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ORIGINAL RESEARCH

Cangrelor Use Patterns and Transition to Oral $P2Y_{12}$ Inhibitors Among Patients With Myocardial Infarction: Initial Results From the CAMEO Registry

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BACKGROUND: In clinical trials, cangrelor has been shown to reduce percutaneous coronary intervention–related ischemic complications without increasing major bleeding. This study was performed to examine cangrelor use and transition to oral $P2Y_{12}$ inhibitors in routine clinical practice.

METHODS AND RESULTS: The CAMEO (Cangrelor in Acute Myocardial Infarction: Effectiveness and Outcomes) registry is a multicenter, retrospective observational study of platelet inhibition strategies for patients with myocardial infarction undergoing percutaneous coronary intervention. In phase 1, data were collected on consecutive patients with myocardial infarction (n=482) treated with any $P2Y_{12}$ inhibitor to understand cangrelor use by hospital. In phase 2, data were collected in a 2:1 (cangrelor-:non-cangrelor-treated) ratio of patients with myocardial infarction (n=873). In phase 1, cangrelor use varied across hospitals (overall, 50.4% [range, 6.0%–100%]). Of patients receiving cangrelor in both phases (n=819), 3.3% received either the bolus or infusion only. Cangrelor was infused for a median of 121 (76–196) minutes; and 38.3% received an infusion for <2 hours. Most patients transitioned from cangrelor to ticagrelor (ticagrelor, 85.3%; clopidogrel, 9.5%; prasugrel, 5.2%). Many patients (16.4%) had a >1-hour gap between cangrelor cessation and oral $P2Y_{12}$ inhibitor initiation; this was highest among those transitioned to clopidogrel (56.6% versus 34.5% prasugrel versus 10.8% ticagrelor; $P<0.001$). Only 27.3% were dosed with cangrelor and transitioned to an oral $P2Y_{12}$ inhibitor in a fashion consistent with the pivotal trials and US Food and Drug Administration label.

CONCLUSIONS: This multicenter registry demonstrated interhospital variability in how cangrelor was administered and transitioned to an oral $P2Y_{12}$ inhibitor. These findings highlight opportunities for optimization of cangrelor dosing, infusion duration, and transition of care from the catheterization laboratory to the ward setting.

Key Words: antiplatelet ■ cangrelor ■ myocardial infarction

Cangrelor, an intravenous direct-acting $P2Y_{12}$ receptor inhibitor, has been shown to provide rapid and potent inhibition of adenosine diphosphate–induced platelet aggregation.[1] Results from 3 large randomized trials found that cangrelor reduced percutaneous coronary intervention (PCI)-related ischemic complications without increasing major bleeding.[2,3] In the CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous

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CLINICAL PERSPECTIVE

What Is New?

- This is an early report of cangrelor use, dosing, and transition to oral $P2Y_{12}$ inhibitors in routine clinical practice.
- Significant interhospital variability in cangrelor use is observed, with only 27% patients dosed with cangrelor and transitioned to an oral $P2Y_{12}$ inhibitor in a fashion consistent with the pivotal trial and US Food and Drug Administration label and more than a third of patients treated with a cangrelor infusion shorter in duration than recommended by the package label (<2 hours).

What Are the Clinical Implications?

- This study identifies opportunities to improve $P2Y_{12}$ inhibitor transition among patients with myocardial infarction undergoing percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

ACTION	Acute Coronary Treatment and Intervention Outcomes Network
CAMEO	Cangrelor in Acute Myocardial Infarction: Effectiveness and Outcomes
CHAMPION PHOENIX	A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
FDA	Food and Drug Administration
MACE	major adverse cardiovascular event

Coronary Intervention) trial, the protocol specified that patients randomized to cangrelor were to have received a 30-μg/kg bolus, followed by a 4-μg/kg per minute infusion of cangrelor for at least 2 hours, and then were transitioned to an oral $P2Y_{12}$ inhibitor (clopidogrel) given as a loading dose at the time of cangrelor infusion discontinuation. The patients treated with cangrelor in this randomized clinical trial had a significantly lower risk of the primary composite efficacy end point of death, myocardial infarction (MI), ischemia-driven revascularization, or stent thrombosis at 48 hours compared with those randomized to clopidogrel alone.[2] With the approval of cangrelor, early $P2Y_{12}$ inhibition is now a feasible treatment strategy for both patients with ST-segment–elevation myocardial infarction (STEMI) and patients with non–ST-segment–elevation myocardial infarction (NSTEMI). However, there are few data on how cangrelor is used in routine practice.[4]

CAMEO (Cangrelor in Acute Myocardial Infarction: Effectiveness and Outcomes) is an ongoing registry designed to examine antiplatelet selection strategies and cangrelor use patterns among patients with acute MI with or without ST-segment elevation treated in real-world practice. Using data collected from diverse hospital practice settings, we aimed to describe the frequency and type of the patient population selected for treatment with cangrelor; examine adherence in real-world practice to cangrelor dosing and infusion duration established in clinical trials and consistent with the drug's US Food and Drug Administration (FDA) labeling; and evaluate the transition of patients from cangrelor to an oral $P2Y_{12}$ inhibitor. We hypothesized that there would be significant variation in the use of cangrelor by site, and that a significant number of patients would be administered cangrelor or transitioned to an oral $P2Y_{12}$ inhibitor in a manner inconsistent with that established in clinical trials and the drug's FDA labeling.

METHODS

The authors declare that all supporting data are available within the article. Each participating site obtained institutional review board approval.

Hospital Criteria

The CAMEO registry (NCT04076813) began in October 2019 and is an ongoing study among US centers that meet the following criteria: (1) capability to perform PCI and coronary artery bypass graft surgery; (2) minimum of 10 patients with MI treated monthly; and (3) minimum use of cangrelor in at least 2 patients with MI monthly. At the time of this analysis, 9 hospitals were included. Each hospital obtained approval for study participation from their local institutional review board. With anonymous data collection, the registry was conducted under a waiver of consent and Health Insurance Portability and Accountability Act authorization.

