer patients (i.e., stable angina pectoris, unstable angina pectoris, STEMI, and NSTEMI) referred to cardiac catheterization and underwent PCI and received intraprocedure cangrelor. All patients received cangrelor in the Cardiac Catheterization Laboratory at the time of the decision to perform PCI.

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For this analysis, the patients were first stratified according to their preprocedure clinical status hemodynamic stability as either cardiogenic shock or no shock. Patients were further submitted to a lesion-level analysis of the preprocedure TIMI-Flow (grade 0 to 3). The noncardiogenic shock subjects were categorized either TIMI-Flow 0/1 or TIMI-Flow 2/3 subgroups.

The primary efficacy end point was angiographic, that is, a pre- and post-PCI assessment of the changes in coronary blood flow, intraluminal thrombus, and myocardium microcirculation. Secondary clinical efficacy and safety end points were in-hospital outcomes, including major adverse cardiovascular events (MACE), a composite of death, myocardial infarction (MI), and repeat revascularization; definite ST; and major bleeding (as per protocol).

Acute MI definition includes STEMI and NSTEMI. *STEMI* was defined as CK-MB elevation ≥2 times the upper limit of normal with the presence of ischemic electrocardiographic changes including new Q waves or ST elevation ≥1 mm. *NSTEMI* was defined as CK-MB elevation ≥2 times the upper limit of normal without ischemic electrocardiographic changes. Periprocedural *MI* was described by Baker et al as an increment of CK-MB ≥2 the upper limit of normal, along with symptoms and/or electrocardiographic changes suggestive of myocardial ischemia.[12] *Repeat revascularization* included any re-PCI of a target lesion revascularization (TLR) and any coronary artery bypass grafting (CABG) after the index procedure. *TLR* was defined as a reintervention (PCI) of an index procedure target lesion. *CABG* was defined as any coronary artery bypass graft required emergently, urgently, or electively postprocedure. *Major Bleeding* was the composite of Gastrointestinal Bleeding (GIB), Hematocrit decrease, or major hematoma. *GIB* was defined as the evidence of bleeding in the gastrointestinal tract upper or lower to the Angle of Treitz. *Hematocrit decrease* is defined as a decrease in the hematocrit >15 points without evidence of a vascular complication. *Major Hematoma* was defined as the presence of Hematomas 20 × 40 mm or greater or those requiring transfusions or necessitating prolonged hospitalization. *Cardiogenic Shock* (at the time of the admission)was defined as a maximum systolic blood pressure < 90 mm Hg for at least 30 minutes, unless treated with inotropes or intra-aortic balloon pump insertion, or pump failure as manifested by a cardiac index <2.2 and a pulmonary capillary wedge pressure >18 mm Hg and/or persistence of hypotension.

The adjunctive, intraprocedure pharmacologic therapy was either unfractionated heparin or bivalirudin, and also the pre- and postprocedure antiplatelet therapy regimen followed the operator's discretion. Cangrelor was administered in all patients as an IV bolus of 30 μg/kg and subsequent continuous pump infusion of 4 μg/kg/min during the entire procedure. The use of cangrelor was started at the time the decision was made to proceed with PCI. At the end of the procedure, the patients were transitioned to oral $P2Y_{12}$ therapy. All patients also received acetylsalicylic acid with loading dose of 325 mg and followed by 81 mg/day. Dual antiplatelet therapy was prescribed according to current guidelines for at least 6 months for stable patients and 12 months for patients presenting with ACS.[7] The oral medications were administrated in the tablet form unless the patient was not able to swallow it.

The angiographic assessment of the cases was done by an independent core laboratory at Medstar Cardiovascular Research Network (Washington, District of Columbia). All materials were analyzed using an offline quantitative coronary analysis software (CAAS, PieMedical, Maastricht, Netherlands). The qualitative and quantitative parameters of the treated vessel were initially used to evaluate the complexity of the lesion according to the American College of Cardiology/American Heart Association)lesion classification,[13,14] followed by the pre- and postindex procedure angiographic outcomes analysis. Angiographic indexes were defined according to the original publication in which the scores were first described or updated. The estimation of coronary blood flow was done using TIMI flow grade (TIMI-Flow).[1,2] The angiographic presence of intracoronary thrombus was evaluated using the TIMI thrombus grade (TIMI-Thrombus).[1,2] The myocardial microcirculation was assessed using myocardial blush grade (MBG) and TIMI myocardial perfusion grade (TMPG).[3,4,15]

Continuous variables were represented using means and standard deviation, and the categorical variables by frequencies and percentages. The differences between the TIMI-Flow 0/1 and TIMI-Flow 2/3 groups were assessed using the standardized differences expressed in normalized standard deviation units (Z-score, Z).[16] A standardized difference of 0.2 indicates about 15% nonoverlap of the 2 distributions; 0.3, about 23% nonoverlap; and 0.5, about 33% nonoverlap. Generally, an absolute standardized difference of 0.2 or greater is considered meaningful.

Results

A total of 223 patients (244 lesions) underwent PCI along with cangrelor during the index procedure. There were 106 patients (109 lesions) with preprocedure TIMI-Flow 0/1, 97 patients (115 lesions) with preprocedure TIMI-Flow 2/3, and 20 patients (20 lesions) under cardiogenic shock (and TIMI-Flow 0 to 3; Figure 1). Overall, the mean age was 63 ± 12 years, and 144 (71%) were men. Acute MI was the clinical presentation in 147 (73%) of the patients. Other baseline characteristics are presented in Table 1. Second-generation drug-eluting stent (DES) was used in 206 (92%) of the lesions and 47 (21%) were thrombus aspirated and remaining lesion and preprocedure characteristics are described in Table 2.

