CONTEMPORARY REVIEW

Cangrelor: Clinical Data, Contemporary Use, and Future Perspectives

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ABSTRACT: Cangrelor is the only currently available intravenous platelet P2Y<sub>12</sub> receptor inhibitor. It is characterized by potent, predictable, and rapidly reversible antiplatelet effects. Cangrelor has been tested in the large CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) program, where it was compared with different clopidogrel regimens, and it is currently indicated for use in patients with coronary artery disease undergoing percutaneous coronary intervention. However, the uptake of cangrelor use varies across the globe and may also include patients with profiles different from those enrolled in the registration trials. These observations underscore the need to fully examine the safety and efficacy of cangrelor in postregistration studies. There are several ongoing and planned studies evaluating the use of cangrelor in real-world practice which will provide important insights to this extent. The current article provides a review on the pharmacology, clinical studies, contemporary use of cangrelor in real-world practice, a description of ongoing studies, and futuristic insights on potential strategies on how to improve outcomes of patients undergoing percutaneous coronary intervention.

Key Words: acute coronary syndromes • cangrelor • percutaneous coronary intervention

The ADP P2Y<sub>12</sub> receptor subtype plays a key role in platelet activation and amplification processes. The pivotal role of this platelet signaling pathway is supported by a plethora of studies conducted over the past 2 decades showing that the use of P2Y<sub>12</sub> receptor inhibitors in adjunct to aspirin, in high-risk patients with coronary artery disease (CAD), such as those undergoing percutaneous coronary interventions (PCIs) or presenting with an acute coronary syndrome (ACS), significantly reduces short- and long-term ischemic events. Most investigations have been conducted with oral formulations of P2Y<sub>12</sub> inhibitors. Although clopidogrel is the most commonly used oral P2Y<sub>12</sub> inhibitor, it is characterized by impaired platelet inhibitory effects in a considerable number of patients. Prasugrel and ticagrelor are more potent oral P2Y<sub>12</sub> inhibitors compared with clopidogrel and associated with greater efficacy, albeit at the expense of increased bleeding risk. However, pharmacodynamic studies have shown a gap in their onset of action, especially in patients with ST-segment–elevation myocardial infarction (STEMI) or hemodynamic impairment, underlining the need for intravenous therapies with a prompt and potent onset of action.

Cangrelor is an intravenous platelet P2Y<sub>12</sub> antagonist characterized by a rapid onset of action and achieving potent P2Y<sub>12</sub> inhibitory effects. Moreover, because of its short half-life and reversibly binding properties, cangrelor has a fast offset of effects. Cangrelor was approved on the basis of its superior efficacy in reducing thrombotic complications compared with clopidogrel in patients undergoing PCI. Accordingly, its use has increased in real-life world practice. Although its clinical efficacy compared with potent oral P2Y<sub>12</sub> inhibitors (ie, prasugrel and ticagrelor) has not been explored, pharmacodynamic studies have shown that cangrelor overcomes limitations of oral therapies by achieving fast and potent platelet inhibition. Pharmacodynamic studies have also allowed to better define the optimal approach to transition from cangrelor to oral P2Y<sub>12</sub> inhibiting
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therapy.18–21 The current article provides a review of pharmacology, clinical studies, contemporary use of cangrelor in real-world practice, a description of ongoing studies, and futuristic insights on potential strategies on how to improve outcomes of patients undergoing PCI.

CANGRELOR: FROM PHARMACOLOGY TO CLINICAL OUTCOMES DATA

Pharmacology
Cangrelor is the only intravenous P2Y12 receptor antagonist approved for use in patients with CAD undergoing PCI.22 Cangrelor is a nonthienopyridine ATP analog acting as a direct, reversible P2Y12 receptor antagonist.23 Maximum concentrations of cangrelor, which are associated with extensive platelet blockade, are rapidly achieved with the use of an intravenous bolus, followed by a continuous infusion, reaching maximum serum concentration (Cmax) within 2 minutes.23 Cangrelor has a half-life of 3 to 6 minutes because of its relatively rapid hydrolysis to its inactive metabolite.23 Cangrelor markedly inhibits ADP-induced platelet aggregation throughout the duration of infusion.23 It has a rapid offset of effect after discontinuation of its infusion, with platelet function returning to normal within 60 minutes (Figure 1).23 These pharmacologic properties make cangrelor not only an attractive agent for protection of ischemic events in patients undergoing PCI, but also a safe one in case of procedural complications, such as bleeding or need for emergent surgery, given its fast offset of effects, obviating the need for an antidote for reversal.24–26

