Intravenous antiplatelet therapies (glycoprotein IIb/IIIa receptor inhibitors and cangrelor) in percutaneous coronary intervention: from pharmacology to indications for clinical use

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Abstract: Oral antiplatelet drugs are crucially important for patients with acute coronary syndrome or stable coronary artery disease undergoing percutaneous coronary intervention (PCI). In recent decades, several clinical trials have focused on reducing periprocedural ischemic events in patients undergoing PCI by means of more rapid platelet inhibition with the use of intravenous antiplatelet drugs. Glycoprotein IIb/IIIa receptor inhibitors (GPIs) block the final common pathway of platelet aggregation and enable potent inhibition in the peri-PCI period. In recent years, however, the use of GPIs has decreased due to bleeding concerns and the availability of more potent oral P2Y12 inhibitors. Cangrelor is an intravenous P2Y12 receptor antagonist. In a large-scale regulatory trial, cangrelor administration during PCI allowed for rapid, potent and rapidly reversible inhibition of platelet aggregation, with an anti-ischemic benefit and no increase in major bleeding. This article aims to provide an overview of general pharmacology, supporting evidence and current status of intravenous antiplatelet therapies (GPIs and cangrelor), with a focus on contemporary indications for their clinical use.

Keywords: Cangrelor, GPIs, P2Y12 inhibitors, intravenous antiplatelets

Introduction
Platelet activation and aggregation play a crucial role in atherothrombotic processes. This underscores the importance of antiplatelet therapy for the treatment of patients with atherothrombotic disease, in particular those undergoing percutaneous coronary intervention (PCI). Importantly, in patients undergoing PCI, thrombotic events such as myocardial infarction (MI) and early stent thrombosis are a leading cause of adverse sequelae and mortality.

Different classes of antiplatelet drugs are currently marketed with varying availability and indications across countries, including cyclooxygenase-1 inhibitors (aspirin), phosphodiesterase inhibitors (dipyridamole, cilostazol), P2Y12 receptor inhibitors (ticlopidine, clopidogrel, prasugrel, ticagrelor, cangrelor), protease-activated receptor 1 inhibitors (vorapaxar) and glycoprotein IIb/IIIa receptor inhibitors [(GPIs), abciximab, tirofiban, eptifibatide]. Among these agents, the only ones available for intravenous (i.v.) administration are aspirin, the P2Y12 inhibitor cangrelor and the three GPIs abciximab, tirofiban and eptifibatide (Figure 1). However, aspirin is mostly administered orally given that an i.v. formulation is not available in many countries. At variance with oral intake, which requires time for most antiplatelet drugs to reach their maximum inhibitory effect, i.v. agents quickly counteract the activation and aggregation of platelets. Therefore, i.v. antiplatelet agents are mostly used in the peri-PCI period, where fast onset of action is desired. This article...
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Aims to provide an overview of general pharmacology, supporting evidence and the current status of GPIs and cangrelor, with a focus on contemporary indications for their clinical use (Figure 2).

Glycoprotein IIB/IIIA inhibitors

The final common pathway of platelet aggregation is the crosslinking of GPIs by means of fibrinogen, which is converted into fibrin by thrombin, resulting in a stabilized clot.\(^4\) Historically, GPIs have been introduced to enable fast platelet inhibition and reduce the risk of ischemic complications associated with an acute coronary syndrome (ACS) or PCI, particularly in the context of upstream use. Large phase III trials of oral GPIs have consistently shown no improvement in clinical outcome and potential for higher mortality.\(^5\) The use of i.v. GPIs is now sporadic in contemporary practice, and mostly limited to bailout use (that is, downstream to coronary angiography). This paradigm shift is explained by bleeding concerns associated with routine use of GPIs, and the availability of more potent oral P2Y\(_{12}\) inhibitors than clopidogrel (prasugrel and ticagrelor) in the ACS setting. Circumstances where GPIs are still used in contemporary practice include the presence of a large intraprocedural thrombus burden, slow flow or ‘no reflow’ complications of PCI, and the opportunity to bridge the full onset of action of oral P2Y\(_{12}\) inhibitors, for example, in patients who were just recently administered an oral P2Y\(_{12}\) inhibitor that has not had enough time to reach its full antiplatelet effect.

General pharmacology of GPIs

A total of three GPIs have been made available for clinical use: abciximab, tirofiban and eptifibatide. Tirofiban and eptifibatide are commonly termed ‘small molecules’ due to their molecular size. Tirofiban, in particular, is a synthetic nonpeptide inhibitor, while eptifibatide is a cyclic heptapeptide derived from a protein found in the venom of rattlesnakes. Abciximab is a fragment of the chimeric human-murine 7E3 monoclonal antibody that noncompetitively prevents fibrinogen from binding at the glycoprotein IIb/IIIa receptor site. Compared with tirofiban and eptifibatide, the molecule of abciximab is larger in size (approximately 50,000 Dalton versus <1000 Dalton). After i.v. administration, the plasma concentrations of abciximab decrease rapidly with an initial half-life of 10 min and a second-phase half-life of about 30 min. The PCI dose is 0.25 mg/kg bolus i.v. followed by 0.125 µg/kg/min

| Molecule     | Fab fragment, chimeric | Synthetic peptide | Nonpeptide mimetic | Analogue of adenosine triphosphate |
|--------------|------------------------|-------------------|-------------------|-----------------------------------|
| Abciximab    | 1:5:2                  | >>>100:1          | >>>100:1          |                                   |
| Binding      | Noncompetitive         | Competitive       | Competitive       | Competitive                       |
| Half life    | 10-15h                 | 2-2.5h            | 2h                | 3-6 minutes                       |
| Dosing       | Bolus: 0.25 mg/kg (10-60 min) | Bolus: 180 mcg/kg (10 min) + 180 mcg/kg | Bolus: 25 mcg/kg (over 3 min) | Bolus: 30 mg/kg |
|              | Infusion: 0.125 mcg/kg/min (12h) | Infusion: 2 mcg/kg/min (up to 18 hours) | Infusion: 0.15 mcg/kg/min (up to 18 hours) | Infusion: 4 mg/Kg/min (at least 2 hours and up to 4 hours) |
| Renal adjustment | No                | Yes               | Yes               | No                                |

Figure 1. Key pharmacological characteristics of glycoprotein IIb/IIIa inhibitors and cangrelor.
i.v. (maximum 10 µg/min) for 12 h, with no need for renal adjustment. According to the package label, platelet function recovers over the course of 48 h after drug discontinuation; however, because abciximab is a chimeric molecule, residual effects of abciximab may persist for a longer period of time. At variance with abciximab, the small molecule GPIs tirofiban and eptifibatide exert competitive binding of the glycoprotein IIb/IIIa receptor due to lower affinity, have a shorter plasma half-life (2–2.5 h) and are mainly eliminated by the kidneys. The PCI dose of tirofiban is 25 µg/kg i.v. over three min, followed by infusion of 0.15 µg/kg/min i.v. for up to 18 h. This PCI regimen has now been largely replaced by the originally approved dosing regimen (0.4 µg/kg/min for 30 min followed by 0.1 µg/kg/min). In the case of renal impairment (defined as an estimated glomerular filtration rate <50 ml/min), only one bolus is given, and the infusion dose is halved. After discontinuation of tirofiban and eptifibatide, platelet function recovers in 4–8 h. Strategies of GPIs bolus-only administration have been investigated, as reported below.

