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Cangrelor — Expanding therapeutic options in patients with acute coronary syndrome

Jacek Kubica et al., Cangrelor in patients with ACS

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Abstract

Cangrelor is the only intravenous P2Y12 receptor antagonist. It is an adenosine triphosphate analog that selectively, directly, and reversibly binds to the platelet P2Y12 receptors exerting its antiaggregatory effect. Cangrelor is characterized by linear, dose-dependent pharmacokinetics and rapid onset of action providing potent platelet inhibition exceeding 90%. Cangrelor is rapidly metabolized by endothelial endonucleotidase; thus, its half-life is 2.9 to 5.5 min, and its antiplatelet effect subsides within 60 to 90 min. Data originating from three pivotal cangrelor trials (CHAMPION PLATFORM, CHAMPION PCI, and CHAMPION PHOENIX) indicate that cangrelor reduces the risk of periprocedural thrombotic complications during percutaneous coronary intervention at the expense of mild bleedings. Its unique pharmacological properties allow it to overcome the limitations of oral P2Y12 receptor inhibitors, mainly related to the delayed and decreased bioavailability and antiplatelet effect of these agents, which are often observed in the setting of acute coronary syndrome. Subgroups of patients who could theoretically benefit the most from cangrelor include those in whom pharmacokinetics and pharmacodynamics of oral P2Y12 receptor antagonists are most disturbed, namely patients with ST-segment elevation myocardial infarction, those treated with opioids, with mild therapeutic hypothermia, or in cardiogenic shock. Cangrelor could also be useful if bridging is required in patients undergoing surgery. According to the current guidelines cangrelor may be considered in P2Y12 receptor inhibitor-naïve patients undergoing percutaneous coronary intervention in both acute and stable settings.

Keywords: antiplatelet therapy, cangrelor, percutaneous coronary intervention, P2Y12 receptor inhibition

Limitations of oral P2Y12 inhibitors

Oral platelet P2Y12 receptor inhibitors are one of the pillars of contemporary treatment of acute coronary syndrome (ACS) [1, 2]. One of the main mechanisms behind ACS is unrestrained platelet aggregation, which is most vivid during the early hours of an acute coronary event. P2Y12 receptor inhibition allows limitation of this excessive activation, thus preventing further thrombotic complications and hindering myocardial ischemia.

Although the benefits of oral P2Y12 receptor inhibitors in ACS are indisputable [3–5], several limitations restricting their efficacy have been identified. Bioavailability of orally administered antiplatelet agents is frequently decreased in patients with ACS, especially in

those diagnosed with ST-segment elevation myocardial infarction (STEMI) [6], in critical condition [7], undergoing targeted temperature management [8, 9], or if morphine is used [10, 11]. The pharmacokinetics of oral P2Y12 receptor inhibitors are often altered not only due to reduced and delayed intestinal absorption, but also due to impaired drug metabolism, particularly when clopidogrel is used [12, 13]. This results in a significant inter-individual variability in onset and potency of antiplatelet response to oral P2Y12 receptor antagonists during the initial phase of ACS treatment, even when novel agents, prasugrel or ticagrelor, are administered [14–16]. As a result, regardless of the oral agent used, a significant proportion of ACS patients do not achieve a sufficient antiaggregatory effect by the time of percutaneous coronary intervention (PCI) or directly following the procedure [6, 11, 14, 15]. Patients with STEMI, receiving morphine, or undergoing mild therapeutic hypothermia are among those at greatest risk of insufficient platelet blockade in the first hours after the loading dose [6, 10, 11, 14, 16–20]. Sufficient platelet inhibition may also be uncertain in patients with nausea or vomiting, or in those who are unable to swallow or promptly absorb orally given P2Y12 receptor antagonists, i.e., patients who are sedated, intubated, or in shock [21–23]. On-treatment high platelet reactivity is a risk factor for stent thrombosis, myocardial infarction (MI), and death; therefore, timely antiaggregatory action is of great importance in all ACS patients, particularly if treated with PCI [24–27]. Additionally, the antiplatelet effect of clopidogrel, prasugrel, and ticagrelor endures for at least several days after the last dosing. Currently no antidote for oral P2Y12 receptor antagonists is commercially available, making attempts to restore platelet function in patients receiving these agents futile if an urgent surgery is necessary or if bleeding occurs [28]. The abovementioned restraints indicate a demand for a potent intravenous P2Y12 receptor inhibitor with rapid recovery of platelet activity after cessation of the infusion.