Overall, 35 (16%) of the patients were already taking $P2Y_{12}$ inhibitors before the clinical event hospitalization, and 63 (28%) patients preloaded with $P2Y_{12}$ inhibitors at the emergency department or Cath Lab, of whom 48 (21%) received ticagrelor, 14 (6.3%) clopidogrel, and 1 (0.4%) prasugrel. The administration of glycoprotein IIb/IIIa inhibitor (GP IIb/IIIa) was used 7 cases (3.5%) only for bailout situations (Table 3). At the end of the procedure, 144 subjects (65%) were transitioned from IV-to-oral $P2Y_{12}$ inhibitors, of whom 57%, 6.7%, and 0.4% of the patients were transitioned from cangrelor to ticagrelor, clopidogrel, or prasugrel, respectively. All patients received acetylsalicylic acid) and $P2Y_{12}$ inhibitors, before admission, preprocedure loading or were transitioned at the end of the procedure. In

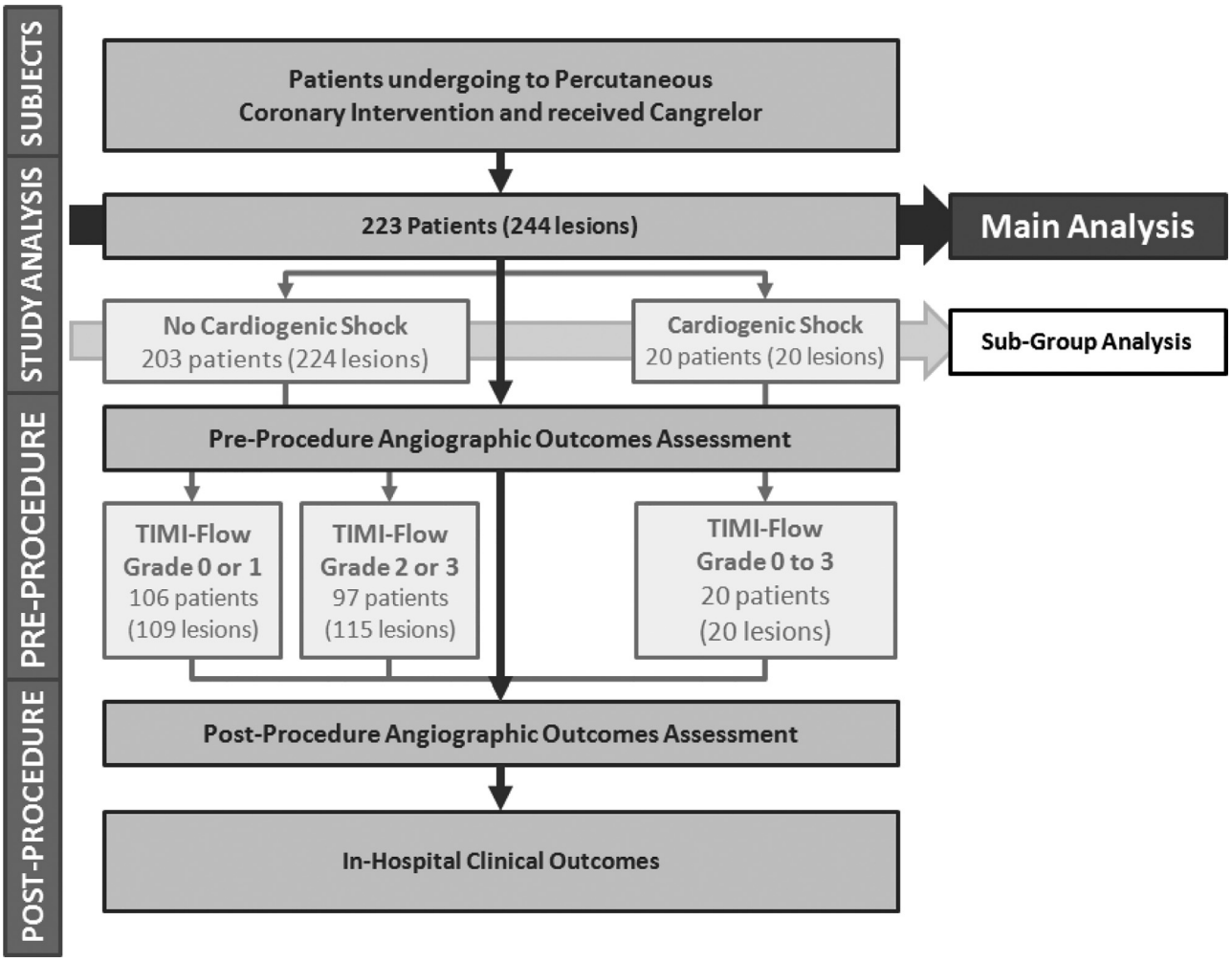


Figure 1. Study flow diagram.
TIMI = thrombolysis in myocardial infarction.

the majority of patients, there was overlap between cangrelor and oral $P2Y_{12}$, and in some patients, the IV $P2Y_{12}$ was continued after the completion of the PCI until the end of the infusion. The subgroup baseline, lesion, and preprocedure and postprocedure characteristics are also presented in the Tables 1 to 3.

The angiographic outcomes were performed in a lesion-level analysis, and the results are shown in Figure 2. In the postprocedure analysis, TIMI-Flow 3 was restored in 96% of cases. In total 57% of the patients presented preprocedure definite presence of Thrombus (TIMI-Thrombus 2 to 5) and 20% probable presence of thrombus (TIMI-Thrombus 1). At the end of the procedure, 96% of lesions had angiographic absence of thrombus (TIMI-Thrombus 0). Before PCI and adjunctive phamacotherapy assessment, MBG and TMPG were absent (grade 0) in 37% and 38% of the lesions, respectively. At postprocedure, MPG was partially (grade 2) or fully restored (grade 3) in 7.1% and 91%, respectively, whereas TPMG 2 or 3 was observed in 5.7% and 92% of the cases, respectively. The angiographic outcomes subgroup data are presented in the Figures 3 and 4. None of the patients experienced abrupt closure of the vessel during the procedure. At the end of the procedure, distal embolization was documented in 9 (4.2%) vessels. There were 2 (0.9%) no reflow cases and 1 (0.5%) type D coronary dissection (Table 3).

The overall mean in-hospital stay was 3.6 ± 3.7 days. Clinical success (MACE-free) was achieved in 197 (97%) of the cases (Table 4). MACE was met in 6 (3.0%) of the cases. All MACE cases were in the TIMI-Flow 0/1 group 6/106 (5.7%), of whom, 1 patient died (cardiac), 6 patients had revascularization (4 by CABG and 2 had TLR by PCI), and no MI cases (Table 4). One patients (0.5%) experienced an ischemic stroke. Major bleeding complications were detected in 4 cases (2.0%), of whom 2 subjects (1.0%) had GIB, and 3 (1.6%) experienced a hematocrit decrease unrelated to GIB or access site. There were 7 access site hematomas not requiring intervention, and no cases of access site pseudoanerysm formation, arteriovenous fistula, limb ischemia, or complications requiring surgical intervention. There were no definite or probable ST cases.

