
Article:
Storey, R.F. orcid.org/0000-0002-6677-6229 and Sinha, A. (2016) Cangrelor for the management and prevention of arterial thrombosis. Expert Review of Cardiovascular Therapy, 14 (6). pp. 991-999. ISSN 1477-9072

https://doi.org/10.1080/14779072.2016.1207528

Cangrelor for the management and prevention of arterial thrombosis

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SUMMARY

Cangrelor is an intravenous, reversibly-binding platelet $P2Y_{12}$ receptor antagonist with ultra-rapid onset and offset of action. It is approved in Europe and United States for use in patients undergoing percutaneous coronary intervention, a setting in which it has proven superiority to initial treatment with clopidogrel. Preliminary clinical evidence suggests it would also be a favourable option in bridging patients from discontinuation of oral antiplatelet therapy to the time of major surgery. This review describes the background for the development of cangrelor, the biology, pharmacology and clinical evidence supporting its use, and its likely position in the future.

KEYWORDS: Cangrelor; platelet receptor inhibitor; $P2Y_{12}$ receptor; percutaneous coronary intervention; arterial thrombosis; stent thrombosis

Introduction

Thrombotic complications of atherosclerosis, as well as revascularisation procedures for its management, place a huge burden on global health care systems and account for a substantial proportion of worldwide morbidity and mortality. Much of this is consequent to acute coronary syndromes (ACS), which include the diagnoses of acute myocardial infarction (ST-elevation or non-ST-elevation) and unstable angina. Percutaneous coronary intervention (PCI) with stent implantation is a key procedure in the management of patients with ACS as well as stable coronary artery disease (CAD). Present guidelines recommend the use of dual antiplatelet therapy, aspirin and an oral platelet $P2Y_{12}$ inhibitor, to prevent peri-procedural thrombotic complications, including stent thrombosis, myocardial infarction or death during or immediately after PCI [1]. Those patients with the most severe and critical CAD may alternatively, or occasionally additionally, require surgical intervention with coronary artery bypass graft (CABG) surgery, in which case there is a delicate balance to strike between preventing thrombotic events prior to surgery and avoiding life-threatening bleeding following surgery.

This Expert Review highlights cangrelor, a novel platelet $P2Y_{12}$ receptor antagonist, and its use in reducing thrombotic events in adult patients with coronary artery disease undergoing PCI.

Atherothrombosis and the role of the platelet $P2Y_{12}$ receptor

Atherosclerosis is a disease involving the formation of focal intimal lesions (plaques) in large- and medium-sized arteries, such as the aorta and coronary arteries respectively. Although often asymptomatic, these plaques have the potential of extensive ischaemic damage to vital organs, including the heart, when an occlusive thrombosis develops on a disrupted plaque; this is termed atherothrombosis [2]. The role of platelets in the initial phase of atherogenesis is uncertain [3] but their role in thrombus formation is critical. Atherosclerotic plaque rupture or erosion exposes thrombogenic components, such as collagen and von Willebrand factor (vWF). Exposed endogenous vWF in subendothelial matrix binds to platelet glycoprotein (GP) Ib-IX-V complex causing the platelet to decelerate and tether on the subendothelium; the platelets can subsequently bind with collagen through GPVI and α2β1 receptors to achieve firm adhesion and further platelet activation [4]. These interactions lead to secretion of platelet dense granules, from which are released platelet agonists including adenosine diphosphate (ADP), 5-hydroxytrytamine (5-HT) and adenosine triphosphate (ATP) (Figure 1)[5]. The platelets also metabolise arachidonic acid to thromboxane A_2, which binds to thromboxane-prostanoid (TP) receptors and in turn causes aggregation and vasoconstriction [2]. Platelet α-granules are also secreted which contain many prothrombotic and pro-inflammatory factors such as fibrinogen, coagulation factors, P-selectin and soluble CD40L [6]. Expression of P-selectin on the activated platelet surface mediates binding to leukocytes via PSGL-1 and augmentation of vascular inflammatory responses [7].