Comparison of P2Y12 inhibitors

Clopidogrel and prasugrel are prodrugs that require hepatic activation, and their active metabolites irreversibly inhibit the P2Y12 receptor. In contrast, ticagrelor and cangrelor are active drugs that directly and reversibly block this receptor. The characteristics of the key features of P2Y12 inhibitors are presented in Table 1. All P2Y12 inhibitors require a loading dose to achieve prompt onset of antiplatelet action, which is almost immediate for intravenous cangrelor, relatively fast for ticagrelor and prasugrel (30 min), and delayed for clopidogrel (2 h). The level of platelet inhibition is also the highest for intravenous cangrelor (> 90%), lower for prasugrel and ticagrelor (65–80%), and only 40–60% for clopidogrel. The longest time

required to offset the antiplatelet effect of oral P2Y12 antagonists is for prasugrel, shorter for clopidogrel, and the shortest for ticagrelor; thus, recommended discontinuation of treatment before surgery is only 3–5 days for ticagrelor and 7 days for prasugrel. Recommended cessation of intravenous infusion of cangrelor is only 1 hour, due to its rapid metabolism. None of the P2Y12 inhibitors requires dose adjustment in renal failure; however, data for patients with creatinine clearance < 15 mL/min or dialyzed are limited.

Structure and mechanism of action

Cangrelor, N^6-[2-(methylthio)ethyl]-2-[(3,3,3-triflouropropyl)thiol]-5'-adenylic acid, is an adenosine triphosphate (ATP) analog. ATP is an agonist of the P2X1 receptor. Stimulation of the P2X1 receptor initiates the influx of Ca^{2+} to platelets translating into shape change and amplification of platelet activation induced by other agonists [29]. Although the P2X1 receptor mediates platelet activation, its stimulation cannot initiate platelet aggregation; therefore, it has not become the target of antiplatelet therapies. Cangrelor, unlike the parent compound, has high affinity for the adenosine diphosphate (ADP) P2Y12 receptor and longer half-life. It selectively, directly, and reversibly binds to the P2Y12 receptor.

A body of evidence suggests antithrombotic properties of cangrelor beyond P2Y12 receptor antagonism. Cangrelor can inhibit platelet function through an increase in cyclic adenosine monophosphate levels not related to P2Y12 receptor antagonism [30]. In a pharmacodynamic in vitro study in patients with coronary artery disease (CAD) cangrelor reduced platelet reactivity not only via potent P2Y12 blockade, but also through non-purinergic pathways with no influence on thrombin generation [31]. On the other hand, the antiplatelet effect of cangrelor was not observed in P2Y12 receptor-deficient mice [32]. In two experimental animal studies cangrelor exerted a cardioprotective effect in a mechanism resembling post-conditioning, reducing infarct size by up to 50% in rabbit and a primate model [33, 34]. The mechanism of the observed cardioprotective effect is likely to affect the signaling pathway seen in pre- and postconditioning [33].

Pharmacokinetics and pharmacodynamics

Cangrelor is the only intravenous P2Y12 receptor antagonist. The drug is characterized by a rapid onset of action, providing significant platelet inhibition within 2 minutes of bolus injection [31, 35]. Administration of initial bolus followed by an infusion provides inhibition of platelet aggregation exceeding 90% [36, 37]. Cangrelor follows linear, dose-dependent pharmacokinetics, achieving a steady-state plasma concentration within 30-

minutes [37, 38]. Its volume of distribution is mainly limited to circulation [36]. Cangrelor plasma half-life ranges from 2.9 to 5.5 minutes, as it is rapidly dephosphorylated by endothelial endonucleotidase [39]. Platelet function returns to baseline within 60–90 minutes of cessation of the infusion [37, 38]. The main pharmacological features of cangrelor are presented in the Central illustration.

The metabolism of cangrelor is not liver or renal dependent, allowing administration in patients with abnormal liver or kidney function. The pharmacokinetics and pharmacodynamics of the drug are not affected by gender, age, ethnic background, diabetic status, administration of acetylsalicylic acid, heparin, nitroglycerin, bivalirudin, low-molecular-weight heparin, fondaparinux, glycoprotein IIb/IIIa inhibitors (GPI), or morphine [40–42].

The unique properties of rapid onset and offset of the antiplatelet effect make cangrelor an attractive therapeutic option complementary to available oral antiaggregatory drugs.

Scientific evidence for use of cangrelor

The results of three major, randomized, placebo-controlled clinical trials on the efficacy and safety of cangrelor in a broad range of PCI-treated patients with CAD are available: CHAMPION PLATFORM [43], CHAMPION PCI [44], and CHAMPION PHOENIX [45].