Discussion

This study reports the experience of a contemporary use of cangrelor in subjects who underwent PCI in a high-

Table 1
Baseline characteristics

Variable	TIMI-Flow Grade 0 to 3 (Overall)		TIMI-Flow Grade						
			0 or 1		2 or 3		Z-score	0 to 3 + Cardiogenic Shock	
	Summary Statistic	Total (n = 203)	Summary Statistic	Total (n = 106)	Summary Statistic	Total (n=97)		Summary Statistic	Total (n = 20)
Age (years) (mean ± standard deviation)	63.3 ± 12.1		60.5 ± 12.2		66.4 ± 11.1		−0.506	63.05 ± 11.4	
Men	144 (70.9%)		75 (70.7%)		48 (49.5%)		0.445	13 (65.0%)	
Risk factors									
Diabetes mellitus	76 (38.2%)	199	39 (37.5%)	104	37 (38.9%)	95	−0.298	8 (40.0%)	
Systemic arterial hypertension†	163 (81.1%)	201	80 (76.2%)	105	83 (86.5%)	96	−0.266	13 (65.0%)	
Hyperlipidemia‡	142 (71.0%)	200	67 (64.4%)	104	75 (78.1%)	96	−0.306	10 (50.0%)	
Smoker	63 (31.0%)		57 (53.8%)		54 (55.7%)		−0.038	9 (45.0%)	
Heart failure	45 (22.8%)	197	25 (24.0%)	104	20 (21.5%)	93	0.060	3 (15.0%)	
Left ventricle ejection fraction % (% ± standard deviation)	0.46 ± 0.14	152	0.42 ± 0.13	77	0.49 ± 0.13	75	−0.538	0.38 ± 0.14	
Chronic kidney disease, dialysis	4 (2.0%)	200	1 (0.9%)	105	3 (3.2%)	95	−0.155	1 (5.0%)	–
Previous myocardial infarction	38 (18.7%)		18 (16.9%)		20 (20.6%)		−0.093	1 (5.0%)	
Previous Percutaneous coronary intervention	49 (24.4%)	201	18 (17.3%)	104	31 (31.9%)		−0.345	2 (10.0%)	
Previous coronary artery bypass graft	16 (7.9%)	202	8 (7.6%)	105	8 (8.2%)		−0.232	0 (0.0%)	
Graft age, (months) (mean ± standard deviation)	88.6 ± 74.9	17	87.8 ± 82.5	8	89.43 ± 72.4	9	−0.020	–	–
Clinical presentation									
Stable angina pectoris	14 (7.0%)	201	3 (2.8%)		11 (11.6%)	95	−0.343	0 (0.0%)	
Unstable angina pectoris	40 (19.9%)	201	9 (8.5%)		6 (6.3%)	95	0.083	0 (0.0%)	
Acute myocardial infarction*	147 (73.1%)	201	94 (88.7%)		53 (55.8%)	95	0.789	20 (100.0%)	

Data are mean ± one standard deviation for continuous variables; n (%) for categorical variables.
Negative value indicates smaller value of TIMI 0/1.
TIMI = thrombolysis in myocardial infarction.
* Acute myocardial infarction (AMI) definition includes STEMI and NSTEMI.
† Systemic Arterial Hypertension was defined as patients with previous documented history of hypertension on medication.
‡ Hyperlipidemia was defined as patients with a previously documented diagnosis of hypercholesterolemia. A new diagnosis was made with an elevated cholesterol >250 ng/dl (but does not include isolated elevated triglycerides).

volume tertiary center in the United States. There are 4 main findings derived from the study analysis: (1) The concomitant use of cangrelor improved the angiographic outcomes in patients with a visible intracoronary thrombus, including in hemodynamically stable patients with the preprocedure TIMI flow grade 0 or 1; (2) Overall, the adjunct administration of cangrelor was associated with a low rate of clinical events and no ST; (3) The transition of cangrelor to oral antiplatelet therapy (predominantly ticagrelor) was safe; and (4) Use of cangrelor was associated with a low in-hospital major bleeding rate.

Patients with STEMI often present with spontaneous intracoronary thrombus leading to a reduction of antegrade coronary artery blood flow.[1,2] The presence of intracoronary thrombus during PCI is associated with poor clinical outcomes.[5,6] The management of spontaneous intracoronary thrombus remains a therapeutic challenge, particularly in de novo lesions.[6,17] The present study is the first to detail the impact of cangrelor, as adjunct therapy, on the postprocedure angiographic indexes and clinical outcomes in a contemporary practice in subjects underwent PCI. The study showed that the use of cangrelor resulted in improvement of the angiographic indexes in patients with or without cardiogenic shock. The gain was more prominent in lesions with preprocedure TIMI-Flow 0/1, which is notoriously known to result in poor outcomes. Finally, there was nearly complete avoidance of the no reflow phenomenon that is common in patients with large thrombus burden who underwent PCI.

There are several contributors, preventable or not, to the formation of ST, and still today, the motality rate is high (20% to 40%).[10,18,19] These contributors could be related to the patient, the device, or the actual procedure. Particularly in patients with genetic polymorphism, co-morbidities (erratic gastro-intestinal absorption and metabolization), concomitant pharmacologic interactions (i.e., fentanyl and morphine), and left ventricle impairment. In the stent type was also related to ST, now reduced by second-generation DES to <1.0%. Lesion type B2 or C were associated with procedure-related ST; along with final TIMI grade flow <3; under sized or under expanded stents, stent malapposition, stent fracture, residual dissection or stenosis; and lack of adequate endothelial coverage.[5,6,17] There are several mechanical and pharmacological strategies to prevent and to treat intracoronary thrombus. Among the mechanical approaches for treatment are the aspiration devices, which