**History of GPI studies across the spectrum of coronary artery disease**

Over the past few decades, multiple studies of GPIs have been conducted, using a wide variety of posologies, timing and route of administration, concurrent antithrombotic treatments and endpoints. A comprehensive description of such a large number of clinical trials goes beyond the scope of the present review, which will focus on a selection of studies that have been pivotal in the understanding of GPI benefits, risks and best-use modalities.

**Elective PCI.** Several trials of GPIs for low-risk patients undergoing elective PCI were conducted...
prior to the advent of clopidogrel, and their results are therefore no longer relevant to current practice.7,8 Selected trials published in the era of dual antiplatelet therapy are summarized in Table 1. The ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial randomized 2159 low-risk patients with stable coronary artery disease (SCAD) who were pretreated with clopidogrel 600 mg at least 2 h before PCI to abciximab plus a reduced dose of heparin or placebo plus a standard heparin dose.9 The trial concluded no benefit of abciximab on the primary endpoint of death, MI or urgent TVR within 30 days.4% versus 4%, RR 1.05; CI 95%, 0.69–1.59; p = 0.82 Abciximab is associated with no clinically measurable benefit within the first 30 days

ISAR SWEET trial (2004)
Abciximab + pretreatment with clopidogrel versus placebo + pretreatment with clopidogrel

Table 1. Key studies of glycoprotein IIb/IIIa inhibitors in stable coronary artery disease.

| Study | Groups | Population | Primary efficacy endpoint | Results | Conclusions |
|-------|--------|------------|--------------------------|---------|-------------|
| ISAR-REACT trial (2004) | Abciximab + pretreatment with clopidogrel versus placebo + pretreatment with clopidogrel | 2159 patients | Composite of death, MI, and urgent TVR within 30 days | 4% versus 4%, RR 1.05; CI 95%, 0.69–1.59; p = 0.82 | Abciximab is associated with no clinically measurable benefit within the first 30 days |
| ISAR SWEET trial (2004) | Abciximab + pretreatment with clopidogrel versus placebo + pretreatment with clopidogrel | 701 diabetic patients | The cumulative incidence of death and MI during the 12 months after PCI | 8.3% versus 8.6%, RR 0.97; CI 95%, 0.58–1.62; p = 0.91 | Abciximab has no impact on the risk of death and MI in diabetic patients undergoing elective PCI after pretreatment with a 600-mg loading dose of clopidogrel at least 2 h before the procedure. However, abciximab reduces the risk of restenosis in diabetic patients treated with bare metal stents |

CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk; TVR, target vessel revascularization.

prior to the advent of clopidogrel, and their results are therefore no longer relevant to current practice.7,8 Selected trials published in the era of dual antiplatelet therapy are summarized in Table 1. The ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial randomized 2159 low-risk patients with stable coronary artery disease (SCAD) who were pretreated with clopidogrel 600 mg at least 2 h before PCI to abciximab plus a reduced dose of heparin or placebo plus a standard heparin dose.9 The trial concluded no benefit of abciximab on the primary endpoint of death, MI or urgent TVR at 30 days. Although there were no differences in major bleeding, abciximab was more frequently associated with thrombocytopenia. A similarly designed trial performed in 701 patients with diabetes mellitus, named ISAR SWEET (Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics), also did not show a difference between abciximab and placebo on the primary endpoint of death and MI at 1 year.10 Recently, a meta-analysis of 10,123 patients on thienopyridines, from 22 trials of GPIs for elective PCI, concluded a significant reduction in nonfatal MI with GPIs compared with control (5.1% versus 8.3%, p = 0.0001), with a similar risk of major bleeding.11 However, no reduction in mortality was observed, and GPIs increased bleeding. In aggregate, there is a lack of valid arguments in the contemporary era to advocate the routine use of GPIs in patients with SCAD undergoing PCI on a background of clopidogrel therapy.

Non-ST segment elevation acute coronary syndromes. Prior to the introduction of clopidogrel, multiple studies established a beneficial role for GPIs in patients with ACS undergoing PCI.7 These trials are also no longer relevant to contemporary practice and as such, will not be discussed in the following text. Table 2 summarizes key studies of GPIs in ACS without ST segment elevation. The first trial conducted in the era of thienopyridines, actually in a mixed population of 202 patients with and without ACS undergoing PCI, showed a reduction in the composite of death, MI, TVR and GPIs rescue use with tirofiban versus placebo at a median of 6 months (20% versus 35%, p = 0.01).12 Subsequently, in the ISAR-REACT 2 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2) trial, encompassing 2022 patients with ACS pretreated at least 2 h before PCI with clopidogrel 600 mg, abciximab was shown to reduce the composite of death, MI and
### Table 2. Key studies of glycoprotein IIb/IIIa inhibitors in ACSs without ST segment elevation.