The CHAMPION PLATFORM trial consisted of 5362 patients requiring PCI due to non-ST-segment elevation myocardial infarction (NSTEMI) (59.4%) or unstable angina (35.4%) [43]. Patients with stable angina (5.2%) were also initially eligible before a protocol amendment. The occurrence of the primary efficacy endpoint, defined as a composite of death, MI, or ischemia-driven revascularization within 48 hours after PCI, was numerically lower in the cangrelor group than in the placebo group, but the difference was not significant. The rate of stent thrombosis was significantly lower in the cangrelor group at 48 hours and at 30 days. All-cause mortality rate was significantly lower in patients treated with cangrelor at 48 hours, but not at 30 days (Table 2). The rates of bleeding did not differ significantly between the two groups according to TIMI and GUSTO criteria. However, according to more sensitive ACUITY criteria, the bleeding rates were significantly higher in the cangrelor group. The difference in rates of bleeding defined as major according to the ACUITY criteria, was solely due to an excess of groin hematomas, with no contribution of more serious forms of bleeding [43].

The CHAMPION PCI trial included 8877 patients treated with PCI due to stable angina (15.0%), unstable angina (24.6%), NSTEMI (49.2%), or STEMI (11.2%; n = 996) [44]. The primary endpoint of death from any cause, MI, or ischemia-driven revascularization at 48 hours occurred in similar proportions in both study arms: the experimental arm (cangrelor plus clopidogrel) and the active control arm (placebo plus clopidogrel). No significant differences between the groups with regard to any single efficacy endpoint at 48 hours were found (Table 2). Minor, but not major, bleedings occurred more frequently in the cangrelor arm according to the ACUITY and GUSTO criteria. According to the TIMI criteria, no increase in bleeding was seen, irrespective of the type of bleeding [44].

Both CHAMPION trials were discontinued following a decision by the interim analysis review committee claiming that the studies would not show the persuasive clinical efficacy needed for approval, although 98% of the planned 9000 patients for CHAMPION PCI and 83% of the scheduled 6000 patients for CHAMPION PLATFORM had been enrolled [43, 44].

The definitions of all endpoints used in the CHAMPION PLATFORM and CHAMPION PCI trials were mutually consistent [43, 44]. The primary composite endpoint of these trials was negative; therefore, any single endpoint should be interpreted with caution. Interestingly, the primary endpoint in the CHAMPION trials was driven by the occurrence of MI. The universal definition of MI was developed after initiation of the CHAMPION PCI and CHAMPION PLATFORM trials.

Because both CHAMPION trials had the same composite primary endpoint and used similar inclusion and exclusion criteria, the studies were pooled together. The clinical events committee adjudicated all cases of MI, and the new universal definition was used. A total of 13,049 patients were included [46]. No effect of cangrelor with regard to the primary endpoint was revealed with the original definition of MI. However, after application of the universal definition of MI a significant reduction of the primary endpoint with the cangrelor–clopidogrel combination, compared with clopidogrel alone, was observed (Table 2). No increase in blood transfusions or major bleeding assessed with the TIMI or GUSTO bleeding scales were observed with cangrelor compared with clopidogrel. Only the more sensitive ACUITY scale showed an increase in clinically significant major bleedings with cangrelor, mainly because of an increased occurrence of groin hematomas [43, 44, 46].

The CHAMPION PHOENIX trial was designed to evaluate whether cangrelor reduces ischemic complications of PCI [45]. A total of 10,942 patients requiring PCI for stable angina (56.1%), non-ST-segment elevation ACS (NSTE-ACS) (25.7%), or STEMI (18.2%) received

a bolus with a subsequent infusion of cangrelor or placebo. The rate of the primary composite efficacy endpoint of death from any cause, MI (according to the universal definition of MI), ischemia-driven revascularization, or stent thrombosis at 48 hours was significantly lower in the cangrelor group than in the clopidogrel group (Table 2). Apart from the reduction in stent thrombosis, the benefits of cangrelor in the CHAMPION PHOENIX trial were mostly attributed to the decreased occurrence of MI. The observed 22% reduction in the likelihood of ischemic event in patients treated with cangrelor was not accompanied by a significant increase in severe bleeding or in the need for transfusions compared with patients on clopidogrel. More sensitive measures showed an increase in bleeding with cangrelor, as would be expected of a potent antiplatelet agent. The composite endpoint of the net rate of efficacy and safety adverse clinical events was 4.8% in the cangrelor group and 6.0% in the clopidogrel group (odds ratio [OR] 0.80; 95% confidence interval [CI] 0.68–0.94; p = 0.008) [45].