Table 2
Lesion and preprocedure characteristics

Variable	TIMI-Flow Grade 0 to 3 (Overall)		TIMI-Flow Grade					0 to 3 + Cardiogenic Shock	
			0 or 1		2 or 3		Z-score		
	Summary Statistic	Total (n = 224)	Summary Statistic	Total (n = 109)	Summary Statistic	Total (n = 115)		Summary Statistic	Total (n = 20)
Previous stent	26 (11.6%)		16 (14.7%)		10 (8.7%)		0.187	2 (10.0%)	
In-Stent restenosis	8 (3.6%)	222	6 (5.6%)	108	2 (1.8%)	114	0.203	1 (5.0%)	
Target vessel									
Left main coronary artery	4 (1.8%)		0 (0.0%)		4 (3.5%)		−0.268	0 (0.0%)	
Left anterior descending	83 (37.1%)		44 (40.4%)		39 (33.9%)		0.134	7 (35.0%)	
Left circumflex	48 (21.4%)		23 (21.1%)		25 (21.7%)		−0.155	5 (25.0%)	
Right coronary artery	87 (38.8%)		42 (38.5%)		45 (39.1%)		−0.012	8 (40.0%)	
In-Graft	2 (0.9%)		0 (0.0%)		2 (1.7%)		−0.188	0 (0.0%)	
Preprocedure TIMI Flow Grade									
Grade 0	80 (35.7%)		80 (73.4%)		0 (0.0%)		–	15 (75.0%)	
Grade 1	29 (12.9%)		29 (26.6%)		0 (0.0%)		–	3 (15.0%)	
Grade 2	9 (4.0%)		0 (0.0%)		9 (7.8%)		–	1 (5.0%)	
Grade 3	106 (47.3%)		0 (0.0%)		106 (92.2%)		–	1 (5.0%)	
Lesion Classification[†]									
Type A	11 (4.9%)		0 (0.0%)		11 (9.6%)		−0.460	1 (5.0%)	
Type B1	22 (9.8%)		0 (0.0%)		22 (19.1%)		−0.690	1 (5.0%)	
Type B2	30 (13.4%)		3 (2.8%)		27 (23.5%)		−0.645	0 (0.0%)	
Type C	161 (71.9%)		106 (97.2%)		55 (47.8%)		1.329	18 (90.0%)	
Preprocedure									
% Diameter stenosis (% ± standard deviation)	91.0 ± 12.0		97.0 ± 12.0		86.0 ± 10.0	114	–	90.0 ± 27.0	
Lesion Length, (mm) (mean ± standard deviation)	11.89 ± 6.55	115	–		11.89 ± 6.55		–	14.5 ± 9.19	4
Minimum lumen diameter, (mm) (mean ± standard deviation)	0.63 ± 0.61		0.24 ± 0.48		1.00 ± 0.49		−1.567	0.18 ± 0.39	
Reference vessel diameter, (mm) (mean ± standard deviation)	2.39 ± 0.87		2.15 ± 1.06		2.62 ± 0.56		−0.554	2.18 ± 0.57	

Data are mean ± one standard deviation for continuous variables; n (%) for categorical variables.
Negative value indicates smaller value of TIMI 0/1.
TIMI = thrombolysis in myocardial infarction.
[†] American College of Cardiology/American Heart Association (ACC/AHA) lesion Classification.

failed to show efficacy and safety in pivotal randomized clinical trials and meta-analysis.[17,20,21] In contrast, second-generation DES[5,6] and improvements of the standard PCI technique, including invasive imaging guidance, demonstrated reduction of acute and subacute ST.[22,23] Pharmacological approaches that have been used for the prevention and treatment of intracoronary thrombus in patients with ACSinclude preloading of $P2Y_{12}$ inhibitors before the PCI, the use of GP IIB/IIIA inhibitors systematically or as a bail-out option, and thrombolytic therapy.[1,23–25] These medication strategies showed modest efficacy and were associated with a substantial increase of major bleeding, drawing attention to the fine balance between bleeding and thrombotic risk for these patients.[26,27] Albeit second-generation $P2Y_{12}$ inhibitors have superior platelet inhibition, it may still take over 60 minutes from loading to have sufficient platelet inhibition and ability to prevent thrombus formation in patients who underwent primary PCI.[28–30]

Cangrelor is a direct rapid-onset and -offset platelet inhibitor that acts immediately after IV administration. Based on the CHAMPION PHOENIX trial results, it was approved for use in the United States on June of 2015 in patients who underwent stent implantation with STEMI, NSTEMI, or stable angina pectoris who were not previously loaded with $P2Y_{12}$ receptor inhibitors.[8,19] Cangrelor showed a significant decrease in ischemic events, including ST and peri-PCI ischemic complications, but not at the expense of an increase in major bleeding.[8,19,29,30] Further, cangrelor showed a reduction in the formation of new thrombus during PCI in the CHAMPION trials.[8] The present study details the use of cangrelor in patients presenting with ACS primarily with STEMI and associated with significant thrombus burden. Overall, 95% of patients were MACE-free and only 2.6% with major bleeding events. There were no ST cases in any of the treated patients regardless of clinical presentation or hemodynamic status. This result goes in-line with previous publications of Bhatt et al showing less ST in the cangrelor group during the intraprocedure infusion time from 0 to 2 hours (i.e., the required infusion time as per protocol after the drug prescribing information dose).[8,29]

Platelet $P2Y_{12}$ inhibition with cangrelor occurs regardless of presentation or renal function, which could be particularly important in an emergent setting. The transitioning