| Study                     | Groups                                                                 | Population                          | Primary efficacy endpoint                                      | Results                                                                 | Conclusions                                                                                           |
|---------------------------|------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| ADVANCE trial (2004)      | Placebo versus tirofiban                                               | 202 patients with ACS               | Death, MI, TVR, and bailout use of GPI IIb/IIa                  | 35% versus 20%, HR 0.51, 95% CI, 0.29–0.88; \( p = 0.01 \)            | Tirofiban is well tolerated and significantly reduces the incidence of ischemic/thrombotic complications during high-risk PCI |
| ISAR-REACT 2 trial (2006) | Abciximab + pretreatment with clopidogrel versus placebo + pretreatment with clopidogrel | 2022 patients with non-ST segment elevation | Composite of death, MI, or urgent TVR occurring within 30 days | 8.9% versus 11.9%, RR 0.75; 95% CI, 0.58–0.97; \( p = 0.03 \)          | Abciximab reduces the risk of adverse events in patients with non-ST segment elevation ACS undergoing PCI after pretreatment with 600mg of clopidogrel. The benefits provided by abciximab appear to be confined to patients presenting with an elevated troponin level |
| ACUITY trial (2006)       | UFH or enoxaparin + GPI versus bivalirudin + GPI versus bivalirudin    | 13,819 patients with ACS            | Composite ischemia endpoint (death, MI, or unplanned revascularization for ischemia), major bleeding, and net clinical outcome within 30 days | Bivalirudin versus heparin + GPI: Composite ischemia endpoint: 7.8% versus 7.3%; \( p = 0.32; RR, 1.08; 95\% CI, 0.93–1.24 \) Major bleeding: 3.0% versus 5.7%; \( p < 0.001; RR 0.53; 95\% CI, 0.43–0.65 \) Net clinical outcome end point: 10.1% versus 11.7%, RR 0.86, 95% CI, 0.77–0.97, \( p = 0.02 \) | Bivalirudin alone was associated with similar rates of ischemia and significantly lower rates of bleeding |
| ACUITY TIMING trial (2007) | Deferred versus routine upstream selective GPI administration         | 9207 patients with moderate-high-risk ACS | Composite ischemic events (death, MI, unplanned revascularization) at 30 days | 7.9% versus 7.1%, RR 1.12, 95% CI, 0.97–1.29, \( p = 0.44 \) for noninferiority, \( p = 0.12 \) for superiority | Deferring the routine upstream use of GPI resulted in a numerical increase in composite ischemia that, while not statistically significant, did not meet the criterion for noninferiority |

(Continued)
| Study                  | Groups                                | Population                  | Primary efficacy endpoint                                                                 | Results                                                                 | Conclusions                                                                                       |
|-----------------------|---------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| EARLY-ACS trial (2009) | Early routine administration of eptifibatide versus delayed administration | 9492 patients with ACS-NSTE | Composite of death, MI, recurrent ischemia requiring urgent revascularization, or the occurrence of a thrombotic complication during PCI that required bolus therapy opposite to the initial study group assignment (‘thrombotic bailout’) at 96 h | 9.3% versus 10.0%, OR 0.92; 95% CI, 0.80–1.06; p = 0.23. | The use of eptifibatide 12 h or more before angiography was not superior to the provisional use of eptifibatide after angiography |
| ISAR-REACT 4 trial (2011) | Abciximab + UFH versus bivalirudin | 1721 patients with non-ST segment elevation | Primary composite end point of death, large recurrent MI, urgent TVR, or major bleeding within 30 days | 10.9% versus 11%, RR 0.99; 95% CI, 0.74–1.32; p = 0.94 | Abciximab and UFH, compared with bivalirudin, failed to reduce the rate of the primary endpoint and increased the risk of bleeding |
| MATRIX trial (2016) | Bivalirudin + GPI versus UFH with or without GPI | 7213 patients with ACS | MACE (death, MI or stroke and net adverse clinical events (major bleeding or major adverse cardiovascular events) at 30 days | MACE: 5.9% versus 6.5%, RR 0.9, 95% CI, 0.70–1.16, p = 0.43 Net adverse clinical events: 7% versus 8.2%, RR 0.84, 95% CI, 0.67–1.05, p = 0.13 | Bivalirudin monotherapy compared with UFH with or without GPI, did not result in reduced MACE or net adverse clinical events in patients with ACS |
| BRIEF PCI trial (2009) | Abbreviated infusion (<2 h) versus 18 h infusion of eptifibatide | 624 patients with SCAD, ACS or recent STEMI | Incidence of periprocedural myocardial infarction defined as troponin-I elevation >0.26 µg/l | 30.1% versus 28.3%, 95% CI, p < 0.012 for noninferiority | After uncomplicated PCI, eptifibatide infusion can be abbreviated safely to <2 h |

ACS, acute coronary syndrome; CI, confidence interval; GPI, glycoprotein inhibitors; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; NSTE, nonsegment ST elevation; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; SCAD, stable coronary artery disease; STEMI, ST segment elevation myocardial infarction; TVR, target vessel revascularization; UFH, unfractionated heparin.
urgent TVR at 30 days compared with placebo (8.9% versus 11.9%, \( p = 0.03 \)) but this benefit was confined to patients with troponin elevation.\(^{13}\)

Some indirect evidence on the role of GPIs in clopidogrel-treated patients with ACS-PCI came from two trials of the anticoagulant bivalirudin. In the three-arm ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial (\( n = 13,819 \)), bivalirudin monotherapy and bivalirudin plus GPIs were associated with similar 30-day rates of ischemic events (death, MI, or unplanned revascularization for ischemia) compared with heparin plus GPIs.\(^{14}\) However, only bivalirudin monotherapy significantly reduced major bleeding (3.0% versus 5.7%, \( p < 0.001 \)) and the net clinical outcome of bleeding and ischemia (10.1% versus 11.7%, \( p = 0.02 \)) compared with heparin plus GPIs. Similarly to ACUITY, the ISAR-REACT 4 (The Intracoronal Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4) trial, encompassing 1721 patients with troponin-elevated ACS and pretreated with clopidogrel 600 mg, found no differences in ischemic events with abciximab plus heparin compared with bivalirudin alone, and more bleeding was observed with abciximab plus heparin (4.6% versus 2.6%, \( p = 0.02 \)).\(^{15}\) It remains undefined whether the worse safety outcomes of these trials were attributable to GPIs, heparin or a combination of both, but some perspectives come into respect from more contemporary trials of bivalirudin versus heparin, where GPIs were recommended only as a bailout strategy. In particular, in 7213 patients with ACS from the MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial, bleeding was increased with heparin (2.5% versus 1.4%, \( p < 0.001 \)), likely as the consequence of a higher final rate of GPI use (26% versus 5%).\(^{16,17}\)

Conversely, no bleeding difference was observed between bivalirudin and heparin in the VALIDATE-SWEDEHEART (Bivalirudin versus Heparin in ST Segment and Non-ST Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry) trial, where GPIs were used in only about 2% of patients in both groups. Thus, it is reasonable to assume that GPIs acted as a treatment modifier in earlier comparisons of bivalirudin and heparin, with detrimental effects on bleeding outcomes.\(^{18}\)

Clopidogrel is now no longer a preferable option in ACS, and prasugrel and ticagrelor have shown better ischemic outcomes in the large TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) and PLATO (Platelet inhibition and patient Outcomes) trials, respectively.\(^{19,20}\) It has been questioned that the availability of prasugrel or ticagrelor may obviate the need of GPIs in patients with ACS undergoing PCI. In TRITON and PLATO, the benefit of prasugrel and ticagrelor over clopidogrel was irrespective of concurrent GPI use, but their study designs do not allow to establish conclusively if adjunctive benefit of GPIs exists on top of newer generation P2Y\(_{12}\) inhibitor administration. Overall, there is no compelling evidence for routine use of GPIs in patients with non-ST segment elevation ACS undergoing PCI in the context of potent platelet inhibition with prasugrel or ticagrelor.