Study Population and Design

Nine hospitals with established use of cangrelor were selected for this registry. Sites were selected to represent a wide variety of types of US hospitals (academic versus nonacademic) with 6 of the 9 hospitals being large tertiary care academic centers. Two of these hospitals participated in the CHAMPION PHOENIX trial.[2] There was also a wide distribution of geographic locations. Two sites had protocols in place to help direct when cangrelor should be used for patients presenting with MI. For other sites, cangrelor use was largely left up to the discretion of the individual operators. Each hospital began participation in phase 1 of the registry by retrospectively collecting data on ≈50 consecutive patients within the 4 months before site activation who met the following criteria: (1) ≥18 years of age; (2) underwent coronary angiography for STEMI or NSTEMI; and (3) received any $P2Y_{12}$ inhibitor (cangrelor or oral) during the first 48 hours after hospitalization for MI. After completion of phase 1, each hospital proceeded to phase 2, in which data were collected in a 2:1 ratio for patients with MI treated with cangrelor and those not treated with cangrelor. Phase 2 was designed to focus on the evaluation of patients treated with cangrelor while compiling a contemporary "control cohort." Criteria for inclusion of patients not treated with cangrelor are shown in Table S1.

The design of the study is depicted in Figure 1. In phase 1 of the registry, each site screened patients retrospectively after hospital discharge based on relevant MI diagnosis and coronary angiography status within the 4 months before site activation. Phase 1 screening and data entry were expected to be completed within 2 months after site activation. In phase 2 of the registry, sites screened retrospectively beginning with patients who were discharged in the month following site activation. Sites screened at minimum monthly, for eligible patients who were discharged in the prior month.

Data Collection

Trained personnel at each hospital abstracted patient-level data into a web-based electronic data collection tool using standardized data definitions. Collected data included patient demographics, past medical history, MI admission features, medications taken within 24 hours before hospital arrival (including antiplatelet therapy, opioids, anticoagulants, thrombolytics, and glycoprotein IIb/IIIa inhibitors), in-hospital medications, in-hospital labs and imaging, and cardiac catheterization and PCI data. The data collection form also included in-hospital clinical events, discharge status, and medications prescribed at discharge. Bleeding events were captured in-hospital and up to 7 days postdischarge. All other events and complications captured in the registry were in-hospital and were not adjudicated.

Definitions

Sites were instructed to enter in the start and stop times for all medications, including $P2Y_{12}$ inhibitors, parenteral anticoagulants, glycoprotein IIb/IIIa inhibitors, thrombolytics, and opioids. The duration of cangrelor infusion was defined by the start and stop times indicated in the medication administration records. Cangrelor bolus dosing was entered in units of μg/kg, and infusion dosing was entered in units of μg/kg per minute.

As described in prior clinical trials of cangrelor as well as the prescribing information,[2,5–8] the

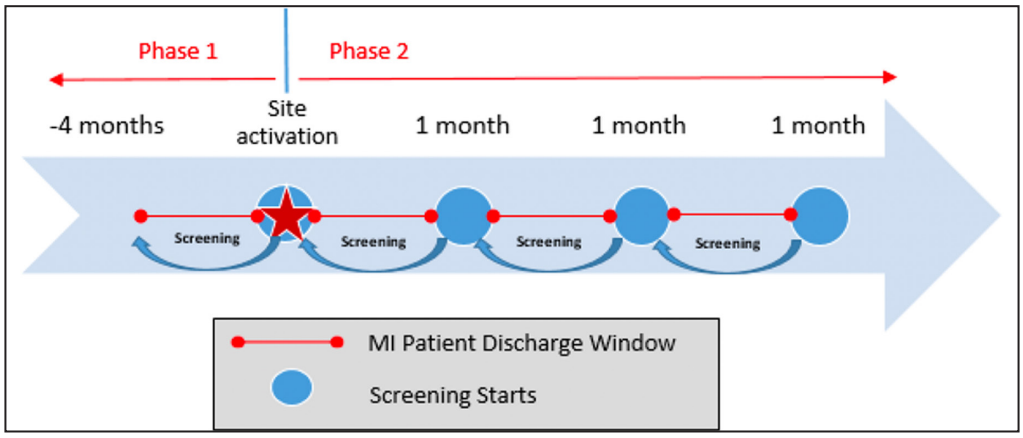

Figure 1. Screening and enrollment schema for phases 1 and 2. MI indicates myocardial infarction.

recommended dosage of cangrelor is a 30-μg/kg intravenous bolus followed by a 4-μg/kg per minute intravenous infusion for at least 2 hours or for the duration of PCI, whichever is longer. To maintain platelet inhibition, an oral $P2Y_{12}$ platelet inhibitor should be administered—ticagrelor 180 mg at any time during cangrelor infusion or immediately after discontinuation, or prasugrel 60 mg or clopidogrel 600 mg immediately after discontinuation of cangrelor.[7,8] Therefore, among patients without bleeding or recurrent MI before the end of PCI, we described the proportion of patients who received cangrelor consistent with the above established treatment strategy. If the cangrelor bolus dose was <29 μg/kg (as weight may be estimated rather than measured), infusion dose was <4 μg/kg per minute, infusion duration was <1.5 hours or >2.5 hours, or the oral $P2Y_{12}$ inhibitor was administered >1 hour after cangrelor discontinuation; these patients were defined as not being treated in a fashion consistent with the *established treatment strategy* based on how cangrelor was previously studied or is currently labeled.

Bleeding events were defined as any event associated with a hemoglobin drop ≥3 gm/dL; any event requiring blood transfusion (platelet or red blood cell); or any bleeding event that required an intervention or surgery to stop bleeding, such as surgical closures, exploration of the arteriotomy site, balloon angioplasty to seal an arterial tear, or endoscopy with cautery of a gastrointestinal bleed.[9] Bleeding was defined as major if the hemoglobin drop was ≥3 gm/dL, if a surgical intervention was required, an intravenous vasoactive agent was required, or if the patient required transfusion. Major adverse cardiovascular events (MACEs) are a composite of in-hospital recurrent MI, stroke, or death. Other in-hospital events captured hypertensive urgency/emergency, postcatheterization vasopressor or inotrope use, and if therapeutic hypothermia was indicated.