A prespecified, pooled analysis of data from the three pivotal CHAMPION trials [47] indicated that cangrelor reduces the risk of periprocedural thrombotic complications during PCI at the expense of mild bleedings. On the other hand, an exploratory analysis of pooled patient-level data from the CHAMPION trials revealed lower risk-adjusted bleeding risk in patients receiving cangrelor alone compared with GPI on the background of clopidogrel or placebo (TIMI-defined major or minor bleeding: 0.7% vs. 2.4%; OR 0.29; 95% CI 0.13–0.68) with no significant differences between the groups regarding the primary endpoint (the composite of all-cause mortality, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours: 2.6% vs. 3.3%; OR 0.79; 95% CI 0.48–1.32) [48].

Specific indications for cangrelor

Cardiogenic shock

Cardiogenic shock (CS) is a life-threatening clinical syndrome caused by primary cardiac dysfunction, resulting in an inadequate cardiac output, comprising a state of tissue hypoperfusion, which can result in multi-organ failure and death. It may occur in up to 8–12% of patients with STEMI and up to 4% of patients with NSTE-ACS, with 30-day mortality of 40–55% [49, 50].

Acute myocardial ischemia is a predominant cause of CS in patients presenting with ACS. Mechanical complications of ACS, such as papillary muscle rupture with severe mitral valve regurgitation, ventricular septal defect, or free wall rupture, are additional causes of CS often requiring cardiac surgery [49]. Immediate coronary angiography and PCI of the culprit

lesion is indicated for patients with ACS and CS, irrespective of initial clinical presentation (STEMI or NSTE-ACS) and time delay of symptom onset, if coronary anatomy is amenable to PCI [50].

In patients presenting with STEMI and CS it is usually difficult to exclude possible contraindications for aggressive antithrombotic treatment in the pre-hospital phase [51]. In patients with NSTE-ACS routine pretreatment with P2Y12 inhibitors is no longer recommended [52]. Thus, most patients with ACS and CS who arrive to the cath lab are P2Y12 receptor inhibitor naïve, and the decision to administer antiplatelet therapy is made after coronary angiography. The effect of oral P2Y12 receptor inhibitors is delayed in CS patients due to slower absorption in the gastrointestinal tract, which is exacerbated by morphine use and inefficient conversion of the prodrugs to their active forms in the liver, and challenges with adequate enteral access in intubated patients. In such cases, intravenous medications, such as GPI or cangrelor, are a reasonable option. Nonetheless, scientific evidence supporting their use in patients undergoing PCI in CS remains very limited.

Two meta-analyses and a “real-world” registry indicate that therapy with GPI as an adjunct to the standard treatment in CS is associated with better outcomes, including both short- and long-term survival, without increasing the risk of bleeding [52–54]. However, the limitations of the abovementioned studies limit the generalization of their results.

Excellent bioavailability, fast-acting properties, and safety in renal impairment make cangrelor an attractive option for P2Y12 receptor inhibitor-naïve patients with CS undergoing PCI. However, CS was an exclusion criterion in the abovementioned landmark clinical trials, and only few single-center experiences have evaluated the impact of intravenous P2Y12 receptor inhibition in high-risk patients with cardiopulmonary resuscitation or CS, especially compared with use of newer oral P2Y12 receptor inhibitors, prasugrel and ticagrelor. In a global, multicenter, matched pair analysis with oral P2Y12 inhibition from the IABP-SHOCK II trial, cangrelor treatment was associated with similar bleeding risk and significantly better TIMI flow improvement compared with oral P2Y12 receptor inhibitors in CS patients undergoing PCI. Thus, the use of cangrelor in CS offers a potentially safe and effective antiplatelet option and should be evaluated in randomized trials [55].

Out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) frequently occurs in the early phase of acute MI. OHCA survivors presenting symptoms of acute MI require primary PCI with concomitant dual antiplatelet therapy (DAPT), including acetylsalicylic acid and a P2Y12 receptor

inhibitor [55–57]. Several studies showed insufficient efficacy of clopidogrel in patients undergoing targeted temperature management (TTM) at 32–34°C after OHCA, with an alarmingly high incidence of acute stent thrombosis [19, 58, 59]. This was mostly explained by accelerated platelet turnover, increased platelet activation, as well as by decreased bioavailability of clopidogrel due to its impaired absorption and diminished generation of active metabolite [19, 55, 60]. However, Joffre et al. [61] found TTM in patients after OHCA to be an independent risk factor for confirmed stent thrombosis (OR 12.9; 95% CI 1.3–124.6, p = 0.027), regardless of the type of oral P2Y12 antagonist, even when prasugrel or ticagrelor were used. The results of the ISAR-SHOCK registry demonstrated a weaker antiplatelet effect in shock patients receiving either clopidogrel or prasugrel without hypothermia [62]. This observation may suggest that the impaired effect of oral P2Y12 inhibitors in OHCA is related not only to hypothermia, but also to centralization of circulation in critically ill patients [7, 9, 12, 62–64]. Regardless of the exact mechanisms of ineffectiveness of these drugs, intravenous infusion of cangrelor is capable of inhibiting life-threatening platelet-mediated prothrombotic events in the setting of TTM. This innovative pharmacological strategy could significantly improve the safety of TTM; however, it still warrants evaluation in properly designed randomized trials in this setting [65–67].