In the attempt to ameliorate the bleeding outcomes of GPIs, multiple studies have also compared a variety of administration strategies (e.g. upstream versus downstream use, shorter versus longer infusions). The EARLY-ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST Segment Elevation Acute Coronary Syndrome) trial compared early versus delayed (e.g. after coronary angiography) provisional administration of eptifibatide in 9492 patients with ACS undergoing PCI, showing no differences in ischemic outcomes at 96 h and 30 days, and a significantly higher risk of bleeding and red blood transfusion with early eptifibatide administration.\(^{21}\) Similarly, in the ACUTTY Timing (Acute Catheterization and Urgent Intervention Triage Strategy Timing) trial (\( n = 9207 \)), no difference between upstream and downstream GPI use was observed in ischemic events at 30 days, but there was a significant reduction of major bleeding with deferred use (4.9% versus 6.1%, \( p < 0.009 \)).\(^{22}\) A meta-analysis of 19,929 patients from seven trials did not show any difference in 30-day mortality and MI between upstream and downstream GPI use, but upstream use increased the rate of major bleeding (1.8% versus 1.3%, \( p = 0.0002 \)).\(^{23}\) In parallel with the advent of the newer P2Y\(_{12}\) inhibitors, these studies led to drastically abandoning the strategy
of upstream GPI use, particularly if patients are pretreated with a P2Y12 inhibitor. The impact of shorter GPI administration has been also investigated as a strategy to reduce the risk of bleeding complications. The BRIEF PCI (Brief Infusion of Eptifibatide Followed Percutaneous Coronary Intervention) trial randomized patients with ACS to an 18-h, or maximum 2-h, infusion and concluded for the noninferiority of the shorter regimen with respect to periprocedural MI, paralleled by less bleeding (1.0% versus 4.2%, \( p = 0.02 \)).

ST segment elevation ACSs. Patients with acute ST segment elevation MI (STEMI) undergoing primary PCI conceptually embody an ideal setting for the use of GPIs, particularly if they present early and their thrombus burden is large. In a meta-analysis of 27,115 patients from 11 randomized trials, published in 2005, De Luca and colleagues reported a significant reduction in the frequency of MI and mortality at 30 days with the use of GPIs (mostly abciximab). Another meta-analysis of individual patient data from Montale- scot and colleagues, published in 2007, found similar results. In addition, several trials investigated whether the upstream use of GPIs was beneficial in patients with STEMI with respect to clinical and angiographic outcomes, with mixed results (Table 3). In the BRAVE 3 (Third Bavarian Reperfusion Alternatives Evaluation) trial, upstream abciximab did not reduce the infarct size as assessed by SPECT before discharge and ischemia at 30 days compared with placebo in 800 patients with STEMI treated with clopidogrel and undergoing primary PCI. In contrast, in the On-TIME 2 trial, upstream tirofiban reduced the proportion of residual ST segment elevation and improved ischemic outcomes at 30 days in 984 patients with STEMI who also received aspirin and clopidogrel. GPIs were also studied as part of investigations of facilitated PCI, with negative results. The FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial randomized 2452 patients with STEMI undergoing PCI and presenting within 6h to a reduced dose of reteplase plus abciximab, abciximab alone or placebo. There was a significantly higher rate of early ST segment resolution with abciximab plus reteplase (43.9%) compared with abciximab-facilitated PCI (33.1%) or primary PCI (31.0%, \( p = 0.01 \) and 0.003 respectively), but no differences were noted with respect to the primary endpoint (a composite of death from all causes, ventricular fibrillation occurring more than 48h after randomization, cardiogenic shock, and congestive heart failure) and mortality at 3 months. In addition, bleeding was increased in the PCI-facilitated groups. As such, the trial concluded that the facilitated approaches did not lead to a significant improvement in clinical outcomes and were actually detrimental. A subanalysis of the same trial concluded that higher-risk patients who were early presenters and had a thrombolysis in myocardial infarction (TIMI) risk score of 3 or greater actually benefited from facilitated PCI with abciximab plus half the reteplase dose, with higher rates of 1-year survival. Similarly to non-ST segment elevation ACS, the role of GPIs in STEMI has been indirectly explored in a trial of bivalirudin. The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial compared heparin plus a GPI and bivalirudin in 3602 patients who underwent primary PCI for STEMI. Bivalirudin led to a reduction in net adverse clinical events (9.2% versus 12.1%, \( p = 0.005 \)) and major bleeding (4.9% versus 8.3%, \( p < 0.001 \)) at 30 days, but increased the risk of acute stent thrombosis 24h.