Statistical Analysis

We described the percentage of patients in phase 1 with STEMI and NSTEMI who were treated with cangrelor by site. Using data from all patients in phase 1 only, baseline demographic and clinical characteristics, home medications, presenting features, and procedural characteristics were compared between patients with STEMI treated with cangrelor versus those treated with an oral $P2Y_{12}$ inhibitor and patients with NSTEMI treated with cangrelor versus those treated with an oral $P2Y_{12}$ inhibitor. We then compared characteristics of cangrelor administration and duration among patients with STEMI and NSTEMI in both phases 1 and 2. We included both phases 1 and 2 in our description of cangrelor administration, duration, and transition, as all uses of cangrelor are described retrospectively. As such, the use and administration of cangrelor should not be impacted by whether the patient was enrolled in phase 1 or 2. Finally, we examined cangrelor infusion duration and transition patterns from cangrelor to oral $P2Y_{12}$ inhibitors, stratified by oral $P2Y_{12}$ inhibitor (ticagrelor versus prasugrel versus clopidogrel), among patients in phases 1 and 2 who transitioned to an oral $P2Y_{12}$ inhibitor after cangrelor infusion. *P* values were calculated using a Wilcoxon rank-sum test for continuous variables and a chi-square or Fisher's exact test for categorical variables.

We examined the association between any bleeding or MACE events and appropriate treatment, where appropriate treatment was defined as the patient's being treated with cangrelor with a transition to an oral $P2Y_{12}$ inhibitor in a fashion consistent with use in prior clinical trials. As there were few clinical events, for the bleeding events, we adjusted for potential confounders using a modified CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) bleeding risk score.[10] For MACE events, we adjusted for potential cofounders using a modified ACTION (Acute Coronary Treatment and Intervention Outcomes Network) mortality risk score.[11] Details about the modified risk scores and how they were calculated are listed in Data S1. For both clinical outcomes, we used logistic regression to calculate unadjusted and adjusted odds ratios (95% CIs) for appropriate treatment.

RESULTS

A total of 1355 patients were captured in the CAMEO registry between October 2019 and April 2021. There were 482 consecutive patients with MI included in phase 1. Of the 1355 patients from both phases 1 and 2, 567 presented with STEMI (41.8%).

The baseline characteristics of phase I patients with MI enrolled in the registry stratified by type of MI and cangrelor status are presented in Table 1. In patients with STEMI, there were few significant differences in baseline demographic and clinical characteristics between those who were and were not treated with cangrelor. Patients with STEMI treated with cangrelor were significantly less likely to be Hispanic compared with patients not treated with cangrelor (4.9% versus 18.4%; *P*=0.008). Additionally, patients with STEMI who were treated with cangrelor were significantly more likely to be smokers compared with those patients with STEMI not treated with cangrelor (45.9% versus 21.1%; *P*=0.006). These patients were more likely to have visualized thrombus on coronary angiography but were

Table 1. Baseline Demographic and Clinical Characteristics of Patients Treated With Cangrelor Versus Those Not Treated With Cangrelor Stratified by Type of MI

	STEMI			NSTEMI		
	Cangrelor (n=122)	No Cangrelor (n=38)	*P* value	Cangrelor (n=121)	No Cangrelor (n=201)	*P* value
Demographics						
Age, y, median (25th–75th percentile)	62 (53–70)	61 (56–78)	0.17	64 (56–72)	68 (58–75)	0.01
Female sex, n (%)	23 (18.9)	12 (31.6)	0.10	38 (31.4)	67 (33.3)	0.72
Non-White*, n (%)	33 (27.0)	14 (36.8)	0.25	55 (45.5)	112 (55.7)	0.07
Hispanic, n (%)	6 (4.9)	7 (18.4)	0.008	14 (11.6)	76 (37.8)	<0.001
Private health insurance, n (%)	58 (47.5)	19 (50.0)	0.79	66 (54.5)	83 (41.3)	0.02
Clinical history, n (%)						
Diabetes	37 (30.3)	16 (42.1)	0.18	50 (41.3)	91 (45.3)	0.49
Hypertension	79 (64.8)	28 (73.7)	0.31	90 (74.4)	174 (86.6)	0.006
Dyslipidemia	67 (54.9)	23 (60.5)	0.54	83 (68.6)	158 (78.6)	0.05
Prior MI	19 (15.6)	9 (23.7)	0.25	25 (20.7)	64 (31.8)	0.03
Prior PCI	23 (18.9)	8 (21.1)	0.76	22 (18.2)	85 (42.3)	<0.001
Prior CABG	4 (3.3)	1 (2.6)	0.84	7 (5.8)	40 (19.9)	<0.001
Prior HF	8 (6.6)	4 (10.5)	0.42	17 (14.0)	40 (19.9)	0.18
PAD	7 (5.7)	2 (5.3)	0.91	5 (4.1)	23 (11.4)	0.02
Stroke/TIA	10 (8.2)	4 (10.5)	0.66	5 (4.1)	21 (10.4)	0.04
Atrial fibrillation/flutter	4 (3.3)	3 (7.9)	0.22	3 (2.5)	26 (12.9)	0.002
Dialysis	2 (1.6)	2 (5.3)	0.21	4 (3.3)	14 (7.0)	0.17
Current/recent smoker	56 (45.9)	8 (21.1)	0.006	30 (24.8)	43 (21.4)	0.48
Chronic lung disease	16 (13.1)	3 (7.9)	0.39	11 (9.1)	19 (9.5)	0.91
Home medications, n (%)						
$P2Y_{12}$ inhibitors overall	13 (10.7)	6 (15.8)	0.393	24 (19.8)	61 (30.3)	0.038
Clopidogrel†	5 (38.5)	4 (66.7)		9 (37.5)	50 (82.0)	
Prasugrel†	1 (7.7)	1 (16.7)		0	0	
Ticagrelor†	7 (53.8)	1 (16.7)		15 (62.5)	11 (18.0)	
Oral anticoagulant	10 (8.2)	2 (5.3)	0.55	20 (16.5)	21 (10.4)	0.11
Presenting features						
Killip class IV, n (%)	11 (9.0)	3 (7.9)	0.83	4 (3.3)	1 (0.5)	0.048
Admission creatinine (mg/dL), mean (SD)	1.4 (1.8)	1.3 (1.5)	0.53	1.4 (1.8)	1.4 (1.4)	0.12
Admission hemoglobin g/dL, mean (SD)	14.5 (2.2)	14.1 (1.8)	0.18	13.6 (2.2)	13.3 (2.2)	0.23
Admission platelets (10^9/L), mean (SD)	256.6 (69.1)	251.4 (81.5)	0.35	248.2 (70.0)	242.8 (87.3)	0.19
LVEF <40%, n (%)	32 (29.6)	10 (29.4)	0.98	20 (20.0)	34 (19.1)	0.86
Procedural characteristics, n (%)						
PCI performed	119 (97.5)	36 (94.7)	0.39	115 (95.0)	144 (71.6)	<0.001
Signs/Symptoms present at time of PCI, n (%)						
Emesis	1 (0.8)	1 (2.8)	0.37	1 (0.9)	0.0	0.27
Active chest discomfort	41 (34.5)	8 (22.2)	0.17	19 (16.5)	23 (16.0)	0.91
ST elevation	50 (42.0)	13 (36.1)	0.53	4 (3.5)	4 (2.8)	0.75
Sustained VT/VF	9 (7.6)	2 (5.6)	0.68	2 (1.7)	1 (0.7)	0.44
Cardiogenic shock	18 (15.1)	2 (5.6)	0.13	4 (3.5)	2 (1.4)	0.27
Cardiac arrest	7 (5.9)	0	0.14	1 (0.9)	1 (0.7)	0.87

