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CONTEMPORARY REVIEW

Cangrelor: Clinical Data, Contemporary Use, and Future Perspectives

Leonardo De Luca, MD, PhD; Philippe Gabriel Steg, MD; Deepak L. Bhatt, MD, MPH; Davide Capodanno, MD, PhD; Dominick J. Angiolillo, MD, PhD

ABSTRACT: Cangrelor is the only currently available intravenous platelet $P2Y_{12}$ 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 $P2Y_{12}$ receptor subtype plays a key role in platelet activation and amplification processes.[1,2] 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 $P2Y_{12}$ 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.[3,4] Most investigations have been conducted with oral formulations of $P2Y_{12}$ inhibitors. Although clopidogrel is the most commonly used oral $P2Y_{12}$ inhibitor, it is characterized by impaired platelet inhibitory effects in a considerable number of patients.[5,6] Prasugrel and ticagrelor are more potent oral $P2Y_{12}$ inhibitors compared with clopidogrel and associated with greater efficacy, albeit at the expense of increased bleeding risk.[7–9] 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.[10–12]

Cangrelor is an intravenous platelet $P2Y_{12}$ antagonist characterized by a rapid onset of action and achieving potent $P2Y_{12}$ inhibitory effects.[13] Moreover, because of its short half-life and reversibly binding properties, cangrelor has a fast offset of effects.[2,14] Cangrelor was approved on the basis of its superior efficacy in reducing thrombotic complications compared with clopidogrel in patients undergoing PCI.[15] Accordingly, its use has increased in real-life world practice.[16] Although its clinical efficacy compared with potent oral $P2Y_{12}$ 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.[10,11,17] Pharmacodynamic studies have also allowed to better define the optimal approach to transition from cangrelor to oral $P2Y_{12}$ inhibiting

Correspondence to: Leonardo De Luca, MD, PhD, Division of Cardiology, Department of Cardiosciences, Azienda Ospedaliera San Camillo-Forlanini, Circonvallazione Gianicolense, 87, 00152 Roma, Italy. E-mail: leo.deluca@libero.it; ldeluca@scamilloforlanini.rm.it

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Nonstandard Abbreviations and Acronyms

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/IIIa 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	stent thrombosis
SWAP	Switching Anti Platelet

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 $P2Y_{12}$ receptor antagonist approved for use in patients with CAD undergoing PCI.[22] Cangrelor is a nonthienopyridine ATP analog acting as a direct, reversible $P2Y_{12}$ 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 (C_{max}) 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 interaction[29,30] 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