In recent years, the debate on the use of GPIs has focused on optimizing their posology and route of administration to drug safety profiles. The AIDA STEMI (Abciximab Intracoronary versus Intravenously Drug Application in ST Elevation Myocardial Infarction) trial (\( n = 2065 \)) tested the intracoronary administration of a bolus of abciximab during primary PCI compared with an intravenous bolus plus standard subsequent infusion, showing no differences between groups on the primary composite endpoint of all-cause mortality, recurrent MI and new congestive heart failure at 90 days. The INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction) trial investigated with a factorial design whether, in 452 high-risk patients with anterior STEMI within 4h, the administration of an intracoronary bolus of abciximab (delivered to the infarct lesion by means of a perfusion balloon), manual thrombectomy, or both, reduced infarct size as assessed by cardiac magnetic resonance imaging at 30 days. Notably, patients randomized to abciximab had a significant reduction in infarct size at 30 days as assessed by cardiac magnetic resonance imaging (\( p = 0.03 \)).
| Study                        | Groups                                      | Population                  | Primary efficacy endpoint                                                                 | Results                                                                 | Conclusions                                                                 |
|------------------------------|---------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| On-Time 2 trial (2008)       | High-bolus dose tirofiban versus placebo    | 984 patients with STEMI     | Extent of residual ST segment deviation 1 h after PCI                                       | Before PCI: 10.9 mm versus 12.1 mm, p = 0.028 1 h after PCI: 3.6 mm versus 4.8 mm, p = 0.003 | Routine prehospital initiation of high-bolus dose tirofiban improved ST segment resolution and clinical outcome after PCI |
| FINESSE trial (2008)         | Combination-facilitated PCI versus abciximab-facilitated PCI versus primary PCI | 2452 patients with STEMI    | Death from all causes, ventricular fibrillation occurring more than 48 h after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization | 9.8% versus 10.5% versus 10.7%, p = 0.55 | Neither facilitation of PCI with reteplase plus abciximab nor facilitation with abciximab alone significantly improved the clinical outcomes, as compared with abciximab given at the time of PCI, in patients with STEMI |
| HORIZONS-AMI trial (2008)    | Bivalirudin versus UFH + GPI                | 3602 patients with STEMI    | Major bleeding and combined adverse clinical events, defined as the combination of major bleeding or MACE (death, reinfarction, TVR for ischemia, and stroke) 'net adverse clinical events' within 30 days | 30-day rate of net adverse clinical events: 9.2% versus 12.1%, RR 0.76, 95% CI, 0.63–0.92, p = 0.005 Major bleeding: 4.9% versus 8.3%, RR 0.60, 95% CI, 0.46–0.77, p < 0.001 | Anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in significantly reduced 30-day rates of major bleeding and net adverse clinical events |
| BRAVE 3 trial (2009)         | Abciximab versus placebo                    | 800 patients with STEMI     | Infarct size of the left ventricle measured by single-photon emission computed tomography with technetium-99m sestamibi before hospital discharge | 15.7 ± 17.2% versus 16.6 ± 18.6%, p = 0.47 | Upstream administration of abciximab is not associated with a reduction in infarct size in patients presenting with acute myocardial infarction within 24 h of symptom onset and receiving 600 mg clopidogrel |
| AIDA STEMI trial (2012)      | IC versus IV abciximab                      | 2065 patients with STEMI    | Composite of all-cause mortality, recurrent infarction, or new congestive heart failure within 90 days | 7% versus 7.6%, OR 0.91, 95% CI, 0.64–1.28, p = 0.58 | Intracoronary as compared with intravenous abciximab did not result in a difference in the combined endpoint of death, reinfarction, or congestive heart failure |
| INFUSE-AMI trial (2012)      | IC versus manual aspiration thrombectomy versus no thrombectomy | 452 patients with STEMI due to proximal or mid left anterior descending artery occlusion | Infarct size at 30 days assessed by cardiac magnetic resonance imaging (cMRI) | 15.1% versus 17.9%, p = 0.03 | Infarct size at 30 days was significantly reduced by bolus intracoronary abciximab delivered to the infarct lesion site but not by manual aspiration thrombectomy |

ACS, acute coronary syndrome; CI, confidence interval; GPI, glycoprotein inhibitors; IC, intracoronary; IV, intravenous; MACE, major adverse cardiac events; MI, myocardial infarction; NSTE, nonsegment ST elevation; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; STEMI, ST segment elevation myocardial infarction; TVR, target vessel revascularization; UFH, unfractionated heparin;
meta-analysis of 3754 STEMI patients from 14 studies of intracoronary versus intravenous GPI use did not show statistically significant differences in major adverse cardiac events.35 Another recent meta-analysis by Sun and colleagues analyzed 751 patients from six randomized controlled trials of intracoronary abciximab administration versus intracoronary administration, concluding that intracoronary administration improves TIMI 3 flow and achieves higher rates of ST segment resolution, with no difference in major adverse cardiac events and bleeding.36 Finally, the use of a bolus of tirofiban not followed by infusion has been advocated by the FABULOUS PRO (Facilitation through Aggrastat by Dropping or Shortening Infusion Line in Patients with ST Segment Elevation Myocardial Infarction Compared to or on top of Prasugrel given at Loading Dose) trial (n = 100) as a means of bridging platelets to the full effect of prasugrel, which is slower in STEMI than in elective conditions, likely due to delayed absorption.37

GPIs in clinical practice guidelines

The most recent guidelines for PCI by the American College of Cardiology (ACC), American Heart Association (AHA) and Society for Cardiovascular Angiography and Interventions (SCAI) were published in 2011, thereby pre-dating the most recent evidence on GPI use.38 At that time, recommendations were given as follows. For patients undergoing elective PCI for SCAD, GPIs were indicated as class IIa if patients were not pretreated with clopidogrel and class IIb if patients were pretreated with clopidogrel. For patients with non-ST segment elevation ACS and high-risk features, GPIs were indicated as class I if patients were not pretreated with clopidogrel and class IIa if patients were pretreated with clopidogrel. These recommendations were unchanged in the 2014 ACC/AHA guidelines for non-ST segment elevation ACS.39 For patients with STEMI, the class was IIa regardless of whether patients were pretreated with clopidogrel, and a class IIb recommendation was given for intracoronary abciximab. Conversely, routine upstream use of GPIs was not recommended (class III).38 In the more recent 2013 guidelines for STEMI, these recommendations were confirmed with the exception of an upgrade for upstream GPIs for patients in whom primary PCI is intended (class IIb).40 In the 2018 practice guidelines for myocardial revascularization from the European Society of Cardiology (ESC), GPIs are recommended only for bailout use, with class IIa across the broad spectrum of PCI scenarios (e.g. either elective or urgent).41 An additional class IIa recommendation allows for the use of GPIs in P2Y12-inhibitor naïve patients undergoing PCI in the context of non-ST segment elevation ACS. Pretreatment with GPIs in patients in whom the coronary anatomy is unknown is not recommended (class III).

Cangrelor

Cangrelor is approved by the United States (US) Food and Drug Administration to reduce periprocedural thrombotic events in patients not pretreated with a P2Y12 receptor antagonist, in which GPIs were not administered. Similarly, the drug is approved by the European Medicines Agency for patients who have not received an oral P2Y12 receptor antagonist before PCI and in whom the use of oral therapy is not possible or desirable.

General pharmacology

Cangrelor is a nonthienopyridine analog of adenosine triphosphate, a reversible antagonist of the platelet P2Y12 receptor. It is administered intravenously as a bolus of 30 mg/kg i.v. followed by 4 mg/kg/min continuous infusion for at least 2 h or the duration of PCI, whichever is longer. Cangrelor reaches its maximum concentration in 2 min, and interrupting the infusion results in a restoration of normal platelet function within 60 min.42,43 Unlike GPIs, cangrelor overdose is not associated with increased bleeding, owing to its short half-life, and rapid offset of action.44 Also importantly, at variance with GPIs, no dose modification is needed based on renal function. According to the drug label, transition from cangrelor to oral P2Y12 inhibitors requires the loading doses of clopidogrel and prasugrel to be administered at the end of the cangrelor infusion to avoid drug interactions.45 In fact, cangrelor blocks the binding of the active metabolites of the thienopyridines clopidogrel and prasugrel on the P2Y12 receptor, impairing their antiplatelet effect.46,47 However, recent findings of a pharmacodynamic study showed that 60 mg of prasugrel administered at the start of cangrelor infusion resulted in more effective platelet inhibition compared with clopidogrel 600 mg after discontinuation of cangrelor, avoiding gaps in platelet
inhibition and underscoring the need for more studies to understand the nature of drug interactions between cangrelor and thienopyridines. The US labeling recommends administration of prasugrel or clopidogrel immediately after discontinuation of cangrelor, and administration of ticagrelor during PCI or thereafter. Conversely, the European labeling indicates that the three oral drugs should be given after discontinuation of cangrelor (clopidogrel) or 30 min earlier (ticagrelor and prasugrel).