Cangrelor is associated with high P2Y12 receptor occupancy, thus not allowing for other agents to bind with the receptor.22 The active metabolites of the thienopyridines, clopidogrel and prasugrel, are unstable and have a limited half-life. For this reason, if thienopyridines are given during cangrelor infusion or when cangrelor is still present at a high concentration in the blood, the active metabolites will not be able to bind to the P2Y12 receptor, preventing them from achieving any antiplatelet effects and ischemic protection.27 Accordingly, thienopyridines, in particular clopidogrel, should be administered immediately after discontinuation of cangrelor infusion.18,28 Prasugrel can be administered immediately after or up to 30 minutes before cangrelor infusion is discontinued.18,21 The reason for the latter is prasugrel generates more active metabolite than clopidogrel, which remains in circulation for a slightly longer time.18 Although some investigations did support the feasibility of administering prasugrel at the start of cangrelor infusion, these studies were not designed to rule out a drug interaction29,30 and thus this is a strategy that is not recommended. On the other hand, ticagrelor is a derivative of ATP, with a half-life ranging from 8 to 12 hours, and, like cangrelor, it binds

Nonstandard Abbreviations and Acronyms

| Abbreviation | Description |
|--------------|-------------|
| ARCANGELO | Italian Prospective Study on Cangrelor |
| BRIDGE | The Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery |
| CAMEO | Cangrelor in Acute Myocardial Infarction: Effectiveness and Outcomes |
| CANTIC | Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention |
| CHAMPION | Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition |
| DAPT-SHOCK-AMI | Dual Antiplatelet Therapy for Shock Patients With Acute Myocardial Infarction |
| FABOLUS-FASTER | Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients With ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention |
| GPI | glycoprotein IIb/IIa inhibitor |
| IDR | ischemia-driven revascularization |
| MARS | Management of Antiplatelet Regimen During Surgical Procedures |
| MONET BRIDGE | Maintenance of Antiplatelet Therapy in Patients With Coronary Stenting Undergoing Surgery |
| ST SWAP | Switching Anti Platelet |

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reversibly to the platelet $P_2Y_{12}$ receptor. For these reasons, ticagrelor can be administered before or during the infusion of cangrelor without resulting in a drug interaction.

The ongoing SWAP (Switching Anti Platelet)-5 (ClinicalTrials.gov Identifier: NCT04634162) and SWAP-6 (ClinicalTrials.gov Identifier: NCT04668144) studies will further clarify the pharmacodynamic effect of the transition from cangrelor to ticagrelor and prasugrel, respectively.

### Registration Trials Leading to Approval of Cangrelor

The efficacy of cangrelor was assessed in the large phase 3 CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) program that included 3 randomized controlled trials and >25 000 patients: PCI, PLATFORM, and PHOENIX (Table). The first 2 studies, CHAMPION PCI and CHAMPION PLATFORM, randomized patients to cangrelor (bolus of 30 µg/kg plus infusion of 4 µg/kg per minute) or clopidogrel (loading dose of 600 mg) either before or soon after PCI in patients with ACS, but both were stopped prematurely for futility. No difference in the primary composite of death, myocardial infarction (MI), or ischemia-driven revascularization (IDR) at 48 hours was observed in either study. These neutral outcomes were mostly attributed to the definition of MI, a key driver of outcomes in PCI trials. Indeed, MI was defined as the presence of new Q waves in 2 contiguous ECG leads, cardiac biomarkers at least 3 times the upper limit of normal, or ≥50% increase above baseline when biomarkers were initially elevated.