Therapy with opioids

Opioids are the most commonly administered group of medications for pain management in the course of acute MI. Morphine and fentanyl have been found to negatively influence pharmacokinetic and pharmacodynamic profiles of P2Y12 receptor inhibitors, mainly by reducing the bioavailability of these agents. Of note, impairment of gastrointestinal motility, as well as pro-emetic effects of opioids, contribute to unfavorable outcomes of concomitant administration of P2Y12 receptor inhibitors. The IMPRESSION trial showed that patients diagnosed with MI who received morphine needed up to 4 hours to achieve adequate platelet inhibition after the ticagrelor loading dose [11]. A similar observation was made for prasugrel in STEMI patients [14]. Based on the CRUSADE registry, NSTE-ACS patients who received morphine were at higher risk of adverse effects including MI (OR 1.34, 95% CI 1.22–1.48), death (adjusted OR 1.48, 95% CI 1.33–1.64), or a composite of death and MI (adjusted OR 1.44, 95% CI 1.34–1.56) [68]. To date, several methods to overcome the so-called “morphine effect” have been proposed. Sublingual administration of ticagrelor, co-administration of metoclopramide or oral naloxone, as well as chewing or crushing tablets have aimed at improving the pharmacokinetics and pharmacodynamics of particular P2Y12

receptor inhibitors, but the outcomes were unsatisfactory [69–73]. Only crushing or chewing P2Y12 inhibitor tablets was associated with noticeably better results in ACS patients [69, 72–75].

The CANTIC trial showed that in STEMI patients the addition of cangrelor to crushed ticagrelor allows adequate platelet inhibition as little as 5 minutes after the initiation of a cangrelor infusion. A superior antiaggregatory effect of cangrelor with crushed ticagrelor vs. crushed ticagrelor alone was documented for the whole duration of cangrelor infusion. No differences in levels of platelet reactivity between the study arms were present after discontinuation of cangrelor, excluding a drug-drug interaction when cangrelor and ticagrelor were concomitantly administered [76].

Cangrelor provides rapid and effective platelet inhibition, and its antiplatelet activity is independent of gastrointestinal tract function. Based on the above, it appears that cangrelor could be considered as an optimal antiplatelet agent for ACS patients on concomitant therapy with morphine who are qualified for invasive treatment.

PCI in P2Y12-naïve patients

Despite the common availability of P2Y12 receptor inhibitors in ambulances, many ACS patients still arrive in the cath lab not pretreated. In STEMI, where time to primary PCI is critical, the delayed action of clopidogrel makes the platelets fully active at the time of reperfusion and stent deployment [77, 78]. Even in cases where potent and fast-acting oral agents are given (prasugrel, ticagrelor), their effect is often delayed due to selective shunting of blood to vital organs, vomiting, or malabsorption caused by opiate use [11]. New compounds with the potential to overcome these limitations and provide a timely and potent antiaggregatory effect in the acute setting are selatogrel and zalunfiban. These are new parenteral antiplatelet agents that are currently under investigation in phase 3 trials. The SOS-AMI trial (Selatogrel Outcome Study in Suspected Acute Myocardial Infarction; NCT04957719) and the CELEBRATE study (A Phase 3 Study of Zalunfiban in Subjects With ST-elevation MI; NCT04825743) will explore the efficacy and safety of the respective agents in the prehospital phase of MI treatment. However, at this point it is unknown when they will be commonly available.

The problem of inappropriate platelet inhibition is not limited to ACS patients. In Poland, most elective PCI procedures are performed immediately after coronary angiography. Inadequate pretreatment with P2Y12 receptor inhibitors may contribute to a significantly

increased risk of periprocedural thrombotic complications, mainly if complex PCI techniques are used.

An intravenous bolus of cangrelor fills this gap perfectly in all these situations, ensuring an extensive platelet blockade within minutes of administration. Later, cangrelor markedly inhibits platelet aggregation throughout infusion duration at all critical moments of PCI itself and immediately after [37]. As mentioned before, in the CHAMPION PHOENIX study, in P2Y12-naïve patients undergoing PCI with stable CAD and ACS, cangrelor significantly reduced the primary endpoint of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours, and the key secondary endpoint of stent thrombosis alone (OR 0.62; 95% CI 0.43–0.90; p = 0.01), without a significant increase in the rate of major bleeding [79]. Importantly, cangrelor showed a more significant absolute effect with the increased complexity of the coronary procedure [80].