Vessel wall injury also leads to the expression of tissue factor, which in turn leads to formation of thrombin, a potent platelet agonist as well as the final instigator of fibrin deposition, via the coagulation cascade; thrombin activates platelets via protease-activated receptors (PARs), specifically PAR1 and PAR4 in humans, and mediates fibrin formation from cleavage of fibrinogen [8]. Platelet activation through all the myriad of receptor pathways causes activation of the integrin $\alpha_{IIb}\beta_3$, otherwise known as GPIIb/IIIa, which then binds to soluble plasma ligands such as fibrinogen that forms intercellular bridges and crosslinks the platelets into aggregates [6]. Eventually, this crosslinking leads to formation of a platelet plug that halts bleeding at the site of vessel injury or, in the case of atherosclerotic plaque rupture, leads to the formation of thrombus.

The significance of ADP in the process of thrombosis has been established mutually by its high concentration in platelet dense granules that are released in response to other platelet agonists to reinforce platelet aggregation, antiplatelet drugs that target its receptors and by prolonged bleeding in patients with deficiency of $P2Y_{12}$ ADP receptors [9].

Receptors activated by extracellular nucleotides are classified as P2 receptors with two subclasses: P2X- intrinsic ion channels and P2Y- receptors coupled to heterotrimeric G-proteins; $P2Y_1$ and $P2Y_{12}$ receptors involve Gq and Gi signalling respectively [6]. The receptors are numbered in the order of their cloning. Three distinct P2 receptors have been identified as playing important roles on platelets, namely $P2X_1$, $P2Y_1$ and $P2Y_{12}$ [10]. The $P2X_1$ receptor on platelets mediates rapid calcium influx and is selectively activated by ATP [11]. The other two platelet P2 receptors are selectively activated by ADP: $P2Y_1$ is coupled to Gq, which mediates mobilization of intracellular calcium and platelet shape change, whereas $P2Y_{12}$ is coupled to Gi, which mediates inhibition of adenylate cyclase and activation of PI3 kinase [10, 12]. Activation of both $P2Y_1$ and $P2Y_{12}$ receptors is necessary for sustained ADP-induced platelet aggregation[13, 14]. The success of the $P2Y_{12}$ receptor as a therapeutic target relates to its central role in the potentiation of dense granule secretion, platelet aggregation, pro-coagulant activity and overall thrombus growth and stability [14-17].

Initially, the receptor-mediated action of ADP was revealed by true competitive inhibition of adenylyl cyclase and ADP-induced platelet aggregation by ATP and several other nucleoside triphosphates [10]. This discovery supported the development of ATP analogues to be used as antagonists of ADP-induced platelet aggregation[14], one of these being cangrelor (Figure 2); these ATP analogues were later shown to act selectively on the platelet $P2Y_{12}$ receptor without influencing $P2Y_1$ and $P2X_1$[13, 18]. Yet, several $P2Y_{12}$ antagonists, including cangrelor, were developed when a single ADP receptor on platelets was postulated and described as the P_{2T} receptor (T indicating 'thrombocyte')[14], designated so since its pharmacologic profile did not correspond to any cloned P2Y receptor at the time [10]. Subsequently there were demonstrated to be two distinct ADP receptors on platelets, eventually identified as $P2Y_1$ and $P2Y_{12}$ [10, 13, 18].

It should be noted that these pathways contributing to thrombosis are also critical to haemostasis. Thus, any antiplatelet therapy, including ADP receptor antagonists, is associated with some increase in risk of bleeding. Therefore, studies constantly strive for identification of antagonists that strike a good balance consisting of high efficacy and relatively lower risk of bleeding compared to other available antithrombotic therapies.

Unmet need in antiplatelet therapy

The use of oral $P2Y_{12}$ inhibitors has been well established in dual antiplatelet therapy to prevent thrombosis at the time of, and following, PCI. The thienopyridines ticlopidine and clopidogrel belong to another class of drugs that block ADP-mediated platelet activation by irreversibly inhibiting the $P2Y_{12}$ receptors; these were shown to have superior efficacy, alone or combined with aspirin, than aspirin alone or aspirin plus anticoagulant therapy in preventing major cardiovascular complications [19]. The use of clopidogrel has predominated over ticlopidine due to its fewer adverse effects [20].