(*Continued*)

Table 1. Continued

	STEMI			NSTEMI		
	Cangrelor (n=122)	No Cangrelor (n=38)	*P* value	Cangrelor (n=121)	No Cangrelor (n=201)	*P* value
Thrombus visualized	70 (58.8)	13 (36.1)	0.02	49 (42.6)	14 (9.7)	<0.001
Bypass graft treated	0	1 (2.8)	0.07	3 (2.6)	7 (4.9)	0.35
Multivessel PCI performed	19 (16.0)	6 (16.7)	0.92	15 (13.0)	38 (26.4)	0.008
Thrombectomy	21 (17.6)	5 (13.9)	0.60	16 (13.9)	7 (4.9)	0.01
Mechanical circulatory support	15 (12.6)	3 (8.3)	0.48	8 (7.0)	6 (4.2)	0.32
Glycoprotein IIb/IIIa inhibitor	2 (1.6)	4 (10.5)	0.01	3 (2.5)	7 (3.5)	0.62

CABG indicates coronary artery bypass grafting; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Non-White indicates Black/African American, East Asian, South Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, other.

†Taken before admission. The percentage shown for clopidogrel, prasugrel, and ticagrelor are the percentage of overall P2Y12 inhibitor use prior to admission. For example, 42.9% of patients who received cangrelor and had a STEMI AND were on an oral P2Y12 inhibitor prior to admission received clopidogrel.

less likely to be treated with a glycoprotein IIb/IIIa inhibitor (Table 1) than patients not treated with cangrelor.

Patients treated with cangrelor presenting with NSTEMI were significantly younger with fewer comorbidities, such as stroke/transient ischemic attack and prior MI or PCI, compared with those not treated with cangrelor (Table 1). Patients with NSTEMI treated with cangrelor were more likely to have PCI performed (95.0% versus 71.6%; *P*<0.001), less likely to be taking a $P2Y_{12}$ inhibitor before admission, and more likely to have a thrombus visualized on coronary angiography and/or be treated with thrombectomy than patients not treated with cangrelor.

Among the 482 patients in phase 1, cangrelor use rates varied across hospitals (overall, 50.4% [range, 6.0%–100%]), and the use of cangrelor was higher in patients with STEMI compared with those with NSTEMI (76.3% versus 37.6; P≤0.0001). Figure 2 presents the variability in the use of cangrelor among consecutive patients with MI in phase 1 across hospitals.

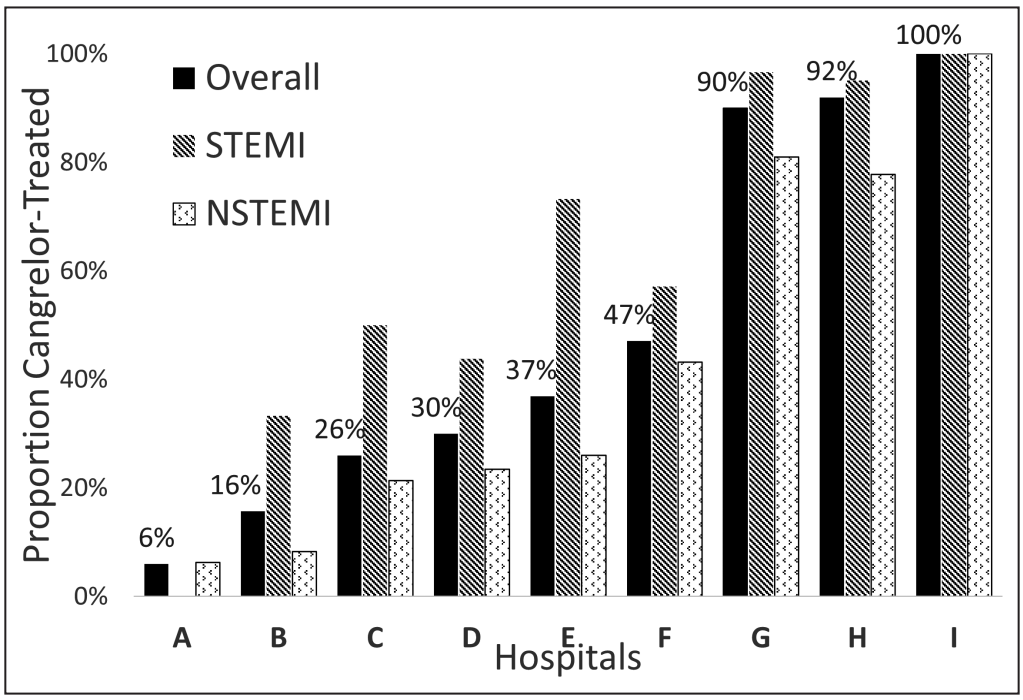

Figure 2. Variation in use of cangrelor among consecutive patients with MI in phase 1 across registry sites.