History of cangrelor studies

There are three large randomized clinical trials of cangrelor (Table 4). In the CHAMPION-PLATFORM trial, 5362 patients naïve to clopidogrel were randomized to cangrelor or placebo, followed by a clopidogrel loading dose of 600 mg. The composite death endpoint, MI or ischemia-driven revascularization at 48 h, did not differ between cangrelor and placebo. Conversely, major bleeding was highest among patients treated with cangrelor (5.5% versus 3.5%, p < 0.001), mainly due to higher rates of hematoma at the access site. In the CHAMPION-PCI trial, encompassing 8877 patients, cangrelor was compared with clopidogrel 600 mg administered before PCI. The 48-hour composite endpoint of all-cause death, MI or ischemia-driven revascularization was again similar in the two groups, and bleeding trended towards higher rates with cangrelor. Notably, the enrollment in both these studies was terminated early due to futility. Also importantly, in the CHAMPION-PLATFORM and CHAMPION-PCI studies, different definitions of MI were used. In a pooled analysis of the two trials, using the universal definition of MI resulted in cangrelor significantly reducing the rate of periprocedural ischemic events compared with clopidogrel, including stent thrombosis, with no increasing in severe bleeding. Finally, in the CHAMPION PHOENIX trials have been the objective of dedicated publications (Table 5). In subanalyses based on demographic characteristics, no treatment interactions were noted with respect to age, sex and nationality (US or non-US). Similarly, there was no interaction based on clinical presentation with SCAD or ACS, and based on a number of angiographic and procedural aspects, including vascular access, PCI complexity, number of treated lesions, number of treated vessels and use of unfractionated heparin or bivalirudin. Several studies have been also conducted and published using the pooled dataset of all CHAMPION trials. In a comparison of 10,929 patients treated with cangrelor and 1211 treated with clopidogrel or placebo and routine GPs, the primary composite efficacy endpoint did not differ significantly between matched groups, while major or minor bleeding according to the TIMI classification was lower with cangrelor. In two analyses of patients with a history of cerebrovascular events or MI the efficacy and safety profile of cangrelor compared with clopidogrel were consistent with the overall population. In another study, cangrelor was not associated with acquired thrombocytopenia, a cause of early morbidity and major bleeding, whose main predictor was the use of GPs. Finally, in the three CHAMPION trials combined, the use of GPIs was not shown to reduce ischemic complications, and rather caused an increase in bleeding rates in the cangrelor and clopidogrel or placebo groups.

Cangrelor in subgroups of interest

Multiple post hoc analyses of the CHAMPION PHOENIX trials have been conducted using the pooled dataset of all CHAMPION trials. A comprehensive pooled analysis of patient-level data from the CHAMPION trials confirmed the superiority of cangrelor compared with clopidogrel and placebo for the reduction of periprocedural ischemic events. In particular, cangrelor reduced the odds of the primary outcome by 19% (3.8% for cangrelor versus 4.7% for control; odds ratio (OR) 0.81, 95% confidence interval (CI) 0.71–0.91, p = 0.0007), and stent thrombosis by 41% (0.5% versus 0.8%, OR 0.59, 95% CI 0.43–0.80, p = 0.0008) with no difference in the primary safety outcome. The majority of these MIs (n = 433, 93.7%) were type 4a (periprocedural MI), and the reduction in MI was insensitive to the adopted definition.

Cangrelor significantly reduced intraprocedural stent thrombosis by 35% (p = 0.04) resulting in improved clinical outcomes at 48 h and 30 days. A comprehensive pooled analysis of patient-level data from the CHAMPION trials confirmed the superiority of cangrelor compared with clopidogrel and placebo for the reduction of periprocedural ischemic events. In particular, cangrelor reduced the odds of the primary outcome by 19% (3.8% for cangrelor versus 4.7% for control; odds ratio (OR) 0.81, 95% confidence interval (CI) 0.71–0.91, p = 0.0007), and stent thrombosis by 41% (0.5% versus 0.8%, OR 0.59, 95% CI 0.43–0.80, p = 0.0008) with no difference in the primary safety outcome.
Table 4. Overview of landmark cangrelor trials.

| Study type | CHAMPION-PCI | CHAMPION-PLATFORM | CHAMPION PHOENIX |
|------------|--------------|--------------------|-----------------|
| Population | 8877 patients with ACS | 5362 patients with ACS or SCAD | 11,145 patients with ACS or SCAD |
| Intervention | Cangrelor versus clopidogrel 600 mg before PCI | Clopidogrel + cangrelor versus Clopidogrel + placebo during PCI | Cangrelor versus clopidogrel |
| Primary efficacy and safety endpoint | Efficacy: composite of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 h Safety: bleeding at 48 h. Definitions were based on criteria from the GUSTO trial, TIMI trial and ACUITY trial | Efficacy: composite of death, myocardial infarction, or ischemia-driven revascularization at 48 h | Efficacy: composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 h Safety: severe bleeding not related to coronary artery bypass grafting, according to the GUSTO criteria, at 48 h |
| Results | Primary Efficacy composite end point at 48 h: cangrelor was not superior to clopidogrel (7.5% versus 7.1%, odds ratio, 1.05; 95% CI, 0.88–1.24; p = 0.59) Primary safety end point, major bleeding: ACUITY criteria: 3.6% versus 2.9%, odds ratio 1.26, p = 0.06 GUSTO criteria: 0.2% versus 0.3%, odds ratio 0.91, p = 0.82 TIMI criteria: 0.6% versus 0.3%, odds ratio 1.36, p = 0.39 | Primary efficacy composite end point at 48 h: cangrelor was not to superior to placebo (7% versus 8%, odds ratio 0.87; 95% CI, 0.71–1.07; p = 0.17). Enrollment was stopped when an interim analysis concluded that the trial would be unlikely to show superiority for the primary endpoint | Primary efficacy composite end point at 48 h: cangrelor was superior to clopidogrel (4.7% versus 5.9%, odds ratio 0.78, 95% CI, 0.66–0.93; p = 0.005) Primary safety end point at 48 h: 0.16% versus 0.11%, odds ratio, 1.50; 95% CI, 0.53–4.22; p = 0.44 |
| Conclusions | Cangrelor, when administered intravenously 30 min before PCI and continued for 2 h after PCI, was not superior to an oral loading dose of 600 mg of clopidogrel, administered 30 min before PCI, in reducing the composite end point of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 h. | Cangrelor during PCI was not superior to placebo in reducing primary end point, but stent thrombosis and death were lower in the cangrelor group. | Cangrelor significantly reduced the rate of ischemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding. |