Due to the lack of head-to-head clinical comparative studies, it is still undetermined whether cangrelor is superior to intravenous GPI in P2Y12 receptor inhibitor-treated patients. In the FABOLUS FASTER study, cangrelor provided inferior platelet inhibitory effects than tirofiban, but it was more significant than that achieved with prasugrel [81]. Of note, it has been suggested that the inadequate antiaggregatory effect of cangrelor seen in this trial could have been due to a delay in platelet function testing related with the methodology of light transmittance aggregometry used in this study. Cangrelor has a very short half-life and binds reversibly to the P2Y12 receptors; thus, its antiplatelet effect could have been diminished at the time of pharmacodynamic assessment [82]. A retrospective, observational registry of 2072 patients (66% with ACS) who received adjunctive antiplatelet therapy during PCI (478 cangrelor, 1594 GPI) revealed that in-hospital ischemic events did not differ between the groups. In contrast, major bleeding events (1.7% vs. 5.1%, p = 0.001), or any vascular complication rates, were significantly lower in the cangrelor group [83].

Bridging to coronary artery bypass grafting

The recommended duration of DAPT depends on the clinical manifestation of CAD, the anatomy of coronary lesions, and the type of stent implanted. The risk of ischemic events in PCI-treated patients increases with comorbidities such as diabetes, chronic kidney disease, or heart failure. The necessity of DAPT after drug eluting stent implantation ranges from 3 to 12 months, like in ACS [1]. The shortening of DAPT duration has become possible thanks to rapid advances in stent technology [84, 85].

During DAPT, some patients require cardiac or non-cardiac surgery [86]. The surgery itself generates an inflammatory response, activates platelets, the sympathetic nervous system, vascular spasm, and release of cytokines that inhibit endogenous fibrinolysis and activate the endothelial coagulation cascade. These mechanisms result in an increased risk of thrombotic complications [87, 88].

The highest risk of thrombotic complications is within the first 3 months after drug eluting stent implantation and decreases over time [84]. On one side, interruption of DAPT is associated with the risk of stent thrombosis, and on the other, surgery during DAPT increases the risk of bleeding. Therefore, the use of bridging therapy with rapid and short-acting antiplatelet drugs is justified [87, 88].

Initially GPIs were used as a bridging therapy. Eptifibatide is a reversible GPI with a half-life of 2.5 hours. Platelet reactivity returns 4 hours after stopping the infusion. Bridging therapy with eptifibatide resulted in a reduction of ischemic complications; however, an increased rate of bleeding events was observed [89, 90]. Tirofiban, another short-acting and reversible GPI, showed similar results to eptifibatide in bridging therapy, reducing ischemic complications while major bleeding events and the need for transfusion were higher [90, 91].

Cangrelor with its rapid, predictable, and dose-dependent antiplatelet effect together with quick offset of action predispose it for use in bridging therapy as an alternative to GPI [88]. Cangrelor is the only drug used in bridging therapy with randomized trials evaluating its effectiveness and dosing schedule for these indications [92]. In the bridging therapy, a dose of 0.75 μg/kg/min was established, which shows a high degree of platelet inhibition with no increase in bleeding rate compared to placebo. The dose during PCI is 4 μg/kg/min. The use of a bridging dose of cangrelor is crucial to reduce the risk of perioperative bleeding [93]. Despite the limited number of studies on bridging therapy, such a strategy should be considered in patients at high risk of ischemic complications requiring non-deferrable surgery.

New bridging strategies are being studied, including the use of a fast and short-acting subcutaneous P2Y12 receptor inhibitor (selatogrel), the use of a monoclonal antibody that inactivates ticagrelor, or strategies based on the rapid removal of ticagrelor during extracorporeal circulation [88].

Switching between P2Y12 inhibitors

Switching from intravenous to oral medication for PCI depends on the type of P2Y12 receptor inhibitor. The half-life and possible drug-drug interactions should be taken into account because of the risk of insufficient antiplatelet effect. Prasugrel and clopidogrel are

prodrugs, and their active metabolites reveal an antiplatelet effect. These metabolites are formed sequentially in a one- (prasugrel) or two-step (clopidogrel) process. Cangrelor blocks their bindings to the platelet receptors; therefore, these drugs should not be started simultaneously [94, 95]. The active metabolite of clopidogrel is unstable and has a very short half-life, which means it is rapidly metabolized if not bound to the platelet receptor. The effect of cangrelor begins after 2 minutes and ends soon after stopping the infusion. Thus, clopidogrel in a loading dose of 600 mg should be administered immediately after discontinuation of the cangrelor infusion [39, 94, 95]. On the other hand, prasugrel metabolites have prolonged effects due to a longer half-life and higher plasma concentrations. After discontinuation of the cangrelor infusion platelet reactivity returns to normal within an hour, and, as a consequence, a gap in antiplatelet activity may appear [96, 97]. However, the administration of prasugrel in a dose of 60 mg at the end of the cangrelor infusion, or 30 minutes before the end, prevents complete platelet reactivation, which has not been observed with other P2Y12 inhibitors [96].