In a post hoc analysis, data from 13 000 patients enrolled in both studies were pooled, and the prevalence of periprocedural MI was calculated according to the universal definition (ie, elevations of cardiac biomarkers ≥3 times the 99th percentile upper limit of normal in patients with normal baseline troponin values). Instead, in case of abnormal troponin levels at baseline, only Q-wave MIs were included. Notably, compared with clopidogrel, treatment with cangrelor resulted in significant reduction in early ischemic events under the universal definition of MI (odds ratio [OR], 0.82; 95% CI, 0.68–0.99; $P=0.037$). This finding has important clinical implications, because periprocedural MI, according to contemporary definitions, is associated with an increase in all-cause mortality rate at 10 years following PCI.

In this regard, in CHAMPION PLATFORM, which was a true placebo-controlled trial in that clopidogrel
Table 1. Summary of Published and Ongoing Randomized and Observational Studies Assessing the Clinical Benefits of Cangrelor

| Study Name | No. of Patients | Treatment | Type of Patients | Outcomes |
|------------|-----------------|-----------|-----------------|----------|
| **Randomized studies** | | | | |
| CHAMPION PCI | 8877 | Cangrelor (arm A) vs clopidogrel, 600 mg (arm B), before PCI | Patients undergoing PCI (SA, 5.2%; UA, 35.4%; NSTEMI, 59.4%) | Death/MI/IDR at 48 h
Arm A vs arm B: 7.5% vs 7.1%; \(P=0.59\)
Major bleeding at 48 h (arm A vs arm B):
ACUITY criteria: 3.6% vs 2.9%; \(P=0.06\)
GUSTO criteria: 0.2% vs 0.3%; \(P=0.82\)
TIMI criteria: 0.4% vs 0.3%; \(P=0.39\) |
| | | | | Major bleeding at 48 h (arm A vs arm B):
ACUITY criteria: 3.6% vs 2.9%; \(P=0.06\)
GUSTO criteria: 0.2% vs 0.3%; \(P=0.82\)
TIMI criteria: 0.4% vs 0.3%; \(P=0.39\) |
| CHAMPION PLATFORM | 5362 | Cangrelor (arm A) vs placebo (arm B) during PCI, followed by clopidogrel, 600 mg | Patients undergoing PCI (SA, 15.1%; UA, 24.7%; NSTEMI, 49.2%; STEMI, 11.0%) | Death/MI/IDR at 48 h
Arm A vs arm B: 7.0% vs 8.0%; \(P=0.17^*\)
ST at 48 h
Arm A vs arm B: 0.2% vs 0.6%; \(P=0.02\)
Death from any cause at 48 h
Arm A vs arm B: 0.2% vs 0.7%; \(P=0.02\)
Severe bleeding (GUSTO) at 48 h
Arm A vs arm B: 0.2% vs 0.1%; \(P=0.44\) |
| CHAMPION PHOENIX | 10,942 | Cangrelor (arm A) vs clopidogrel, 300/600 mg (arm B), before PCI | Patients undergoing PCI (SA, 57.0%; NSTEMI, 25.4%; STEMI, 17.6%) | Death/MI/IDR/ST at 48 h
Arm A vs arm B: 4.7% vs 5.9%; \(P=0.005\)
ST at 48 h
Arm A vs arm B: 0.8% vs 1.4%; \(P=0.01\)
Severe bleeding (GUSTO) at 48 h
Arm A vs arm B: 0.2% vs 0.1%; \(P=0.44\) |
| BRIDGE | 210 | Cangrelor (arm A) vs placebo (arm B) | Patients with ACS or with a coronary stent on a thienopyridine awaiting CABG (NSTEMI, 44.5%; STEMI, 11.9%; SA, 44.6%) | Proportion of patients with PRU <240
Arm A vs arm B: 98.8% vs 91.0%; \(P=0.001\)
Excessive CABG surgery-related bleeding
Arm A vs arm B: 11.8% vs 10.4%; \(P=0.76\) |
| **Observational studies** | | | | |
| Vaduganathan et al | 100 | Cangrelor by US SPC | Patients with ACS (STEMI, 52%; NSTEMI, 40%; SA, 7%; other, 6%) | At 48 h
1 ST; no deaths or major bleeding (GUSTO criteria) |
| | 38 | Cangrelor by US SPC | Patients with GS (PCI for ACS, 82%; bridging to surgery, 13%; other reasons, 5%) | At 48 h:
No ST, deaths, or major bleeding (GUSTO criteria) |
| Grimfjärd et al | 915 | Cangrelor by EU SPC | Patients undergoing PCI (STEMI, 98.2%; NSTEMI, 1.8%) | At 30 d
All-cause mortality: 15.1%; ST: 0.7% |
| **Ongoing randomized studies** | | | | |
| Cangrelor OHCA (NCT04005729) | 30 | Cangrelor+ticagrelor vs ticagrelor | Comatose survivors of OHCA undergoing PCI | PRU; bleeding (BARC criteria); final TIMI flow; ST at 30 d; mortality at 90 d |
| MONET BRIDGE (NCT03862651) | 140 | Cangrelor vs placebo | Patients requiring discontinuation of P2Y12 inhibitor because of a significant bleeding risk | Residual PRU; bleeding (BARC criteria) |
| DAPT-SHOCK-AMI (NCT03551964) | 304 | Cangrelor vs ticagrelor | Patients with MI and CS requiring PCI | Composite death/MI/stroke; PRU; composite death/MI/urgent revascularization; bleeding (BARC criteria); ST; death; MI; stroke; urgent revascularization; duration of hospitalization; surgery delay because of bleeding |