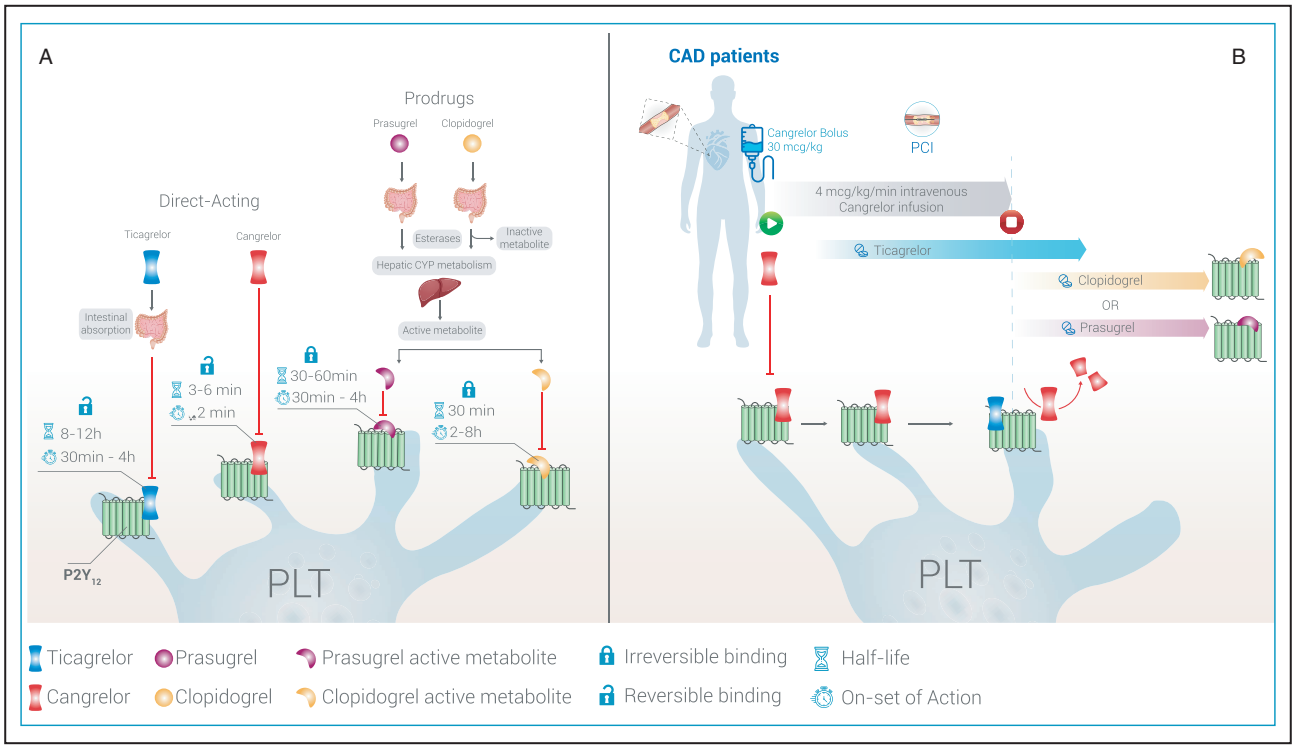

Figure 1. Mechanism of action of oral and intravenous $P2Y_{12}$ inhibitors on platelet receptors (A) and transition to oral platelet $P2Y_{12}$ receptor inhibitors in cangrelor-treated patients (B).
CAD indicates coronary artery disease; CYP, cytochrome P450; PCI, percutaneous coronary intervention; and PLT, platelet.

reversibly to the platelet $P2Y_{12}$ receptor. For these reasons, ticagrelor can be administered before or during the infusion of cangrelor without resulting in a drug interaction.[18,21]

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,[31] PLATFORM,[32] and PHOENIX[15] (Table). The first 2 studies, CHAMPION PCI[31] and CHAMPION PLATFORM,[32] 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[37] (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.[38] 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.[39,40] In this regard, in CHAMPION PLATFORM,[32] 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[31]	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
CHAMPION PLATFORM[32]	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: 0.3% vs 0.2%; *P*=0.45
CHAMPION PHOENIX[15]	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[33]	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 19.0%; *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[34]	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)
Vaduganathan et al[35]	38	Cangrelor by US SPC	Patients with CS (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[36]	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 $P2Y_{12}$ 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*)

Table 1. Continued

Study Name	No. of Patients	Treatment	Type of Patients	Outcomes
Ongoing observational studies				
CAMEO (NCT04076813)	3000	Cangrelor	NSTEMI, STEMI undergoing PCI	Number of antiplatelet medications used and bleedings occurring during hospitalization
MARS (NCT03981835)	1492	DAPT	Patients post-PCI on DAPT undergoing NCS and CS	NACE; intravenous antiplatelet bridging; death; ST; length of hospital stay; health economic analysis
ARCANGELO (NCT04471870)	1000	Cangrelor	ACS undergoing PCI	Bleeding (BARC criteria); MACE

*Enrollment was stopped when an interim analysis concluded that the trial would be unlikely to show superiority for the primary end point.
Italics indicate 'title' for the outcome.
ACS indicates acute coronary syndrome; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; ARCANGELO, Italian Prospective Study on Cangrelor; BARC, Bleeding Academic Research Consortium; BRIDGE, The Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery; CABG, coronary artery bypass grafting; CAMEO, Cangrelor in Acute Myocardial Infarction: Effectiveness and Outcomes; CHAMPION, Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; CS, cardiogenic shock; DAPT, dual-antiplatelet therapy; DAPT-SHOCK-AMI, DAPT for Shock Patients With Acute Myocardial Infarction; EU, European Union; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; IDR, ischemia-driven revascularization; MACE, major adverse cardiac event; MARS, Management of Antiplatelet Regimen During Surgical Procedures; MI, myocardial infarction; MONET BRIDGE, Maintenance of Antiplatelet Therapy in Patients With Coronary Stenting Undergoing Surgery; NACE, net adverse clinical event; NCS, noncardiac surgery; NSTEMI, non–ST-segment–elevation myocardial infarction; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; PRU, platelet reactivity (measured in $P2Y_{12}$ reaction units); SA, stable angina; ST, stent thrombosis; STEMI, ST-segment–elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; and UA, unstable angina.