However, clopidogrel itself has a number of limitations that justified the development of newer ADP antagonists. After oral ingestion, a majority of the clopidogrel molecules are metabolized by plasma esterases into inactive compounds; importantly, the remaining are metabolized by hepatic cytochrome P450 (CYP) isoenzymes into the active form that irreversibly blocks the ADP-binding site on platelet $P2Y_{12}$ receptors [21]. Its hepatic metabolism allows room for potential CYP interactions, rate-limiting saturation of liver metabolic capacity, non-responsiveness and variable efficacy. Due to

its delayed onset of action, clopidogrel is administered for 4-5 days with a maintenance dose of 75mg to achieve stable platelet inhibition; this can be shortened to 4-6 hours by a loading dose of 300mg or 600mg [22, 23]. Even though the active metabolite itself has a very short half-life of 30 to 60 minutes, it has a permanent effect that lasts for the lifetime of the platelet, i.e. 7-10 days, hence recovery of platelet function is established after approximately 5 to 10 days [23]. Its irreversible nature may deter interventional cardiologists from initiating it until the coronary anatomy has been defined to rule out any requirements for coronary artery bypass grafting (CABG) surgery within 5 days due to significant bleeding risks. Furthermore, a combination of factors lead to an unpredictable variation in responsiveness to this agent; these include genetic factors (particularly loss-of-function alleles of the *CYP2C19* gene), drug interactions, variation in metabolism due to disease states and absorption [19].

Prasugrel is a third-generation oral thienopyridine that also acts via an active metabolite that binds irreversibly to $P2Y_{12}$ [24]. Prasugrel has the advantage of more efficient and consistent active metabolite production compared to clopidogrel and therefore achieves higher mean levels of inhibition of platelet aggregation with less variability [24]. However, prasugrel also possesses the limitation of delayed recovery of platelet reactivity following cessation, which can lead to increased rates of major bleeding in patients managed with CABG surgery [25].

Ticagrelor is an oral direct-acting, reversibly-binding $P2Y_{12}$ inhibitor with high potency, rapid onset of action, achieving a high level of platelet inhibition in 1-2 hours after initial administration to stable patients, and a plasma half-life of 6-12 hours [23]. Although ticagrelor offers greater feasibility of use in acute events even if surgery is anticipated, it still requires up to 5 days for complete offset of effect despite its reversible inhibition [23].

It should be noted that about two-thirds of patients with acute cardiovascular illnesses have associated nausea, sometimes associated with vomiting [26], due to either the illness itself or administered opiates. Opiates also delay gastric emptying and therefore can delay the absorption and onset of action of oral $P2Y_{12}$ inhibitors, which rely on intestinal absorption [27-30]. Vomiting of stomach contents may lead to uncertainty about absorption of oral therapy and patients can also be unable to swallow e.g. due to intubation or cardiogenic shock [19, 31]. These factors represent limitations of oral $P2Y_{12}$ inhibitors and favour intravenous administration of antiplatelet therapy in acutely ill patients.

Intravenous GPIIb/IIIa antagonists (abciximab, tirofiban and eptifibatide) can be considered as options for adjunctive strategies for preventing acute stent thrombosis. However, GPIIb/IIIa antagonists are associated with a narrow therapeutic window since therapeutic levels of platelet inhibition are achieved at dose levels that can prolong bleeding time by some 6-7 fold, increasing the risk of major bleeding complications and hindering their extensive use [32]**.** This may theoretically be related to the fact that GPIIb/IIIa antagonists concurrently affect platelet aggregation and platelet activation in a linear fashion, with low levels of GPIIb/IIIa blockade being therapeutically ineffective but high levels compromising platelet function excessively (Figure 1)[33]. This is a particular consideration in patients undergoing PCI who receive in any case aspirin, a $P2Y_{12}$ inhibitor and an anticoagulant so that also administering a GPIIb/IIIa antagonist means inhibiting a fourth pathway involved in platelet activation and aggregation and thus compounding the bleeding risk (Figure 1). Having said this, the use of only oral therapies and short courses of anticoagulation are associated with unacceptable rates of acute stent thrombosis in patients undergoing PCI for ST-elevation myocardial infarction [34, 35].