(Continued)
loading was performed after the PCI, there were significant reductions in the secondary end points of stent thrombosis (ST) and mortality.

On that basis, another trial was designed, the CHAMPION PHOENIX (Figure 2), where a scrupulous assessment of MI, according to the universal definition, was prospectively implemented.\textsuperscript{41} The trial was conducted across the spectrum of CAD manifestations (ie, stable CAD and ACS) in patients who were P2Y\textsubscript{12} naïve and undergoing PCI. Cangrelor significantly reduced the primary end point of death, MI, IDR, or ST at 48 hours (OR, 0.78; 95% CI, 0.66–0.93; \textit{P}=0.005) and the key secondary end point of ST (OR, 0.62; 95% CI, 0.43–0.90; \textit{P}=0.01) compared with clopidogrel. In particular, cangrelor decreased the occurrence of intraprocedural ST (defined as the development of new or increasing thrombus in or adjacent to an implanted stent during the PCI procedure) that is associated with a significant increase in mortality, MI, IDR, and definite or probable ST at 48 hours and at 30 days.\textsuperscript{42} A large-scale, blinded angiographic core laboratory-based analysis studied the association between clinical outcomes of the CHAMPION PHOENIX trial and high-risk PCI target lesion features. It showed that cangrelor consistently reduced the rate of major adverse cardiac events at 48 hours compared with clopidogrel, and it showed a greater absolute effect with the increase of complex coronary lesions treated.\textsuperscript{43} These findings suggest that the clinical benefits of cangrelor could be greatest during PCI in patients with complex coronary anatomy. The rate of the primary safety end point of site-reported Global Use of Strategies to Open Occluded Coronary Arteries—defined severe bleeding or in the rate of transfusions was not increased in patients randomized to cangrelor,\textsuperscript{44} even in patients who received unfractionated heparin or glycoprotein IIb/IIIa inhibitors (GPIs) during PCI.\textsuperscript{45,46} Notably, the incidence of major bleeding events, according to the Global Use of Strategies to Open Occluded Coronary Arteries or the more sensitive Acute Catheterization and Urgent Intervention Triage Strategy definition, was comparable between cangrelor and clopidogrel, even when PCI was performed via the radial artery (26% of the overall population).\textsuperscript{47}

| Study Name       | No. of Patients | Treatment | Outcomes                                                                 |
|------------------|-----------------|-----------|--------------------------------------------------------------------------|
| CAMEO (NCT0076813) | 3000            | Cangrelor | Number of antiplatelet medications used and bleedings occurring during hospitalization |
| MARS (NCT0083639)  | 1492            | DAPT     | Number of antiplatelet medications used and bleedings occurring during hospitalization |
| ARCANGELO (NCT04747870) | 1000        | Cangrelor | Number of antiplatelet medications used and bleedings occurring during hospitalization |

\textbf{Table 1.} Continued...
sensitivity analyses, the effectiveness of cangrelor was consistent, according to alternative end point definitions and patients’ subgroups, including those with a diagnosis of ACS.