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.[41] The trial was conducted across the spectrum of CAD manifestations (ie, stable CAD and ACS) in patients who were $P2Y_{12}$ 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; P=0.005) and the key secondary end point of ST (OR, 0.62; 95% CI, 0.43–0.90; 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.[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.[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,[44] even in patients who received unfractionated heparin or glycoprotein IIb/IIIa inhibitors (GPIs) during PCI.[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).[47]

A patient-level meta-analysis of the 3 CHAMPION studies confirmed the efficacy of cangrelor in terms of death, MI, IDR, or ST without significant increase in Global Use of Strategies to Open Occluded Coronary Arteries severe bleeding.[44] A following post hoc adjudication of site-reported bleeding showed a not significant increase of minor bleeding events in patients randomized to cangrelor, according to the TIMI (Thrombolysis in Myocardial Infarction) classification compared with clopidogrel (hazard ratio, 3.01; 95% CI, 1.52–5.96; P<0.001).[44] In several post hoc and

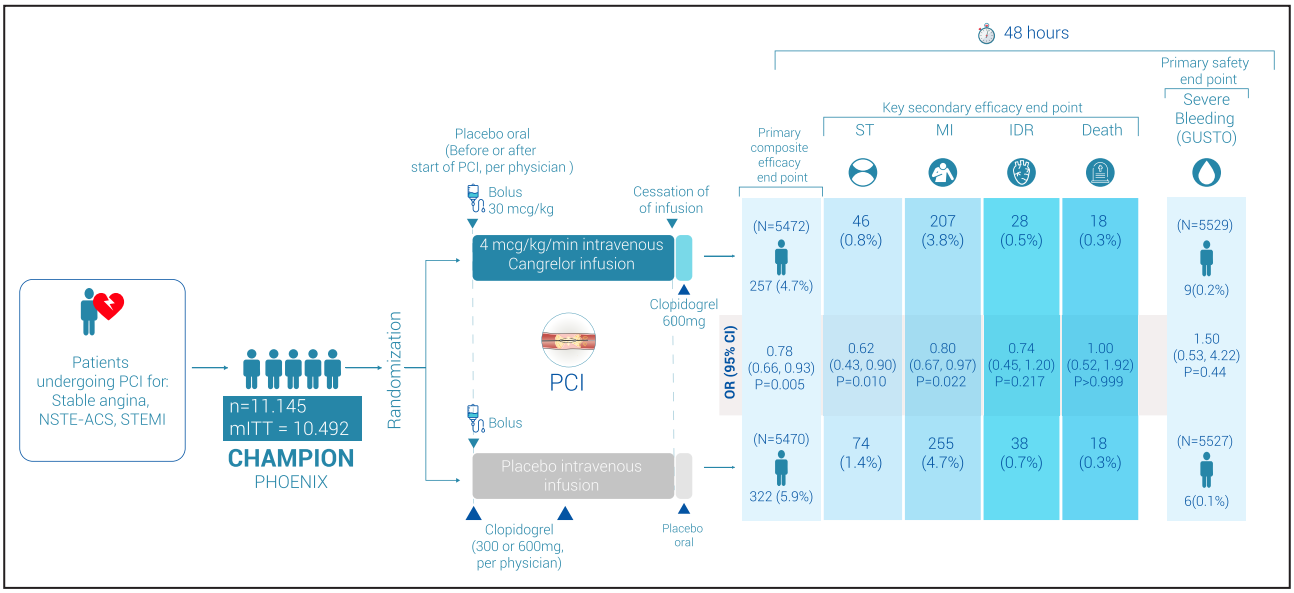

Figure 2. Clinical results of the CHAMPION (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) PHOENIX trial.
GUSTO indicates Global Use of Strategies to Open Occluded Coronary Arteries; IDR, ischemia-driven revascularization; MI, myocardial infarction; mITT, modified intention-to-treat; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; OR, odds ratio; PCI, percutaneous coronary intervention; ST, stent thrombosis; and STEMI, ST-segment–elevation myocardial infarction.