Table 3
Postprocedure characteristics

Variable	TIMI-Flow Grade 0 to 3 (Overall)		TIMI-Flow Grade						
			0 or 1		2 or 3		Z-score	0 to 3 + Cardiogenic Shock	
	Summary Statistic	Total	Summary Statistic	Total	Summary Statistic	Total		Summary Statistic	Total
Per patient data,		(n = 203)		(n = 106)		(n = 97)			(n = 20)
Cangrelor	203 (100.0%)		106 (100.0%)		97 (100.0%)		–	20 (100.0%)	
Infusion time (minutes) (mean ± standard deviation)	81 ± 39	198	78 ± 39	101	84 ± 39	97	0.316	90 ± 38	18
Intraprocedure Medications									
Unfractionated Heparin	150 (73.9%)		67 (63.2%)		83 (85.6%)		−0.530	11 (55.0%)	
Activated clotting time final, (seconds) (mean ± standard deviation)	306 ± 69	190	304 ± 69	100	307 ± 70	90	−0.043	310 ± 66	18
Bivalirudin	46 (22.7%)		33 (31.1%)		11 (11.3%)		0.499	9 (45.0%)	
Bailout Glycoprotein IIb/IIIa inhibitors*	7 (3.5%)	201	4 (3.8%)	104	3 (3.1%)		0.041	3 (15.0%)	
Postprocedure (at discharge)									
Acetylsalicylic acid	188 (94.0%)	200	96 (92.3%)	104	92 (95.8%)	96	−0.150	14 (73.7%)	19
Clopidogrel	54 (27.0%)	200	23 (22.1%)	104	31 (32.3%)	96	−0.230	4 (25.0%)	16
Ticagrelor	145 (72.5%)	200	80 (76.9%)	104	65 (67.7%)	96	0.207	12 (75.0%)	16
Prasugrel	1 (0.5%)	200	1 (1.0%)	104	0 (0.0%)	96	0.139	0 (0.0%)	
Warfarin	41 (20.5%)	200	31 (29.8%)	104	10 (10.4%)	96	0.498	2 (10.5%)	19
Prelesion data,		(n = 224)		(n = 109)		(n = 115)			(n = 20)
Procedural characteristics									
Percutaneous coronary intervention success	222 (99.1%)		107 (98.2%)		115 (100.0%)		−0.193	20 (100.0%)	
Procedure duration, (minutes) (mean ± standard deviation)	81.3 ± 39.4	198	78.5 ± 39.1	101	84.2 ± 39.7	97	−0.145	90.3 ± 38.9	18
Contrast used, (cubic centimeters) (mean ± standard deviation)	167.1 ± 65.9	201	169.8 ± 64.6	105	164.2 ± 67.4	96	0.085	149.7 ± 58.4	19
Bare metal Stent	3 (1.4%)	222	2 (1.8%)		1 (0.9%)	113	0.082	0 (0.0%)	
Drug-eluting stents									
1st generation	0 (0.0%)		0 (0.0%)		0 (0.0%)		–	0 (0.0%)	
2nd generation	206 (92.0%)		95 (87.2%)		111 (96.5%)		−0.347	17 (85.0%)	
Brachytherapy	0 (0.0%)	223	1 (0.9%)		0 (0.0%)	114	0.136	0 (0.0%)	
Thrombus aspiration	47 (21.1%)	223	39 (35.8%)		9 (7.9%)	114	0.717	14 (70.0%)	
Distal protection device	0 (0.0%)	223	0 (0.0%)		0 (0.0%)	114	–	0 (0.0%)	
Laser	0 (0.0%)	223	0 (0.0%)	108	0 (0.0%)		–	0 (0.0%)	
Rotational Atherectomy	10 (4.5%)	222	1 (0.9%)	108	9 (7.9%)	114	−0.344	0 (0.0%)	
Cutting balloon	4 (1.8%)	223	1 (0.9%)	108	3 (2.6%)		−0.128	0 (0.0%)	
Direct stenting	0 (0.0%)	5	0 (0.0%)	3	0 (0.0%)	2	–	0 (0.0%)	
Predilation	136 (60.7%)		70 (64.2%)		66 (57.4%)		0.140	12 (60.0%)	
Postdilation	56 (25.0%)		24 (20.8%)		32 (27.8%)		−0.134	2 (10.0%)	

(*continued on next page*)

Table 3 (***Continued***)

Variable	TIMI-Flow Grade 0 to 3 (Overall)		TIMI-Flow Grade						
			0 or 1		2 or 3		Z-score	0 to 3 + Cardiogenic Shock	
	Summary Statistic	Total	Summary Statistic	Total	Summary Statistic	Total		Summary Statistic	Total
Postprocedure Findings									
No reflow	2 (0.9%)	212	0 (0.0%)	98	2 (1.8%)	114	−0.189	0 (0.0%)	17
Distal embolization	9 (4.2%)	212	7 (7.1%)	98	2 (1.8%)	114	0.263	2 (11.8%)	17
Coronary dissection[†]									
Type D	1 (0.5%)	212	0 (0.0%)	98	1 (0.9%)	114	−0.133	0 (0.0%)	17
Coronary perforation[‡]									
Type 1	1 (0.5%)	212	0 (0.0%)	98	1 (0.9%)	114	−0.133	0 (0.0%)	17
Type 2	1 (0.5%)	212	1 (1.0%)	98	0 (0.0%)	114	0.143	0 (0.0%)	17
Postprocedure									
Stented lesions	209 (93.3%)		97 (89.0%)		112 (97.4%)		−0.338	17 (100.0%)	17
Minimum lumen diameter, (mm) (mean ± standard deviation)	2.10±0.50	95	2.10±0.50	95	–	–	–	2.18±0.34	10
Reference vessel diameter, (mm) (mean ± standard deviation)	2.66±0.57	95	2.66±0.57	95	–	–	–	2.61±0.35	10
% Diameter stenosis (% ± standard deviation)	21.0±9.42	95	21.0 ± 9.42	95	–	–	–	16.7±6.68	10

TIMI = thrombolysis in myocardial infarction.

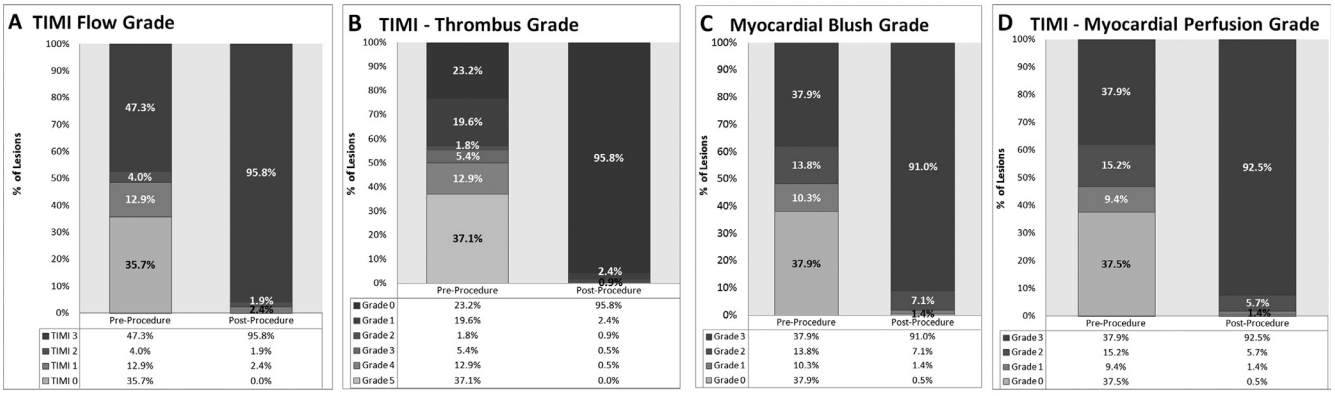
Data are mean ± one standard deviation for continuous variables; n (%) for categorical variables.