MI indicates myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

Characteristics of Cangrelor Administration and Infusion Duration

Among patients in phases 1 and 2 who received cangrelor (n=819), the vast majority of patients with STEMI and NSTEMI received both the bolus and infusion of cangrelor (STEMI, 96.2%; NSTEMI, 97.4%). A small number of patients received either the bolus or infusion only (Table 2). Additionally, 3.5% received a bolus dose less than the established dose, and 2.6% received an infusion dose <4 μg/kg per minute. The median duration of infusion was 121 (25th–75th percentile, 76–196) minutes and was similar for both STEMI and NSTEMI patients. Over one-third of patients (38.3%) treated with cangrelor received an infusion <2 hours with a significant difference between those with STEMI or NSTEMI (41.9% versus 33.5%, *P*=0.017). We observed wide interhospital variability across participating sites for the percentage of patients who received a cangrelor infusion for <2 hours (Figure 3). In 11% of patients, cangrelor infusion was discontinued before leaving the catheterization laboratory; there was also wide interhospital variability in this practice pattern (Figure 4).

Transition From Cangrelor to Oral $P2Y_{12}$ Inhibitors

Transition from cangrelor to an oral $P2Y_{12}$ inhibitor was examined among the 558 patients (68.1% of all cangrelor-treated patients) who did not receive any upstream oral $P2Y_{12}$ inhibitor before cangrelor use. The majority (90.5%) of these were transitioned to a higher-potency $P2Y_{12}$ inhibitor (clopidogrel, 9.5%; prasugrel, 5.2%; ticagrelor, 85.3%) (Table 3). There was a significant difference in the percentage of patients whose oral $P2Y_{12}$ inhibitor overlapped with the cangrelor infusion (clopidogrel, 28.3%; prasugrel, 65.5%; ticagrelor, 82.2%; *P*<0.001). Just under 17% of patients had a gap >1 hour between cangrelor cessation and oral $P2Y_{12}$ inhibitor initiation; this was highest among those transitioned to clopidogrel compared with those transitioned to prasugrel or ticagrelor (56.6% versus 34.5% versus 10.8%; *P*<0.001). There was also significant variation in the percentage of cangrelor-treated patients who received a loading dose of an oral $P2Y_{12}$ inhibitor (clopidogrel, 60.0%; prasugrel, 86.2%; ticagrelor, 94.3%). Few patients received an oral $P2Y_{12}$ inhibitor in the catheterization laboratory, with the lowest percentages in those who were transitioned to clopidogrel (clopidogrel, 2.3%; prasugrel, 20.7%; ticagrelor, 32.7%).

Table 2. Characteristics of Cangrelor Administration and Infusion Duration Among Patients Who Received Cangrelor

	Overall (N=819)	STEMI (n=470)	NSTEMI (n=349)
Bolus+infusion, n (%)	790 (96.7)	451 (96.2)	339 (97.4)
Bolus only, n (%)	14 (1.7)	11 (2.3)	3 (0.9)
Infusion only, n (%)	13 (1.6)	7 (1.5)	6 (1.7)
Oral $P2Y_{12}$ inhibitor use before hospitalization, n (%)	186 (13.7)	52 (9.2)	134 (17.0)
Infusion duration, median (25th–75th percentile), min	121 (76–196)	120 (66–235)	122 (98–187)
Infusion duration, minimum/maximum, min	9, 28 526	15, 28 526	9, 17 639
Infusion duration <2 h, n (%)	301 (38.3)	189 (41.9)	112 (33.5)
Infusion stopped in catheterization laboratory, n (%)	84 (11.0)	60 (13.5)	24 (7.5)

NSTEMI indicates non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

Cangrelor Use Consistent With the Established Treatment Strategy

The proportion of patients who received a cangrelor bolus and infusion at the trial-established dose and duration and transitioned to an oral $P2Y_{12}$ inhibitor according to FDA labeling after cangrelor discontinuation was low (27.3%). It was lowest among those transitioned to prasugrel and highest in those transitioned to ticagrelor (6.7% versus 31.2%). When stratified by whether the patient underwent treatment according to the established treatment strategy (including cangrelor bolus and infusion at the labeled doses with appropriate transition to an oral $P2Y_{12}$ inhibitor), 4.5% of patients treated according to the established treatment strategy had a bleeding event compared with 6.6% of patients not treated according to the established treatment strategy (adjusted odds ratio, 0.66; 95% CI, 0.31–1.41). Additionally, 6.3% of patients treated according to the established treatment strategy had a MACE event compared with 10.3% of patients not treated according to the established treatment strategy (adjusted odds ratio, 0.87; 95% CI, 0.43–1.76). Table 4 describes the event rates and adjusted odds ratios for clinical outcomes when comparing patients who underwent treatment according to the established treatment strategy versus those patients who underwent treatment not according to the established treatment strategy.