sensitivity analyses, the effectiveness of cangrelor was consistent, according to alternative end point definitions and patients' subgroups,[48] including those with a diagnosis of ACS.[49]

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.[20] These findings are consistent with other investigations supporting prompt, potent, and sustained platelet inhibition of cangrelor during primary PCI,[50,51] with important practical implications, especially for patients needing opioids that decrease gastrointestinal motility, contributing to delays in absorption and action of oral $P2Y_{12}$ 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.[52] 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 $P2Y_{12}$ 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 to be 0.75 μg/kg per minute. In a trial comparing cangrelor with placebo in bridging antiplatelet 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 PCI[59] 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 $P2Y_{12}$ 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 $P2Y_{12}$ platelet inhibitor should be administered as follows[60]: 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 updates[3] (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 $P2Y_{12}$ inhibitor before PCI and in whom oral therapy with $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors were given before cangrelor in a few patients, whereas the vast majority received oral $P2Y_{12}$ inhibitor loading doses during or at the end of cangrelor infusion. About 90% of patients were treated with a 30-μg/

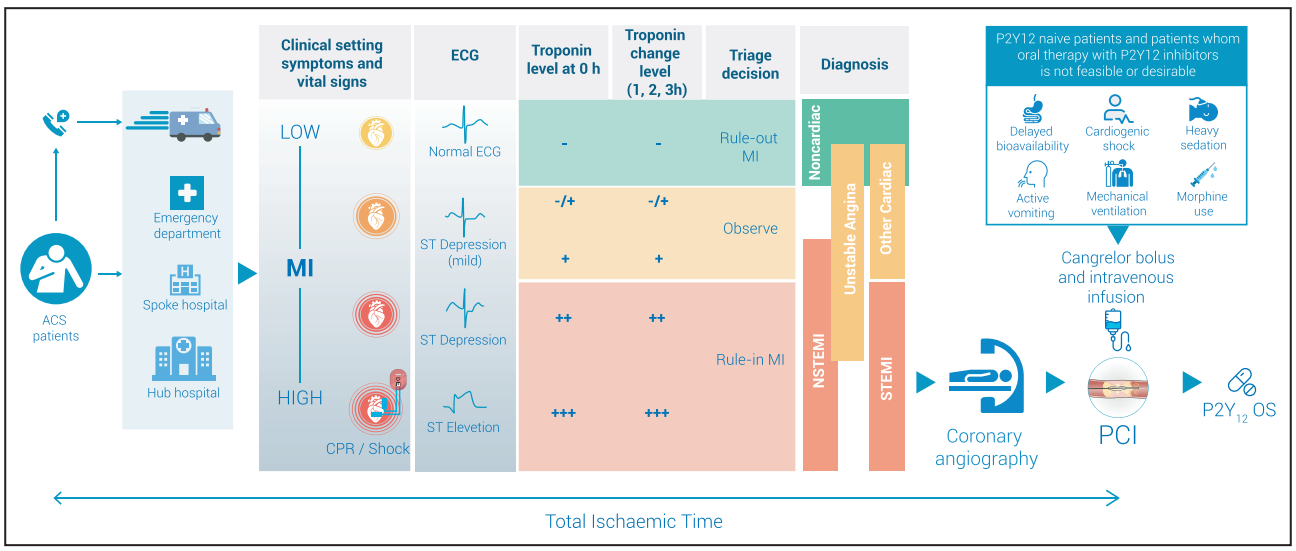

Figure 3. Use of cangrelor in patients with acute coronary syndrome (ACS).
MI indicates myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; OS, oral somministration; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor. However, in real-world practice, cangrelor is more