Negative value indicates smaller value of TIMI 0/1.

* Eptifibatide.

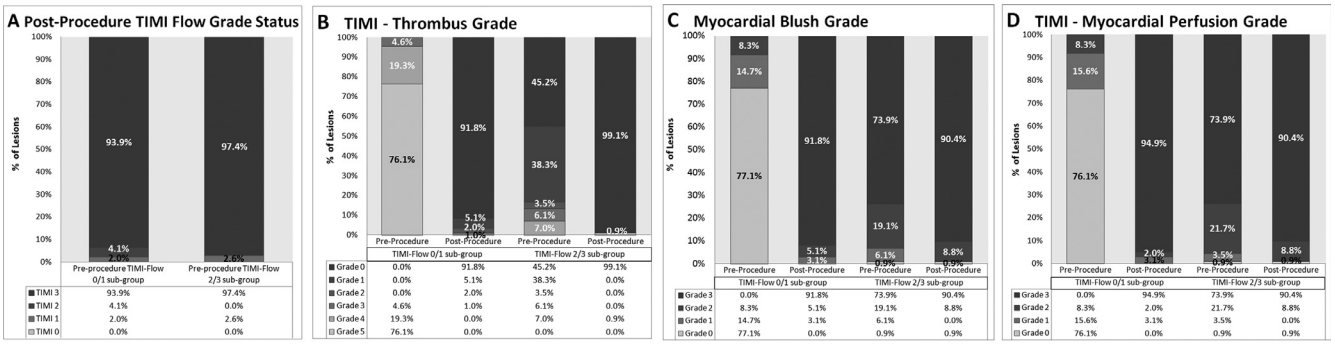
† National Heart, Lung, and Blood Institute (NHLBI) Classification

‡ Ellis classification.



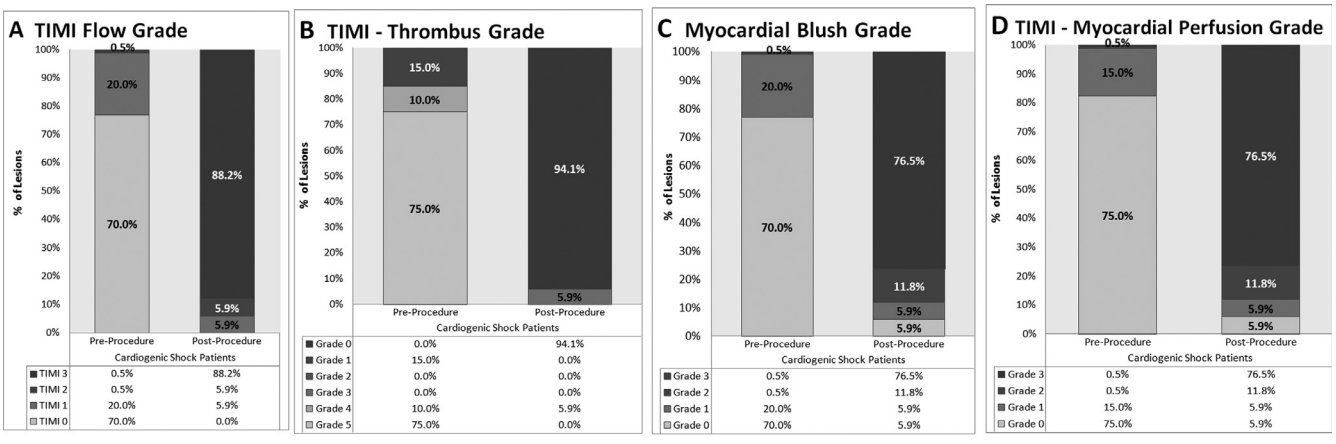
Abbreviations: TIMI = Thrombolysis In Myocardial Infarction.

Figure 2. Preprocedure and postprocedure angiographic outcomes comparison graphs of patients underwent to Percutaneous Coronary Intervention also receiving cangrelor. TIMI Flow Grade (A); TIMI Thrombus Grade (B); Myocardial Blush Grade (C); and TIMI Myocardial perfusion grade (D).
TIMI = thrombolysis in myocardial infarction.



Abbreviations: TIMI = Thrombolysis In Myocardial Infarction.

Figure 3. Preprocedure and postprocedure angiographic outcomes comparison graphs between the TIMI-Flow 0/1 and TIMI-Flow 2/3 subgroups in patients without cardiogenic shock. Postprocedure TIMI Flow Grade Status (A); TIMI Thrombus Grade (B); Myocardial Blush Grade (C); and TIMI Myocardial perfusion grade (D).
TIMI = thrombolysis in myocardial infarction.



Abbreviations: TIMI = Thrombolysis In Myocardial Infarction.

Figure 4. Preprocedure and postprocedure angiographic outcomes comparison graphs of patients underwent to Percutaneous Coronary Intervention also receiving cangrelor with cardiogenic shock. TIMI Flow Grade (A); TIMI Thrombus Grade (B); Myocardial Blush Grade (C); and TIMI Myocardial perfusion grade (D).
TIMI = thrombolysis in myocardial infarction.