**Additional Studies of Cangrelor**

Recent studies assessed the pharmacodynamic efficacy of cangrelor in patients with STEMI. The CANTIC (Platelet Inhibition With Cangrelor and Crushed Ticagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) study was a prospective, randomized, double-blind, placebo-controlled investigation of the pharmacodynamic effects of cangrelor versus placebo in patients undergoing primary PCI treated with crushed 180-mg loading dose of ticagrelor. Cangrelor reduced platelet inhibition after just 5 minutes, with an effect that persisted throughout the infusion and without any drug interactions with ticagrelor given concomitantly with cangrelor at the start of the PCI, proving to be an effective strategy in bridging the latency of platelet inhibition of oral drugs during primary PCI. These findings are consistent with other investigations supporting prompt, potent, and sustained platelet inhibition of cangrelor during primary PCI, with important practical implications, especially for patients needing opioids that decrease gastrointestinal motility, contributing to delays in absorption and action of oral P2Y₁₂ inhibitors.

Most recently, however, a randomized prospective investigation (FABOLUS-FASTER [Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients With ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention]) failed to show potent platelet inhibitory effects associated with cangrelor, resulting in lower platelet inhibition compared with tirofiban, yet greater than that achieved with prasugrel. The counterintuitive finding with respect to tirofiban versus cangrelor may have to do with issues pertaining to the suboptimal methods used to assess platelet inhibition.

The rapid onset and offset of action of cangrelor make it an attractive agent for bridging among patients with recent stent implantation who need to undergo nondeferrable surgery and in whom discontinuation of oral P2Y₁₂ inhibition is required. To this extent, the prospective, randomized, double-blind, placebo-controlled, multicenter BRIDGE (The Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery) trial was conducted, involving 210 patients treated with a thienopyridine awaiting coronary artery bypass grafting. This trial was preceded by a dose-findings study that identified the optimal bridging regimen of cangrelor bolus and infusion to be 0.75 μg/kg per minute. In a trial comparing cangrelor with placebo in bridging antplatelet therapy, infusion was maintained for at least 48 hours and up to 7 days during washout from oral thienopyridine therapy; the infusion was discontinued 1 to 6 hours before coronary artery bypass grafting. A greater proportion of patients treated with cangrelor had
low levels of platelet reactivity throughout the entire treatment period compared with placebo. Despite numerically higher incidence of minor bleeding with cangrelor, results demonstrated no significant differences in major bleeding before or during coronary artery bypass grafting surgery.33 Although the use of cangrelor as a bridging agent is not an approved indication by the Food and Drug Administration or European Medical Agency, it is commonly used with this intent in patients with recent stent implantation requiring both cardiac and noncardiac surgery.22,53–56 Moreover, its use as a bridging agent is currently recommended in several expert consensus recommendations.57,58 Nevertheless, recent data suggesting the safety of early discontinuation of dual antiplatelet therapy after PCI59 might change future consensus recommendations for bridging.

### Indications and Dosage

Cangrelor is currently available in the United States and most European countries. According to the Food and Drug Administration, cangrelor is approved as an adjunct to PCI for reducing the risk of periprocedural MI, repeated coronary revascularization, and ST in patients not treated with an oral P2Y12 inhibitor and not planned to receive a GPI.60 Cangrelor should be administered as a bolus of 30 µg/kg, before initiation of the PCI procedure, followed by an infusion of 4 µg/kg per minute for at least 2 hours or through the duration of the intervention, whichever is longer.60 To maintain platelet inhibition after discontinuation of cangrelor infusion, an oral P2Y12 platelet inhibitor should be administered as follows60: clopidogrel, 600 mg, immediately after discontinuation of cangrelor; prasugrel, 60 mg, immediately after discontinuation of cangrelor; or ticagrelor, 180 mg, at any time during cangrelor infusion or immediately after discontinuation. The American College of Cardiology/American Heart Association guidelines do not provide any recommendations on the use of cangrelor because the drug was approved only after the most recent guideline updates3 (Figure 3). Cangrelor was approved by European Medical Agency for the reduction of thrombotic cardiovascular events in patients with CAD undergoing PCI who have not received an oral P2Y12 inhibitor before PCI and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.61 The European Medical Agency additionally specifies that the infusion must not exceed 4 hours.61 The 2020 European Society of Cardiology Guidelines for the management of ACS without persistent ST-segment elevation suggest the use of cangrelor during PCI (class of recommendation IIb; level of evidence A) and confirm that the timing of administration of oral P2Y12 inhibitors in patients receiving cangrelor infusion at the time of PCI should be drug specific.62,63