ACS, acute coronary syndrome; CI, confidence interval; PCI, percutaneous coronary intervention; SCAD, stable coronary artery disease; TIMI, thrombolysis in myocardial infarction.
Table 5. Subanalyses of the CHAMPION PHOENIX trial.

| Study                          | Aim                                                                 | Population                  | Conclusions                                                                                           |
|-------------------------------|----------------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------|
| Généreux and colleagues57     | To evaluate the clinical impact of IPST                              | 10,939 patients             | Cangrelor reduced IPST at 48 h and 30 days                                                            |
| Gutierrez and colleagues62    | To assess whether the use of the femoral or radial approach for PCI interacted with the efficacy and safety of cangrelor | Radial access = 2855 patients Femoral access = 8064 patients | The absolute rates of bleeding, regardless of the definition, tended to be lower when PCI was performed via the radial artery |
| White and colleagues67        | To examine the efficacy and bleeding outcomes of cangrelor in patients who underwent PCI with bivalirudin | Cangrelor + bivalirudin = 1014 Clopidogrel + bivalirudin = 1045 | Cangrelor may offer an attractive benefit–risk profile when used in combination with bivalirudin |
| Cavender and colleagues56     | Effects of cangrelor on MI using different definitions               | 462 patients                | Cangrelor compared with clopidogrel significantly reduces MI, regardless of the definition            |
| Abtan and colleagues73        | To examine the safety and efficacy of cangrelor in patients with SA or ACS | SA - 6358 patients ACS - 4584 patients | Benefits and risks of cangrelor are consistent in patients with SA and ACS                               |
| O’Donoghue and colleagues60   | Efficacy and safety of cangrelor in women versus men during PCI      | Women - 3051 patients Men - 7891 patients | Cangrelor reduced the odds of major adverse cardiovascular events and stent thrombosis both in men and women |
| Vaduganatham and colleagues61 | To analyze all patients included in US and non-US subgroups          | US = 4097 Non-US = 6845    | Cangrelor consistently reduced rates of ischemic end points without an excess in severe bleeding in both the US and non-US subgroups |
| Cavender and colleagues59     | To determine the outcomes in subgroup of patients ≥75 years old      | 2010 patients              | Cangrelor provides similar efficacy and in patients ≥75 years and increases the risk of mild to moderate bleeding by threefold, but does not increase risk of severe bleeding |
| Vaduganathan and colleagues48 | To examine the efficacy and safety of cangrelor in the subgroup of patients who received UFH during PCI | UFH = 7569 patients Non-UFH = 3370 patients | Cangrelor reduces early ischemic periprocedural complications without increasing severe bleeding compared with clopidogrel in patients undergoing PCI with UFH |
| Abnousi and colleagues64      | To examine the safety and efficacy of cangrelor in patients with SVD and MVD | SVD = 5220 patients MVD = 5701 patients | MVD and SVD patients had similar ischemic outcomes at 48 h and 30 days, without a significant increase in GUSTO severe bleeding |

ACS, acute coronary syndrome; GUSTO, global use of strategies to open occluded arteries; IPST, intraprocedural stent thrombosis; MI, myocardial infarction; MVD, multivessel disease; PCI, percutaneous coronary intervention; SA, stable angina; SVD, single vessel disease; UFH, unfractionated heparin; US, United States.

**Ideal candidates for cangrelor use**

Ideal candidates for cangrelor administration during PCI include patients with SCAD undergoing complex PCI who were not pretreated with oral P2Y$_{12}$ inhibitors and patients with ACS. Periprocedural events after PCI depend on the number of treated high-risk target lesion features. In complex PCI, compared with a loading dose of clopidogrel, cangrelor reduced major adverse cardiac events occurring within 48 h after PCI.
regardless of baseline lesion complexity, suggesting a greater benefit–risk profile in patients with complex coronary anatomy. Addressing thrombotic complications in the periprocedural period may result in less need for bailout GPI use, which potentially adds on the safety profile of a cangrelor-based antiplatelet strategy. Cangrelor availability also avoids postponing PCI to allow for sufficient platelet inhibition after oral P2Y₁₂ inhibitor administration and may impact on the proportions of \textit{ad hoc} PCI performed in catheterization laboratories with high turnover, reducing hospitalization length.

Patients with ACS undergoing emergent PCI are also ideal candidates for cangrelor use. In this context, the use of a high loading dose regimen of ticagrelor and prasugrel has been largely ineffective in accelerating platelet inhibition, while crushing tablets offers an early antiplatelet activity with a gain of approximately 1 h compared with the classic oral loading. However, these or other strategies do not lead to immediate platelet inhibition, which can have a significant impact on periprocedural ischemic events. STEMI represents a clinical scenario where the timeliness of PCI, the hemodynamic instability with reduced gut transit and drug absorption, the administration of morphine and the frequent presence of nausea, vomiting, intubation, and cardiogenic shock impair the feasibility or efficacy of antiplatelet therapy with oral P2Y₁₂ receptor inhibitors. In this context, i.v. administration of antiplatelet drugs could address such practical aspects, thus allowing for prompt and potent pharmacologic platelet inhibitory effects. Moreover, the possibility of administering cangrelor in catheterization laboratories may lead to avoiding surgical delays for patients with mechanical complications of STEMI (e.g. free ventricular wall rupture, ventricular septal defects) or with chest pain due to other causes (e.g. aortic dissection). Because prasugrel and ticagrelor are the first options in combination with aspirin for patients with ACS, a randomized trial comparing cangrelor with newer P2Y₁₂ inhibitors in the context of ACS and STEMI in particular, would undoubtedly be useful to better understand the comparative impact of i.v. antiplatelet therapy on periprocedural ischemic events. The CANCTIC (CANgrelor and Crushed TICagrelor in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention) trial was a prospective, randomized, double-blind, placebo-controlled pharmacodynamic study conducted in patients with STEMI undergoing primary PCI, who received cangrelor or placebo after oral administration of a 180-mg loading dose of ticagrelor. Cangrelor reduced platelet inhibition after just 5 min, with an effect that persisted throughout the infusion, proving to be an effective strategy in bridging the latency of platelet inhibition of oral drugs in the context of primary PCI. This superior pharmacodynamic effect was also supported by \textit{in vitro} investigations in which cangrelor was shown to enhance platelet inhibitory effects in patients treated with a loading dose while already on maintenance therapy with a more potent oral P2Y₁₂ inhibitor (prasugrel or ticagrelor). Several other studies are underway analyzing the effectiveness of cangrelor in different settings (Table 6).