DISCUSSION

CAMEO is a multicenter registry established to examine the contemporary use of cangrelor and patterns of transitioning from cangrelor to oral $P2Y_{12}$ inhibitors in patients with MI. We have observed 3 important findings from this ongoing registry. First, we demonstrated

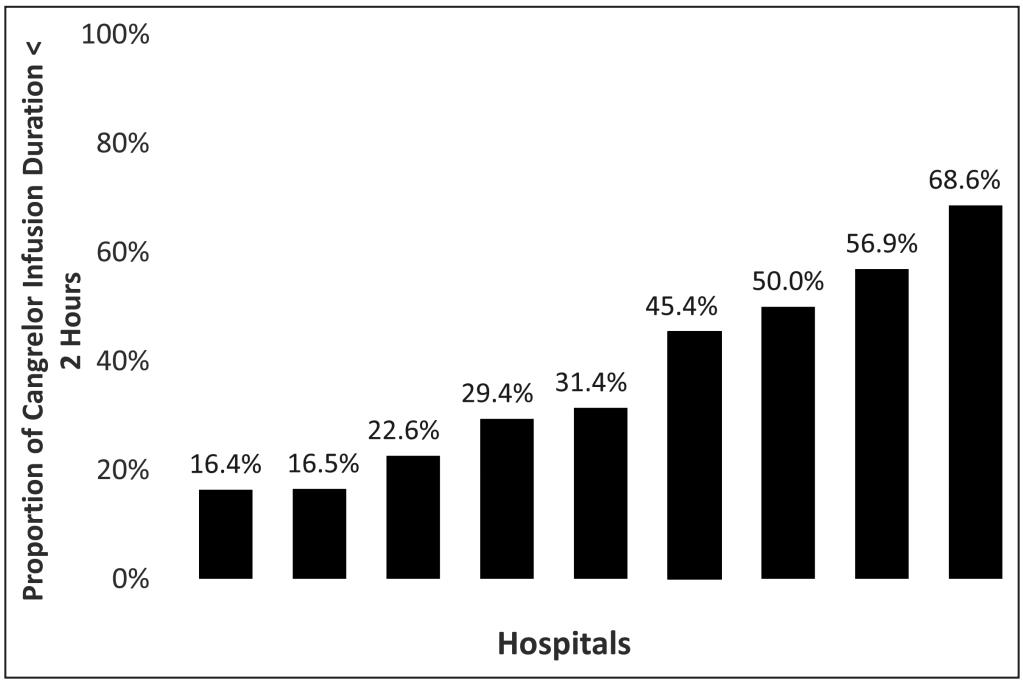

Figure 3. **Proportion of cangrelor infusion duration <2 hours by site.**

that there was significant interhospital variability in cangrelor use, with more patients with STEMI than NSTEMI treated with cangrelor. Second, we found that while the vast majority of cangrelor-treated patients received both the bolus and infusion, 38% of patients received an infusion shorter than the label-recommended 2-hour duration of the drug studied in clinical trials. Finally, we observed that many patients experienced a delay between discontinuation of the cangrelor infusion and initiation of the oral $P2Y_{12}$ inhibitor. In aggregate, only a quarter of patients treated with cangrelor received it and transitioned to oral therapy as recommended.

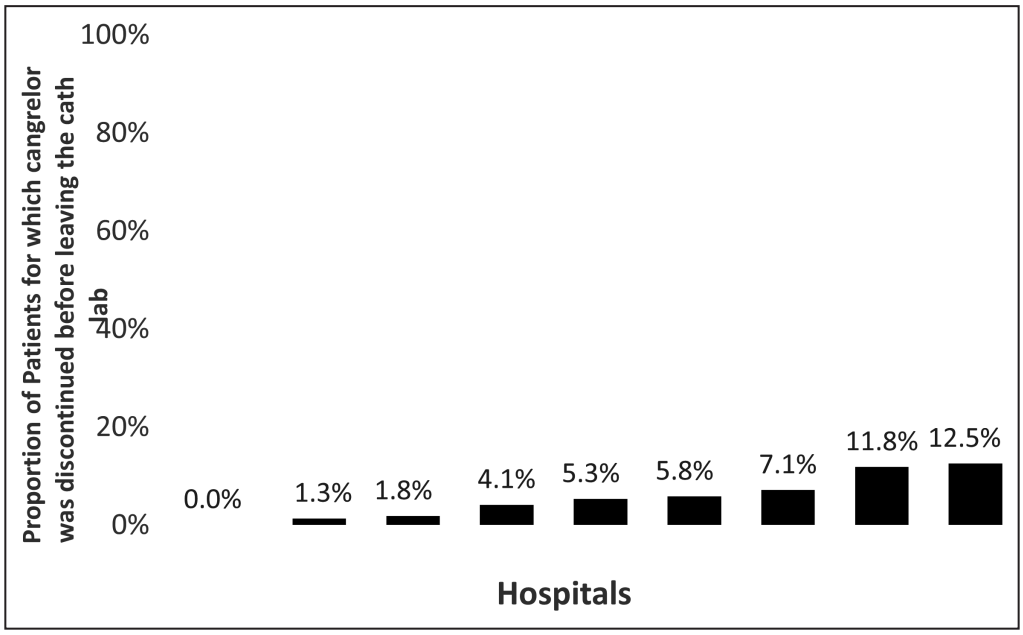

Figure 4. **Proportion of patients for which cangrelor was discontinued before leaving the catheterization laboratory.**

Table 3. Patterns of Transition From Cangrelor to Oral $P2Y_{12}$ Inhibitor (Without Upstream Treatment With an Oral $P2Y_{12}$ Inhibitor) Stratified by Oral $P2Y_{12}$ Inhibitor

	Ticagrelor (n=476)	Prasugrel (n=29)	Clopidogrel (n=53)	*P* value
Duration of cangrelor infusion, median (25th–75th percentile), min	120 (67 to 163)	74 (46 to138)	150 (74 to 907)	<0.001
Overlap between cangrelor infusion and oral $P2Y_{12}$ inhibitor, n (%)	379 (82.2)	19 (65.5)	15 (28.3)	<0.001
Overlap time between cangrelor infusion and oral $P2Y_{12}$ inhibitor, median (25th–75th percentile), min	−49* (−110 to −4)	0 (−14 to 115)	154 (0 to 1477)	<0.001
>1 h gap between cangrelor infusion discontinuation and oral $P2Y_{12}$ inhibitor administration, n (%)	50 (10.8)	10 (34.5)	30 (56.6)	<0.001
Oral $P2Y_{12}$ inhibitor loading dose given	446 (94.3)	25 (86.2)	30 (60.0)	<0.001
Oral $P2Y_{12}$ inhibitor given in catheterization laboratory	154 (32.7)	6 (20.7)	1 (2.3)	<0.001

*Negative minutes indicates that there was an overlap between the cangrelor infusion and administration of an oral $P2Y_{12}$ inhibitor.