### REAL-WORLD USE OF CANGRELOR

Real-world evidence on cangrelor includes initial clinical experiences and large health system analyses. In a US single-center analysis of 147 consecutive cangrelor-treated patients undergoing coronary angiography with the intent of PCI, loading doses of oral P2Y12 inhibitors were given before cangrelor in a few patients, whereas the vast majority received oral P2Y12 inhibitor loading doses during or at the end of cangrelor infusion. About 90% of patients were treated with a 30-µg/
kg bolus, followed by 4 µg/kg per minute, whereas the lower dose of 0.75 µg/kg per minute was used in 6% of them, for a median duration of 70.5 hours. A total of 18 mild to moderate bleeding events were observed, whereas severe, life-threatening, or intracranial bleeding was not observed, confirming cangrelor is effective and well tolerated when used in high-risk patients undergoing PCI. 64 Another report from the same center, including 38 patients with cardiogenic shock (81% with STEMI), suggested that cangrelor is associated with low rates of clinically significant ischemic or bleeding events, even in this setting. 34

In a study analyzing the data from the Swedish Coronary Angiography and Angioplasty Registry, cangrelor was used by 16% of the 5513 patients with STEMI treated with primary PCI; about one third of these patients had a cardiac arrest. Among hospitals, the use of cangrelor in primary PCI varied dramatically, ranging from 4% to 36%. Notably, unlike registration trials, cangrelor was mostly used in STEMI, or during left main PCI or thrombus aspiration. In two thirds of patients, cangrelor was used in combination with ticagrelor; in more than half of them, this combination happened before the hospitalization. Prehospital ticagrelor loading dose was used in 5% of the patients with cardiac arrest treated with cangrelor, compared with 39% of the non–cangrelor-treated cardiac arrest cases. Mean times from diagnostic ECG to PCI were shorter in the cangrelor-treated patients (1.35 hours) than non–cangrelor-treated patients (2.27 hours). Even if cangrelor was more commonly used in high-risk patients, ST rates were low and similar in cangrelor- and non–cangrelor-treated patients at 30 days. 35

Therefore, the data available evaluating its real-world use show that physicians are using cangrelor in high-risk patients undergoing PCI for STEMI, such as those needing endotracheal intubation or complicated by cardiac arrest or cardiogenic shock, independently from their geographic location. 35,36

Accordingly, a recent survey of the American College of Clinical Pharmacy’s Cardiology Practice and Research Network, aimed to evaluate the opinion of cardiovascular clinical pharmacists on the current role of GPIs in ACS, highlighted that cangrelor would be the ideal agent for the management of patients with STEMI undergoing PCI. 65 Indeed, for those with STEMI and nausea or other gastrointestinal symptoms, a route of administration other than oral could be preferable.

**ONGOING STUDIES ON CANGRELOR**

There are several ongoing research studies (Table), including national and international registries, 66–69 that will provide insights on the use of cangrelor in patients undergoing contemporary PCI. In particular, more data are desirable on the transition to potent oral P2Y12 receptor inhibitors, or for patients who need a quick-acting intravenous agent like cangrelor in emergent situations, such as cardiac arrest or cardiogenic shock, or for those who have been preloaded with oral antiplatelet agents or GPI and present angiographic findings requiring an additional antiplatelet agent. Nevertheless, because registries will have no comparator or randomization, they will provide limited insight into the clinical value of cangrelor in combination with the newer P2Y12 agents.

The CAMEO (Cangrelor in Acute Myocardial Infarction: Effectiveness and Outcomes Registry; ClinicalTrials.gov Identifier: NCT04076813) is an ongoing multicenter US registry aimed to retrospectively address optimal platelet inhibition during the early management of patients with MI before coronary angiography or coronary artery bypass grafting.