The above considerations reflect a clear unmet need for an intravenous, reversible, potent anti-platelet drug with predictable effects and a quick onset and offset of action, for use in acute cardiovascular events such as ACS and in PCI procedures. Thus, there was sufficient justification for the clinical development of cangrelor.

Chemistry of cangrelor

Using the observation that ATP was a weak but competitive natural antagonist at the $P2Y_{12}$ receptor (or P_{2T} receptor as it was then known), the anti-platelet properties of potent and selective ATP analogue antagonists of this receptor were explored. Various test compounds led to the identification of two therapeutically useful analogues; one of these was cangrelor, a true ATP analogue (Figure 2) that demonstrated a highly selective nature at the P_{2T} receptor [14]. Using human washed platelets and impedance aggregometry in vitro, cangrelor demonstrated inhibition of ADP-induced (3 µmol/L) platelet aggregation with a pIC50 of 9.35 and 79% platelet recovery in 20 minutes after cessation of infusion [32]. These properties represented a major advantage in the mechanism of action of this antithrombotic agent.

Pharmacodynamics, pharmacokinetics and metabolism

Due to an intravenous method of administration, cangrelor has high bioavailability. Being a potent agent, near-complete inhibition of ADP-induced platelet aggregation is observed within 2 minutes of a bolus injection and infusion rates of 2 and 4µg/kg/min [36]. Cangrelor demonstrates a dose-dependent effect of platelet inhibition, through semi-competitive blockade of the $P2Y_{12}$ receptor, and this is sustained during prolonged infusion over several days [14]. Its mean IC50 value was estimated to be 7.7 ± 9.1 ng/mL [36]. Contained in the plasma with a small initial volume of distribution, cangrelor is rapidly cleared regardless of infusion duration or rate, at a mean rate of 44.3 L/kg [36]. A mean half-life of less than 5 minutes, less than 9 minutes in 90% patients, explains the rapid restoration of baseline platelet function within 1-2 hours after discontinuation of cangrelor infusion [36]. Most of the drug clearance has been shown to be via urine and faeces, presumably after biliary excretion. Therapeutic effects are maintained with continuous infusion since cangrelor avoids any significant renal or hepatic biotransformation, unlike the thienopyridines; as an ATP analogue, cangrelor undergoes rapid dephosphorylation, possibly via endonucleotidases, to its inactive metabolite. Furthermore, when compared to the relatively modest levels of platelet inhibition attained by thienopyridines as well as their slow onset and offset of effects, cangrelor has the greater advantage for use in patients undergoing coronary stent implantation. Antithrombotic levels of cangrelor extended bleeding time by less than 2-fold in animal studies, notably in contrast to the 6-7 fold higher bleeding time seen with GPIIb/IIIa antagonists [32].

Clinical trials

Phase II

An open multicentre study assessed cangrelor's safe use as an adjunct in 39 patients with unstable angina or non-Q wave myocardial infarction receiving aspirin and heparin, assessing varying dosing regimens that involved stepped dose increments over 3 hours to a plateau of either 2 µg/kg/min, for either 21 hours (Part 1; n = 12) or up to 69 hours (Part 2; n = 13), or 4 µg/kg/min for up to 69 h (Part 3: n = 14); at 24 hours, mean inhibition of ADP-induced platelet aggregation assessed by whole bleed impedance aggregometry was 96%, 95% and 99%, respectively[36]**.** No serious adverse events attributable to cangrelor occurred with a 30-day follow-up. There were no major or minor bleeding incidents according to the TIMI criteria but trivial bleeding (56%) was common [36]. More marked increase in bleeding time was noted when cangrelor was co-administered with enoxaparin compared to unfractionated heparin, possibly related to peaking of anticoagulant effect several