While the first finding is to be expected, as practice pattern tends to vary in different health care settings,[12] the latter 2 merit discussion on how to optimize the adoption of therapies from clinical trials into routine practice to be consistent with FDA labeling and preserve the benefit demonstrated by clinical trials.

Cangrelor Administration Characteristics

Few studies have examined how bolus and infusion therapies are used in cardiovascular practice. Alexander and colleagues[13] analyzed the use of eptifibatide in acute coronary syndromes and found that dosing errors were common. In that study, 42% of patients had dosing of eptifibatide that did not conform with established dosing regimen. The dosing errors were predominantly seen among women and patients with reduced kidney function. Dosing discrepancies attributable to body weight tend to affect any acute therapy that has weight-adjusted dosing schemes as was already noticed with dosing of thrombolytic therapy in the 1990s.[14] However, in the CAMEO registry, we found that the differences were more related to practice patterns in infusion duration and subsequent oral loading with $P2Y_{12}$ therapy.

In the CHAMPION PHOENIX trial,[2] in which patients randomly assigned to a 30-μg/kg bolus and a 2-hour infusion of cangrelor and had a significantly lower rate of death, MI, ischemia-driven revascularization, or stent thrombosis compared with patients receiving clopidogrel alone, the median infusion duration was 129 minutes (interquartile range, 120–146 minutes). Prescribing information for the drug recommends an infusion of at least 2 hours or the duration of PCI, whichever is longer. However, more than a third of patients in the CAMEO registry received a cangrelor infusion of <2 hours, many of which were stopped in the catheterization laboratory. This real-world experience presents a challenge, as there are no pharmacodynamic studies or adequately sized clinical studies to assess the impact of abbreviated cangrelor therapy. As the CAMEO registry accrues patients, this will be an area of further research, but we recommend in the meantime that hospitals should follow the established dosing duration.

Transition to Oral $P2Y_{12}$ Therapy

In the CHAMPION PHOENIX trial,[2] all patients were transitioned to 600 mg of clopidogrel given immediately after the cessation of infusion, which is also reflected in the FDA label. Subsequent pharmacodynamic studies provided the established loading strategy with ticagrelor[15] and prasugrel.[16] Ticagrelor can be loaded (180 mg) at any time during the infusion, while prasugrel (60 mg) can be loaded immediately after infusion cessation.[7,8] In the CAMEO registry, we demonstrated that most patients treated with cangrelor in contemporary practice transitioned to ticagrelor. However, 50% of patients who transitioned to clopidogrel had a >1-hour gap between discontinuation of cangrelor and administration of clopidogrel. This occurred less frequently with prasugrel, where about one-third had a gap >1 hour, and with ticagrelor, where 1 in 10 patients had a gap >1 hour. These findings highlight a vulnerable period of antiplatelet interruption among patients with MI that are transitioned from cangrelor infusion to an oral $P2Y_{12}$ inhibitor with some of this explained by the transition of patients between care teams in the cardiac catheterization laboratory and the ward.

Consistency With Established Treatment Recommendations

When all the factors for the use of cangrelor with recommended bolus and infusion with appropriate oral loading were combined, only a quarter of patients were treated consistently with trial-established,

Table 4. Differences in Risks of Bleeding and Major Adverse Cardiovascular Events Between Cangrelor-Treated Patients Treated According to the Cangrelor Established Treatment Strategy vs Cangrelor-Treated Patients Not Treated According to the Established Treatment Strategy

Outcome	Cangrelor-treated patients who received established treatment strategy	Cangrelor-treated patients who did not receive established treatment strategy	Unadjusted		Adjusted*	
			odds ratio	95% CI	odds Ratio	95% CI
Bleed, n (%)	10 (4.5)	39 (6.6)	0.666	(0.327–1.358)	0.659	(0.308–1.409)
MACE, n (%)	14 (6.3)	61 (10.3)	0.584	(0.32–1.066)	0.868	(0.428–1.759)

ACTION indicates Acute Coronary Treatment and Intervention Outcomes Network CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; and MACE, major adverse cardiovascular event.
*Bleed adjusted for CRUSADE score, MACE adjusted for ACTION score.

FDA-approved recommendations. These findings are surprising and suggest that further quality improvement initiatives are required to address this gap in care. Such efforts are now in place in the registry to address this transition in care from leaving the cardiac catheterization laboratory. Some important lessons can be learned from the CAMEO registry.

The CAMEO registry findings suggest that there is an opportunity to explore the transition of care between the catheterization laboratory and intensive care unit in greater detail. The current process relies heavily on electronic health records, and no studies to date have focused on processes to effectively manage this transition and administration of acute time-sensitive therapies. The transition period between the catheterization laboratory and moving to the intensive care unit or to a hospital ward is a vulnerable time that has not previously been described. Nursing staff on the wards may be caring for other patients and focused on admitting and situating the patient so timely administration of an oral $P2Y_{12}$ inhibitor after PCI may be hard to execute. Our work suggests that each catheterization laboratory should develop a strategy that involves pharmacists and nurses for the appropriate use of cangrelor and loading of an oral $P2Y_{12}$ inhibitor. Additionally, increased education of interventional cardiologists, providers, pharmacists, and nurses is important to ensure that appropriate use and transition of cangrelor to an oral $P2Y_{12}$ inhibitor is achieved. Hospitals may also benefit from developing a protocol for cangrelor use that is posted in the catheterization laboratory and integrated into the electronic health record.