The MARS (Management of Antiplatelet Regimen During Surgical Procedures; ClinicalTrials.gov Identifier: NCT03981835) and the MONET BRIDGE (Maintenance of Antiplatelet Therapy in Patients With Coronary Stenting Undergoing Surgery; ClinicalTrials.gov Identifier: NCT03862651) studies will study the area of perioperative antiplatelet therapy management. In particular, the MARS registry is a US multicenter observational registry designed to collect preoperative, intraoperative, and postoperative clinical strategies, therapeutic interventions, and 30-day outcomes data of ~1500 patients post-PCI scheduled to undergo cardiac or noncardiac surgery. The MONET BRIDGE study is a randomized, placebo-controlled study aimed to assess if a prolonged cangrelor infusion is safe and able to maintain an effective platelet inhibition in patients who discontinue an oral P2Y12 inhibitor for cardiac or noncardiac procedures within 1 year from PCI.

Finally, the Cangrelor OHCA (Out-of-Hospital Cardiac Arrest; ClinicalTrials.gov Identifier: NCT04005729) and the DAPT-SHOCK-AMI (Dual Antiplatelet Therapy for Shock Patients With Acute Myocardial Infarction; ClinicalTrials.gov Identifier: NCT03551964) randomized controlled studies will assess the efficacy of cangrelor compared with ticagrelor in high-risk subgroups, such as comatose survivors of OHCA and patients with cardiogenic shock undergoing PCI.

**THE ARCANGELO**

Most real-world evidence on the use of cangrelor is derived from retrospective analyses. 36,68 Such assessment may lack systematic collection of safety data. Furthermore, registration trials were performed only with the use of clopidogrel as an oral P2Y12 inhibitor. However, in real-world practice, cangrelor is more...
commonly used in association with ticagrelor, under-scoring the need for real-world prospective registries.

The ARCANGELO (Italian Prospective Study on Cangrelor) (ClinicalTrials.gov Identifier: NCT04471870) is a multicenter, observational, prospective cohort study, including patients with ACS undergoing PCI who receive cangrelor and transitioning to any oral P2Y₁₂ inhibitor aimed to collect information about the safety of cangrelor in real clinical practice (Figure 4). The primary end point is the incidence of any hemorrhage, according to the product’s approved summary of product characteristics (SPC). In these examples, patients A and B were both eligible, because the Informed and Privacy Consent Form was signed before patient discharge; in particular, patient B was not able to give consent before start of cangrelor and PCI. On the contrary, patient C provided consent after being discharged; therefore, the patient was not eligible. Also, patient D was not eligible because death occurred before being able to obtain Informed and Privacy Consent Form. ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; FPFV, first patient first visit; MACE, major adverse cardiac event; and pts, patients.

CONCLUSIONS

There are several antithrombotic drugs currently being developed for the treatment of ACS, targeting...
multiple pathways, with the potential of reducing recurrent ischemic events without significantly increasing bleeding complications, compared with standard therapies\(^7\) (Figure 5). Cangrelor is the only intravenous platelet P2Y\(_{12}\) inhibitor currently available for clinical use. Cangrelor provides prompt, potent, and reliable antiplatelet effects. Such pharmacologic properties allow to overcome limitations of oral P2Y\(_{12}\) inhibitors characterized by inevitable delay in their onset of action, which is enhanced in high-risk short-term settings in which their gastrointestinal absorption is further compromised. Cangrelor therefore represents an ideal agent to reduce the risk of thrombotic complications in patients undergoing PCI who have not been pre-treated with an oral P2Y\(_{12}\) inhibitor as well as in settings in which absorption of an oral agent is impeded or impaired (eg, hemodynamically unstable or intubated patients who are unable to swallow or who might not fully absorb an oral antiplatelet agent because of STEMI or cardiogenic shock). The introduction of cangrelor in clinical practice has seen its use expand and differ from how this was investigated in registration trials. These observations underscore the need for prospective evaluations that will provide insights on the safety and efficacy of cangrelor in real-world clinical practice.

**ARTICLE INFORMATION**

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