The third agent, ticagrelor, acts directly but has reversible binding. The administration of 180 mg ticagrelor can be initiated simultaneously with the start of the cangrelor infusion, because there is no interaction between these drugs and the half-life time of ticagrelor is longer than the infusion [94].

Prior to cardiac or non-cardiac surgery, switching from oral to intravenous therapy increases the percentage of platelet inhibition compared to placebo [92]. Prasugrel should be stopped 7 days before surgery, while clopidogrel should be withheld for 5 days and ticagrelor for 3–5 days prior to surgery [98]. Intravenous infusion of cangrelor at a dose of 0.75 μg/kg/min should be started within 48 hours of discontinuing oral P2Y12 receptor inhibitor and continued for at least 48 hours, but for a maximum of 7 days. The infusion should be stopped for 1–6 hours prior to the procedure, and then cangrelor should be restarted within 1–6 hours after the end of the procedure.

Official recommendations for cangrelor

Cangrelor is currently available in most European markets. It was approved by the European Medical Agency for a specific subgroup of CAD patients undergoing PCI, who did not receive another P2Y12 receptor inhibitor before the PCI, and in subjects for whom oral P2Y12 inhibitors therapy is not feasible or desirable. Cangrelor should be administered as a bolus of 30 mg/kg IV followed by 4 mg/kg/min infusion for at least 2 hours or the duration of the procedure (whichever is longer). Furthermore, it was specified that the infusion of

cangrelor must not exceed 4 hours [40]. According to the European Society of Cardiology (ESC) guidelines on ACS, cangrelor has a class IIb recommendation with level of evidence A both in STEMI and NSTE-ACS settings, and it may be considered in P2Y12-inhibitor-naïve patients undergoing PCI [50]. Furthermore, the ESC guidelines on myocardial revascularization give the same recommendation for cangrelor use in peri-interventional treatment in stable patients [50]. It must be stressed that in patients receiving an infusion of cangrelor during intervention, the timing of administration of oral P2Y12 inhibitors should be drug specific, as mentioned above: ticagrelor 180 mg, at any time during infusion or immediately after discontinuation; prasugrel 60 mg, immediately after discontinuation of cangrelor; clopidogrel 600 mg, immediately after discontinuation of infusion. The United States Food and Drug Administration approved cangrelor as an adjunct to PCI to reduce the risk of stent thrombosis, periprocedural MI, and repeated revascularization in patients not pre-treated with an oral P2Y12 inhibitor and without indication to receive GPI [99]. This was reflected in the latest ACC/AHA/SCAI Guidelines for Coronary Artery Revascularization, in which cangrelor received class 2B recommendation with level of evidence B-R for patients undergoing PCI, who are naïve to oral P2Y12 receptor inhibitors, to reduce periprocedural ischemic events [100].

Conclusions

Cangrelor is the only available intravenous P2Y12 receptor antagonist, and it is characterized by a rapid onset of potent antiplatelet effect, which subsides quickly after discontinuation of the infusion. Its unique properties may prove very useful not only in ACS or CAD patients treated invasively, but also in specific subgroups of patients at risk of impaired antiaggregatory action after a loading dose of oral P2Y12 receptor inhibitor. According to the current guidelines, cangrelor may be considered in P2Y12 receptor inhibitor-naïve patients undergoing PCI in both acute and stable settings.