Table 4
In-hospital clinical outcomes

Variable	TIMI-Flow Grade 0 to 3 (Overall)		TIMI-Flow Grade						
			0 or 1		2 or 3		Z-score	0 to 3 + Cardiogenic Shock	
	Summary Statistic	Total (n = 203)	Summary Statistic	Total (n = 106)	Summary Statistic	Total (n = 97)		Summary Statistic	Total (n = 20)
In-Hospital stay, (days) (mean ± standard deviation)	3.6 ± 3.7		4.4 ± 4.3		2.7 ± 2.7		–	8.4 ± 6.2	
Clinical success*	197 (97.0%)		100 (94.3%)		97 (100.0%)		–	15 (75.0%)	
Major adverse cardiovascular Events (MACE)†	6 (3.0%)		6 (5.7%)		0 (0.0%)		–	5 (25.0%)	
Death	1 (0.5%)		1 (0.9%)		0 (0.0%)		–	4 (20.0%)	
Cardiac death	1 (0.5%)		1 (0.9%)		0 (0.0%)		–	3 (15.0%)	
Myocardial infarction	0 (0.0%)	201	0 (0.0%)	105	0 (0.0%)	96	–	0 (0.0%)	
Target lesion revascularization (TLR)	2 (1.0%)	200	2 (1.9%)		0 (0.0%)	94	–	1 (5.0%)	
Repeat revascularization‡	6 (3.0%)	202	6 (5.7%)		0 (0.0%)	96	–	2 (10.0%)	
Coronary artery bypass grafting (CABG)	4 (2.0%)	202	4 (3.8%)		0 (0.0%)	96	–	1 (5.0%)	
Percutaneous coronary intervention (PCI)	2 (1.0%)	200	2 (1.9%)		0 (0.0%)	94	–	1 (5.0%)	
Transient ischemic attack	0 (0.0%)	201	0 (0.0%)	105	0 (0.0%)	96	–	0 (0.0%)	
Stroke	1 (0.5%)	201	1 (1.0%)	105	0 (0.0%)	96	–	1 (5.0%)	
Ischemic	1 (0.5%)	201	1 (1.0%)	105	0 (0.0%)	96	–	1 (5.0%)	
Stent thrombosis	0 (0.0%)		0 (0.0%)		0 (0.0%)		–	1 (5.0%)	
Kidney failure requiring dialysis	0 (0.0%)	202	0 (0.0%)		0 (0.0%)	96	–	0 (0.0%)	
Hematoma	7 (3.5%)	202	4 (3.8%)		3 (3.1%)	96	–	0 (0.0%)	
Arteriovenous fistula	1 (1.6%)	202	0 (0.0%)		1 (1.0%)	96	–	0 (0.0%)	
Pseudoaneurysm	0 (0.0%)	202	0 (0.0%)		0 (0.0%)	96	–	0 (0.0%)	
Limb ischemia	0 (0.0%)	202	0 (0.0%)		0 (0.0%)	96	–	0 (0.0%)	
Surgical repair (Access site related)	0 (0.0%)	202	0 (0.0%)		0 (0.0%)	96	–	0 (0.0%)	
Major bleeding	4 (2.0%)		2 (1.9%)		2 (2.1%)	97	–	2 (10.0%)	
Gastrointestinal bleeding	2 (1.0%)	202	0 (0.0%)		2 (2.1%)	97	–	0 (0.0%)	
Major Hematoma	0 (0.0%)	184	0 (0.0%)	93	0 (0.0%)	91	–	0 (0.0%)	17
Hematocrit drop	3 (1.6%)	185	2 (2.2%)	93	1 (1.4%)	92	–	2 (11.8%)	17
Transfusion of red blood cells pack	4 (2.6%)	156	3 (3.6%)	93	1 (1.4%)	73	–	2 (10.0%)	

Data are mean ± one standard deviation for continuous variables; n (%) for categorical variables.
Negative value indicates smaller value of TIMI 0/1.
TIMI = thrombolysis in myocardial infarction.
* Clinical success was defined as MACE-free.
† MACE was defined as a composite of death, MI and repeat revascularization.
‡ Re-PCI (TLR) or any CABG.

from cangrelor to oral $P2Y_{12}$ receptor inhibitor that varies according to each specific drug.[28–30] In the present study, there were no issues with this transition when the majority of the patients switched to ticagrelor while still in the Cardiac catheterization laboratory, irrespective of their pre-PCI treatment. With the lack of ischemic events during the transition and only 2 major bleeding events, the transition overall was seamless.

The present registry has the apparent limitation of a single center registry, including bias in patient selection. There was no control group to evaluate the efficacy of the angiographic indexes and the bleeding complications. Finally, the heterogeneity of the groups stable, ACS, and patients with cardiogenic shock may obscure specific groups that can benefit more from systematic usage of the drug. Nevertheless, the present study shares a tertiary center experience and provides data for contemporary usage of cangrelor as adjunct therapy for patients with visible thrombus who underwent PCI.

In conclusion, cangrelor when administered immediately before PCI in patients with visible thrombus and impaired anterograde coronart blood flow is effective in restoring blood flow (TIMI-Flow), reducing thrombus burden (TIMI-Thrombus), improving myocardial perfusion (TMPG), and blush grades (MBG). Cangrelor is associated with an overall low MACE rate, absence of procedural ST, and low bleeding rates regardless of clinical presentation. Therefore, the use of cangrelor should be considered for the treatment of patients presenting with visible intracoronary thrombus who underwent PCI.

Declaration of Interest

Toby Rogers: Consultant: Medtronic.

Ron Waksman: Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., Cardioset; Consultant: Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., Cardioset; Grant Support: Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