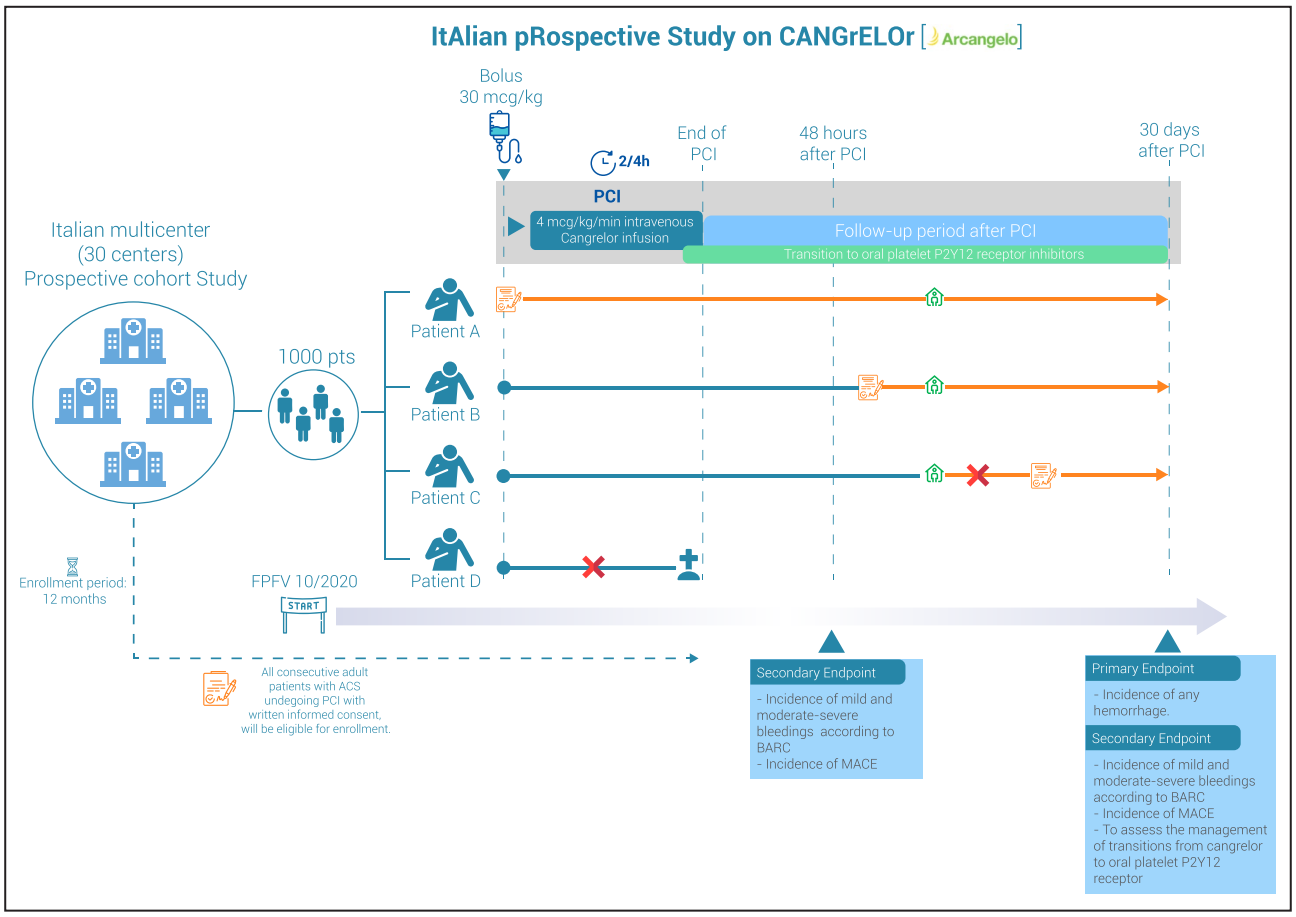

Figure 4. Design of the ARCANGELO (Italian Prospective Study on Cangrelor).
Each letter (A, B, C, and D) represents a patient prototype. Orange boxes identified the Informed and Privacy Consent Form. Green diamonds identify time of discharge. Each horizontal solid line represents the period of observation of each patient, which can be either mainly entirely prospective (orange lines) or could also include, for a small proportion of patients, a retrospective period (blue lines). Cangrelor intravenous infusion could end after percutaneous coronary intervention (PCI) conclusion. Even if adherence to European Medical Agency indications[41] is not required, the transition to oral platelet $P2Y_{12}$ receptor inhibitors may occur before the end of cangrelor infusion, according to the product's approved summary of product characteristics (SPC).[41] 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.

commonly used in association with ticagrelor,[65] underscoring 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 $P2Y_{12}$ 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 Bleeding Academic Research Consortium criteria,[70] in the 30 days following the PCI, calculated as the ratio between the number of patients experiencing at least one event during the 30-day observation period/the total number of evaluable patients. This evaluation will be of added value because bleeding data will be collected and scored in a prespecified standardized manner.