Use of Cangrelor Among Patients With MI

There was significant interhospital variability in cangrelor use across all sites, but cangrelor was used more frequently in patients presenting with STEMI compared with those with NSTEMI in all sites. While phase 2 of the registry is still ongoing, these findings likely result from an inability to achieve adequate upstream loading of platelet inhibition in the STEMI setting or because the STEMI population is often sicker, in shock, or intubated and there may be concerns about the ability for adequate absorption of oral $P2Y_{12}$ inhibitors, as has been noted in several studies.[4] We also noted that a quarter of patients received a cangrelor infusion for >6 hours, suggesting that in some sick patients the infusion duration has to be prolonged until oral loading can be done. More research on the sickest patients needs to be performed, as suggested by others to better explore prolonged infusions of cangrelor.[17]

Clinical Outcomes With and Without Established Dosing With Transition to Oral Therapy

The ischemic and bleeding composite outcomes among those treated with established dosing and transition versus not so treated are presented. They should be interpreted with caution, as evidenced by the wide CIs. While numerically better for those appropriately treated these findings need to be further analyzed with the eventual larger patient cohort from the CAMEO registry. This analysis represents just under half of the targeted enrollment in the registry (≈3000 patients). It remains to be seen if a difference between the groups will be observed as more patients are enrolled in the registry and more bleeding or MACE events are collected.

Limitations

There are several important limitations of this study. While the study protocol called for consecutive patients with MI to be enrolled in phase 1, occasional patients may have been missed. Additionally, only 9 of a total of 12 sites were enrolled at the time of this analysis. However, we felt it was important to publish these initial results now, as suboptimal use and transition to oral therapy were frequently identified, and it would be important that physicians potentially prescribing cangrelor be aware of these and modify their practices. In this analysis, we selected a duration of cangrelor infusion

consistent with the FDA package insert (2 hours), recognizing that in the randomized trials up to 4 hours of cangrelor infusion could be used for prolonged PCI. Such long PCI cases are rare in practice and our study showed that, in fact, shorter durations of cangrelor infusion than specified in the FDA label were used at many sites. Performance and clinical processes at these sites may differ from other sites/hospitals around the country, but many of the sites perform research or are academic sites.

CONCLUSIONS

This multicenter registry demonstrated significant interhospital variability in cangrelor dosing and subsequent administration of oral $P2Y_{12}$ inhibitors. These findings highlight the opportunities for optimization of cangrelor dosing, infusion duration, and transition to an oral $P2Y_{12}$ inhibitor in routine clinical practice to better mimic the regimen used in clinical trials and recommended in the FDA labeling.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Table S1

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SUPPLEMENTAL MATERIAL

Data S1.

Models and Covariates Used for Adjusted Bleeding and MACE Outcomes

Bleeding. We used a modified CRUSADE bleeding risk score. We included sex, history of vascular disease, history of diabetes, and signs of CHF, hematocrit (hemoglobin x 3), and creatinine clearance (captured using the Cockcroft-Gault equation with creatinine). For systolic blood pressure, we examined the points assigned to various systolic blood pressures through the CRUSADE bleeding risk score. If the patient received a post-cath vasopressor or inotrope ("yes") on the data collection form, we assigned them a score of 10 on systolic blood pressure for (sbp<90). If yes was checked for hypertensive urgency/emergency on the data collection form, we assigned the patient a score of 3 (corresponding to bp over 180). If they don't use either a vasopressor or have hypertensive emergency, we assigned them a score of 5 for systolic blood pressure. We did not capture heart rate in the data collection form, so did not include this in the calculation of the patient's bleeding risk score.

MACE. We used a modified ACTION mortality risk score. We included age, baseline serum creatinine, admission troponin with the ULN for the baseline troponin ratio, and prior PAD from the data collection form. We used Killip class 1 from the data collection form to correspond to no HF. We used Killip class II and III to correspond to HF only, and Killip class IV to correspond to shock. For systolic blood pressure, if the patient received a post-cath vasopressor or inotrope ("yes") in the data collection form, we assigned them a score of 19 on systolic blood pressure for (sbp<90). If yes was checked for hypertensive urgency/emergency, we assigned the patient a score of 2 (corresponding to bp over 180). If they didn't get either one (vasopressor of hypertensive emergency) we assigned the patient a score of 11. We did not have information on heart rate, so excluded this. If the patient had a STEMI from the data collection form information, we assigned them a score of 6 to correspond to ST changes under ECG findings. We were not able to assign any other values for ECG findings, based on our information from the data collection form.

Table S1. Inclusion criteria for patients enrolled in phase I or phase II.

Phase I
For the first 50 consecutive patients entered in the registry at each site, the following criteria are required: • Age ≥18 years • Underwent coronary angiography for a STEMI or NSTEMI • Either received cangrelor at any point during the MI hospitalization or an oral P2Y12 inhibitor during the first 48 hours of the MI hospitalization.
Phase II

Age >18 years who underwent coronary angiography for STEMI or NSTEMI and meet at least one of the following criteria:
 	
1. The patient was hospitalized for STEMI and met one of the following inclusion criteria:
• The patient received cangrelor at any time during his/her hospitalization for MI.
• In the absence of cangrelor use, the patient received an oral P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) during his/her MI hospitalization AND either of the following:
  • The patient received an opiate/opioid within 24 hours prior to or during primary PCI for STEMI presentation.
  OR
  • The patient underwent coronary angiography followed by CABG during the index MI admission and received any P2Y12 inhibitor within 7 days prior to CABG.
  •
2. The patient was hospitalized for NSTEMI and met one of the following inclusion criteria:
• The patient received cangrelor during his/her hospitalization for MI.
• In the absence of cangrelor use, the patient received an oral P2Y12 inhibitor during his/her MI hospitalization AND either of the following:
  • The patient underwent coronary angiography followed by CABG during the index MI admission and received any P2Y12 inhibitor within 7 days prior to CABG.
  OR
  • Any 2 of the following criteria without prior PCI or CABG: age > 60 years, male sex, diabetes, EF <40% prior heart failure