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1. Gibson CM, Lemos JAde, Murphy SA, Marble SJ, McCabe CH, Cannon CP, Antman EM, Braunwald E. TIMI Study Group. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation* 2001;103:2550–2554.
2. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with st-segment elevation. *N Engl J Med* 2005;352:1179–1189.
3. Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, McCabe CH, Van De Werf F, Braunwald E. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000;101:125–130.
4. Porto I, Hamilton-Craig C, Brancati M, Burzotta F, Galiuto L, Crea F. Angiographic assessment of microvascular perfusion—myocardial blush in clinical practice. *Am Heart J* 2010;160:1015–1022.
5. Mauri L, Hsieh W, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;356:1020–1029.
6. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. *Eur Heart J* 2015;36:3320–3331.
7. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC, Halperin JL, Levine GN, Al-Khatib SM, Birtcher KK, Bozkurt B, Brindis RG, Cigarroa JE, Curtis LH, Fleisher LA, Gentile F, Gidding S, Hlatky MA, Ikonomidis JS, Joglar JA, Pressler SJ, Wijeysundera DN. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Thorac Cardiovasc Surg* 2016;152:1243–1275.
8. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimský P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Généreux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA. CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med* 2013;368:1303–1313.
9. Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: a direct, parenteral P2Y12 receptor antagonist. *J Clin Pharmacol* 2010;50:27–35.
10. Vaduganathan M, Qamar A, Singh A, Venkateswaran RV, Szumita PM, Croce KJ, Mauri L, Leopold JA, Shah PB, Sobieszczyk P, Faxon DP, Bhatt DL. Cangrelor use since FDA approval. *J Am Coll Cardiol* 2017;69:463–464.
11. Vaduganathan M, Qamar A, Badreldin HA, Faxon DP, Bhatt DL. Cangrelor use in cardiogenic shock. *JACC* 2017;10:1712–1714.
12. Baker NC, Lipinski MJ, Escarcega RO, Magalhaes MA, Minha S, Torguson R, Waksman R. Definitions of periprocedural myocardial infarction as surrogates for catheterization laboratory quality or clinical trial end points. *Am J Cardiol* 2014;113:1326–1330.
13. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winters WL. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 1988;78:486–502.
14. Ellis SG, Vandormael MG, Cowley MJ, DiSciascio G, Deligonul U, Topol EJ, Bulle TM. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study Group. *Circulation* 1990;82:1193–1202.
15. Ding S, Pu J, Qiao Z, Shan P, Song W, Du Y, Shen J-Y, Jin S, Sun Y, Shen L, Lim Y, He B. TIMI myocardial perfusion frame count: a new method to assess myocardial perfusion and its predictive value for short-term prognosis. *Catheter Cardiovasc Interv* 2010;75:722–732.
16. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Comm Stat - Simul Comput* 2009;38:1228–1234.
17. Jolly SS, James S, Džavík V, Cairns JA, Mahmoud KD, Zijlstra F, Yusuf S, Olivecrona GK, Renlund H, Gao P, Lagerqvist B, Alazzoni A, Kedev S, Stankovic G, Meeks B, Frøbert O. Thrombus aspiration in ST-segment—elevation myocardial infarction: an individual patient meta-analysis: Thrombectomy Trialists Collaboration. *Circulation* 2017;135:143–152.
18. Schulz S, Schuster T, Mehilli J, Byrne RA, Ellert J, Massberg S, Goedel J, Bruskina O, Ulm K, Schömig A, Kastrati A. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. *Eur Heart J* 2009;30:2714–2721.
19. Werkum JWvan, Heestermans AA, Zomer AC, Kelder JC, Suttorp M-J, Rensing BJ, Koolen JJ, Brueren BRG, Dambrink J-HE, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol* 2009;53:1399–1409.
20. Jolly SS, Cairns JA, Yusuf S, Rokoss MJ, Gao P, Meeks B, Kedev S, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Bernat I, Cantor WJ, Cheema. AN, Steg PG, Welsh RC, Sheth T, Bertrand OF, Avezum A, Bhindi R, Natarajan MK, Horak D, Leung RCM, Kassam S, Rao SV, El-Omar M, Mehta SR, Velianou JL, Pancholy S, Džavík V. TOTAL Investigators. Outcomes after thrombus aspiration for ST elevation myocardial infarction: 1-year follow-up of the prospective randomised TOTAL trial. *Lancet* 2016;387:127–135.
21. Witzenbichler B, Maehara A, Weisz G, Neumann F-J, Rinaldi MJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Brodie BR, Stuckey TD, Mazzaferri EL, Xu K, Parise H, Mehran R, Mintz GS, Stone GW. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation* 2014;129:463–470.
22. Prati F, Kodama T, Romagnoli E, Gatto L, Di Vito L, Ramazzotti V, Chisari A, Marco V, Cremonesi A, Parodi G, Albertucci M, Alfonso F. Suboptimal stent deployment is associated with subacute stent thrombosis: optical coherence tomography insights from a multicenter matched study. From the CLI Foundation investigators: the CLI-THRO study. *Am Heart J* 2015;169:249–256.
23. Garg P, Galper BZ, Cohen DJ, Yeh RW, Mauri L. Balancing the risks of bleeding and stent thrombosis: a decision analytic model to compare durations of dual antiplatelet therapy after drug-eluting stents. *Am Heart J* 2015;169:222–233. e5.
24. Friedland S, Eisenberg MJ, Shimony A. Meta-analysis of randomized controlled trials of intracoronary versus intravenous administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention for acute coronary syndrome. *Am J Cardiol* 2011;108:1244–1251.
25. Vaduganathan M, Harrington RA, Stone GW, Deliargyris EN, Steg PG, Gibson CM, Hamm CW, Price MJ, Menozzi A, Prats J, Elkin S, Mahaffey KW, White HD, Bhatt DL, Cura F, Ballarino M, Damonte AA, Grinfeld D, Álvarez CA, Fernandez A, Farshid A, Gunalingam B, Jeurgens C, Lowe H, Hallani H, Nelson G, New G, Dick R, Lefkovits J, Duffy S, Bett N, Yadav R, Garrahy P, Lehman R, Aylward P, Horowitz J, Worthley M, Cross D, Rankin J, Thompson P, Roberts-Thomson P, Cross D, Jayasinghe R, Aroney C, Huber K, Leisch F, Altenberger J, Gaul G, Neunteufl T, Weidinger F, et al. Cangrelor with and without glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2017;69:176–185.

26. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-LT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM. DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155–2166.
27. Généreux P, Stone GW, Harrington RA, Gibson CM, Steg PG, Brener SJ, Angiolillo DJ, Price MJ, Prats J, LaSalle L, Liu T, Todd M, Skerjanec S, Hamm CW, Mahaffey KW, White HD, Bhatt DL. CHAMPION PHOENIX Investigators. 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). *J Am Coll Cardiol* 2014;63:619–629.
28. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F-J, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, ESC Scientific Document GroupBadimon L, Vranckx P, Agewall S, Andreotti F, Antman E, Barbato E, Bassand J-P, Bugiardini R, Cikirikcioglu M, Cuisset T, De Bonis M, Delgado V, Fitzsimons D, Gaemperli O, Galiè N, Gilard M, Hamm CW, Ibanez B, Iung B, James S, Knuuti J, Landmesser U, Leclercq C, Lettino M, Lip G, Piepoli MF, Pierard L, Schwerzmann M, Sechtem U, Simpson IA, Uva MS, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018;39:213–260.
29. Schneider DJ. Transition strategies from cangrelor to oral platelet P2Y12 receptor antagonists. *Coron Artery Dis* 2016;27:65–69.
30. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. *Nat Rev Cardiol* 2016;13:11–27.