The secondary outcomes will include the evaluation of the incidence of major adverse cardiac events, including death, MI, IDR, and ST, and different types of bleedings, the type and timing of administration of oral platelet $P2Y_{12}$ inhibitors, and the use of GPI from 48 hours to 30 days after PCI (Figure 4). The study plans to enroll ≈1000 patients from the 30 participating centers in Italy, until September 2021.

CONCLUSIONS

There are several antithrombotic drugs currently being developed for the treatment of ACS, targeting

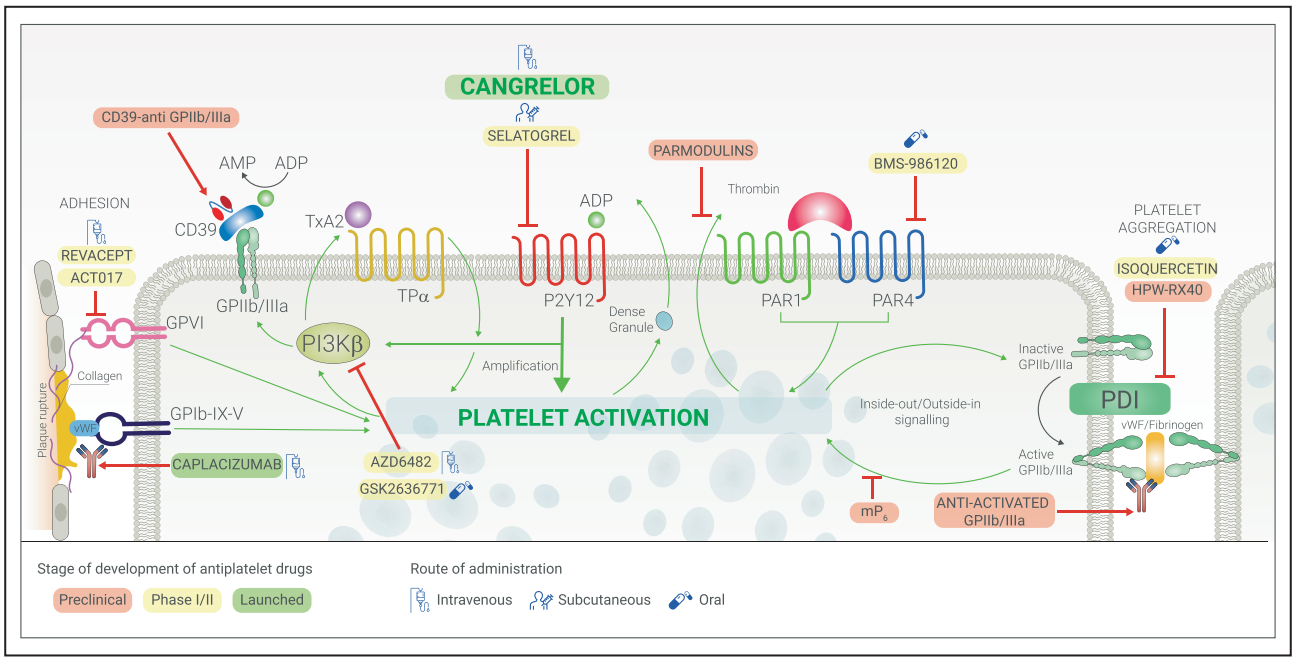

Figure 5. Antithrombotic drugs currently developed for the treatment of acute coronary syndrome.
GP indicates glycoprotein; PAR, protease-activated receptors; and PDI, protein disulfide isomerase.

multiple pathways, with the potential of reducing recurrent ischemic events without significantly increasing bleeding complications, compared with standard therapies[71] (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 pretreated 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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Affiliations

Division of Cardiology, Department of Cardiosciences, Azienda Ospedaliera San Camillo-Forlanini, Roma, Italy (L.D.L.); FACT (French Alliance for Cardiovascular Trials) and INSERM U-1148, AP-HP, Hôpital Bichat, Université de Paris, France (P.G.S.); NHLI (National Heart and Lung Institute), Imperial College, ICMS Royal Brompton Hospital, London, United Kingdom (P.G.S.); Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, MA (D.L.B.); Division of Cardiology, A.O.U. Policlinico "G. Rodolico-San Marco" University of Catania, Catania, Italy (D.C.); and Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL (D.J.A.).

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