\textbf{Other scenarios for cangrelor use}

Pretreatment with oral P2Y₁₂ inhibitors may delay revascularization in patients who are found to be candidates for coronary artery bypass grafting and may unnecessarily increase the risk of bleeding in patients who will not be subsequently treated by PCI. Current guidelines recommend the discontinuation of antiplatelet agents 5–7 days before surgery to enable the recovery of platelet function. This often causes treatment delays, prolongs hospitalization and increases the risk of ischemic events in the window period. In this setting, cangrelor may represent a valuable option due to the rapid return of platelets to normal at drug discontinuation. In the BRIDGE (Bridging Antiplatelet Therapy with Cangrelor in Patients Undergoing Cardiac Surgery) trial, 210 patients waiting for coronary artery bypass grafting were randomly assigned after the discontinuation of the second oral antiplatelet to cangrelor or placebo for at least 48 h, after an initial open-label phase of the study aimed at identifying the correct bridging dose of cangrelor to achieve an antiplatelet effect after oral P2Y₁₂ inhibitor discontinuation. The dose of 0.75 µg/kg per minute met the efficacy endpoint of maintenance of platelet inhibition and was therefore adopted for the randomized, double-blind, placebo-controlled phase of the trial. The primary efficacy endpoint of platelet reactivity demonstrated that the use of cangrelor resulted in a higher rate of maintenance of platelet inhibition. A recent consensus document underlines the
Table 6. Ongoing trials on cangrelor.

| ClinicalTrials.gov Identifier | Name                                                                 | Patients          | Comparison                                      | Primary endpoint                                                                                                                                 |
|------------------------------|----------------------------------------------------------------------|-------------------|------------------------------------------------|-----------------------------------------------------------------------------------------|
| NCT03182855                  | Cangrelor versus Ticagrelor for Early Platelet Inhibition in STEMI (CanTi) | 80 patients with STEMI | In-hospital cangrelor versus prehospital ticagrelor | Platelet reactivity 10 min after PCI is initiated                                      |
| NCT02733341                  | The Effect of Intravenous Cangrelor and Oral Ticagrelor on Platelets, the Microcirculation and Myocardial Damage in Patients Admitted With STEMI Treated by Primary Percutaneous Coronary Intervention: A Randomized Controlled Pilot Trial | 100 patients with STEMI | Cangrelor versus ticagrelor | Degree of platelet inhibition at infarct vessel open time (up to 24–36 h post-dosing) |
| NCT03043274                  | Periprocedural Cangrelor in Patients With ST Elevation Myocardial Infarction to Reduce Development of Myocardial Necrosis | 60 patients with STEMI | Standard STEMI care with standard dosing of cangrelor at the time of PCI versus standard STEMI care without cangrelor | Change in myocardial infarct size at 48 h and 3 months evaluated with cardiac MRI |
| NCT02978040                  | 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 (FABOLUS FASTER Trial) | 120 patients with STEMI | Tirofiban bolus + infusion versus cangrelor bolus + infusion versus prasugrel oral integer or chewed loading dose | Inhibition of platelet activity at 30 min |
| NCT03273075                  | Pharmacokinetic/Pharmacodynamic Effects of add-on Antiplatelet Therapy With Parenteral Cangrelor as Compared to Standard Dual Antiplatelet Treatment in Patients With ST elevation Myocardial Infarction Complicated by Out-of-hospital Cardiac Arrest and Treated With Targeted Temperature Management | 60 patients with resuscitated STEMI receiving targeted temperature management | Prasugrel + cangrelor versus ticagrelor + cangrelor versus prasugrel + placebo versus ticagrelor + placebo | Platelet reactivity at stent placement up to 4 h from study drug administration |
| NCT03551964                  | Dual Antiplatelet Therapy For Shock Patients With Acute Myocardial Infarction (DAPT-SHOCK-AMI) | 304 patients with STEMI and cardiogenic shock | Cangrelor versus ticagrelor | Combined endpoint defined as death/myocardial infarction/stroke at 30 days |
| NCT03862651                  | Maintenance Of aNtiplatElet Therapy in Patients With Coronary Stenting Undergoing Surgery (MONET BRIDGE) | 140 patients who undergoing to surgery | Cangrelor versus placebo | Level of residual platelet reactivity at 1–2 h |
| NCT03102723                  | Platelet Inhibition to Target Reperfusion Injury (PITRI) | 210 patients with STEMI | Cangrelor versus placebo | Myocardial infarct size evaluated with MRI at day 2–7 days after primary PCI |

IV, intravenous; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.
importance of temporary transition with i.v. platelet drugs as a bridging therapy in patients with high ischemic risk undergoing nondeferrable surgery with a high risk of bleeding and therefore requiring an interruption of antiplatelet therapy. The consensus document, building on the results of the BRIDGE trial, advises that cangrelor with a bridge dose regimen can be started after the suspension of the oral P2Y_12 inhibitor, and can be discontinued 1 h before the start of surgery. Subsequently, antiplatelet therapy should be resumed with oral loading of a P2Y_12 inhibitor or, if oral administration is not feasible, with cangrelor.

Cangrelor in clinical practice guidelines

No recommendation for the use of cangrelor can be presently found in the ACC/AHA guidelines, given that the drug was approved only after the most recent guideline updates. Conversely, the most recent guidelines from the ESC recommend cangrelor as a class IIb for patients across the spectrum of patients with coronary artery disease who are P2Y_12-inhibitor-naive while undergoing PCI.

Conclusion

The evolving landscape of antithrombotic agents for coronary artery disease, with a faster time for coronary angiography and the availability of more potent oral agents than clopidogrel, has led to a reappraisal of the role of GPIs as a strategy to reduce PCI periprocedural complications. Current recommendations for GPIs include bailout use and bridging for selected patients. Cangrelor is a newer agent with a faster onset and offset of action, with some more favorable pharmacologic characteristics than GPIs. Cangrelor can be used in patients who are P2Y_12-inhibitor-naive undergoing PCI to reduce the incidence of periprocedural thrombotic complications. Ongoing clinical trials will provide further insights into the comparative role of cangrelor and ticagrelor as developments in the field of antithrombotic pharmacotherapy continue.

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