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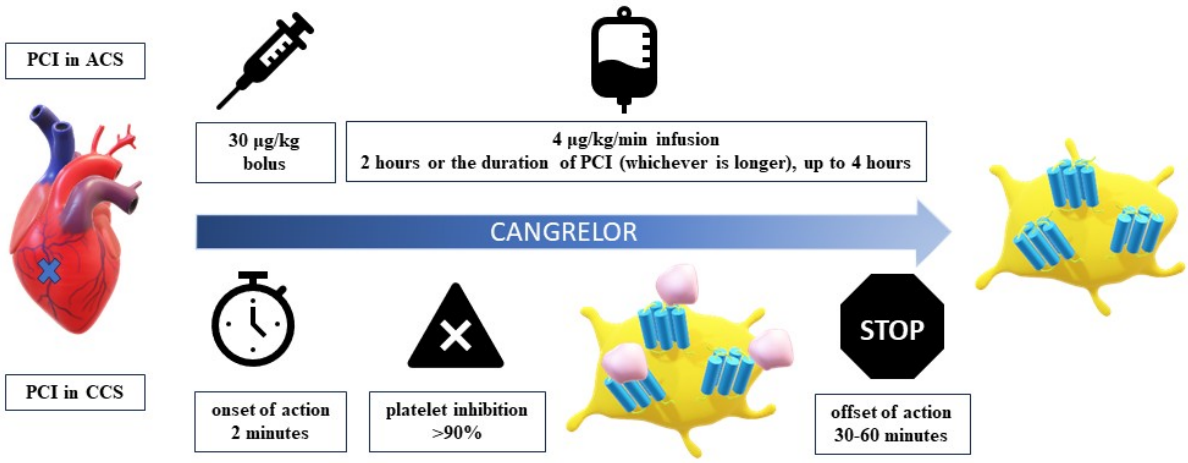

Central illustration. Cangrelor — indications, main pharmacological features, and mechanism of action. Cangrelor may be considered in P2Y12-inhibitor-naïve patients undergoing percutaneous coronary intervention (PCI) for both acute coronary syndrome (ACS) and chronic coronary syndrome (CCS). It is an intravenous adenosine triphosphate analog that reversibly binds to platelet P2Y12 receptors and is characterized by rapid and potent platelet inhibition after an intravenous bolus followed by a continuous infusion, as well as quick offset of antiplatelet effect after discontinuation of infusion thanks to a rapid metabolism.

Table 1. Comparison of P2Y12 inhibitors.

	Clopidogrel	**Prasugrel**	**Ticagrelor**	**Cangrelor**
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Adenosine triphosphate analogue
Route	Oral	Oral	Oral	Intravenous
Prodrug	Yes (pro-drug, CYP dependent, 2 steps)	yes (pro-drug, CYP dependent, 1 step)	No	No
Bioavailability	15%	79%	36%	100%
Standard dosage	600 mg LD, then 75 mg once a day	60 mg LD, then 10 mg once a day	180 mg LD, then 90 mg twice a day	30 μg/kg bolus, then 4 μg/kg/min
Reversibility of binding	Irreversible	Irreversible	Reversible	Reversible
Onset of antiplatelet effect	2–6 h	0.5–4 h	0.5–2 h	2 min
Level of platelet inhibition at steady state	40–60%	65–80%	65–80%	90–98%
Offset of antiplatelet effect	3–10 days	5–10 days	3–4 days	30–60 min
Recommended stop of treatment before surgery	5 days	7 days	3–5 days	1 h
Excretion	50% renal, 46% biliary	68% renal, 27% feces	Biliary	Not dependent on hepatic or renal clearance mechanisms
Kidney failure	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Dialysis or CrCl < 15 mL/min	Limited data	Limited data	Limited data	Limited data

CrCl — creatinine clearance; LD — loading dose

Table 2. Efficacy of cangrelor in the major clinical studies.

Acronym	N	Primary endpoint				All-cause mortality				Myocardial infarction				Stent thrombosis			
		Cangrelor, n (%)	Clopidogrel n (%)	OR	P	Cangrelor, n (%)	Clopidogrel, n (%)	OR	P	Cangrelor, n (%)	Clopidogrel, n (%)	OR	P	Cangrelor, n (%)	Clopidogrel, n (%)	OR	P
CHAMPION PCI	8877	290 (7.5%)	276 (7.1%)	1.05	0.59	8 (0.2%)	5 (0.1%)	1.59	0,42	278 (7.1%)	256 (6.6%)	1.09	0.36	7 (0.2%)	11 (0.3%)	0.63	0.34
CHAMPION PLATFORM	5362	185 (7%)	210 (8%)	0.87	0.17	6 (0.2%)	18 (0.7%)	0.33	0.02	177 (6.7%)	191 (7.2%)	0.92	0.42	5 (0.2%)	16 (0.6%)	0.31	0.02
CHAMPION PHOENIX	11145	257 (4.7%)	322 (5.9%)	0.78	< 0.01	18 (0.3%)	18 (0,3%)	1	> 0.99	207 (3.8%)	255 (4.7%)	0.8	0.02	46 (0.8%)	74 (1.4%)	0.62	0.01
Pooled, redefined 1+2	14239	202 (3.1%)	244 (3.8%)	0.82	0.04	14 (0.2%)	23 (0.4%)	0.6	0.14	171 (2.6%)	194 (3.0%)	0.87	0.2	12 (0.2%)	27 (0.4%)	0.44	0.02

OR — odds ratio; n — number