hours after subcutaneous enoxaparin injection. Subsequently, cangrelor's safety was also assessed in a larger population of 91 patients with unstable angina or non-Q-wave myocardial infarction who received a 4 μg/kg/min infusion for 72 hours or placebo, with a 30 day follow up of outcomes; despite a higher number of minor bleeds with cangrelor (38%) compared to placebo (26%), there was no significant difference in serious bleeds [37]. Comparison of the effects of cangrelor, both ex vivo and in vitro, compared to standard clopidogrel therapy in patients with ischaemic heart disease demonstrated that cangrelor inhibited platelet function more effectively and consistently [38]. When a study compared a 4 μg/kg/min cangrelor infusion against one dose of abciximab, a GPIIb/IIIa inhibitor, there was a non-significant but higher incidence of bleeding in the abciximab (10%) versus cangrelor group (7%); also, abciximab had longer bleeding time prolongation and offset time, as well as lower platelet count, compared to cangrelor [39].

The BRIDGE trial, including 210 patients treated for an ACS or with coronary stent, evaluated the use of cangrelor compared with placebo for bridging thienopyridine-treated patients to coronary artery bypass grafting (CABG) surgery and concluded that cangrelor resulted in higher maintenance of platelet inhibition in the pre-operative period without any penalty in terms of CABG-related bleeding [40].

Interaction with oral $P2Y_{12}$ inhibitors

After the procedure of PCI, many patients are transitioned on to oral antiplatelet therapy for maintenance to prevent stent thrombosis and long-term adverse cardiovascular events. Due to the differences in pharmacological activity, it was important to investigate the ability of oral thienopyridines to inhibit platelet function when administered simultaneously with and immediately after cangrelor infusion. This was carried out by Steinhubl et al using clopidogrel as the oral agent; although no drug-related adverse events were identified in either treatment arm, it was seen that when clopidogrel and cangrelor were administered simultaneously, clopidogrel was unable to effectively inhibit platelet function, even at a 600mg loading dose [41]. The interaction was minimised when the clopidogrel loading dose was administered at the time of cessation of cangrelor infusion. Similarly, the ability of prasugrel to provide platelet inhibition is sensitive to the timing of its administration relative to cangrelor infusion such that it is recommended that prasugrel loading dose is administered 30 minutes before the cessation of cangrelor infusion [42]. This is because of two key considerations: (1) the distribution half-lives of both clopidogrel and prasugrel active metabolites are short (30 to 60 minutes) so that therapeutic levels of the active metabolites decline rapidly following absorption and metabolism of the parent drug [43-46]; and (2) these active metabolites are unable to bind to the platelet $P2Y_{12}$ receptor whilst cangrelor is bound to the receptor [47, 48]. Consequently, if the levels of the active metabolites fall to subtherapeutic concentrations before cangrelor has dissociated from the platelet $P2Y_{12}$ receptors then no effective platelet inhibition will ensue. These observations highlighted a significant gap in platelet inhibition that could occur during the transition from cangrelor infusion to oral $P2Y_{12}$ agents, which can markedly increase the risk of developing complications like stent thrombosis. This is not a concern when transitioning from cangrelor to ticagrelor since the plasma concentrations of ticagrelor and its principal metabolite that is also active are sustained between doses and so ticagrelor can simply bind to $P2Y_{12}$ receptors once cangrelor has dissociated [49].

Using VerifyNow assay, light transmittance aggregometry (LTA) and phosphorylation of vasodilator-stimulated phosphoprotein (VASP-P) as tests to assess platelet function, the impact of the interaction between cangrelor and clopidogrel was investigated in the CHAMPION-PCI and CHAMPION-PLATFORM studies where protocols mandated a 600mg loading dose of clopidogrel immediately following the end of cangrelor infusion [50]. This pharmacodynamic substudy

demonstrated that this protocol minimised the negative interaction. However, ticagrelor currently stands as the best option for use in the transition from cangrelor infusion to an oral agent [49].

Phase III

On the basis of data supporting the feasibility of the use of cangrelor in patients undergoing PCI in need of antiplatelet therapy, cangrelor's phase III programme, two parallel CHAMPION studies (Cangrelor versus standard tHerapy to Achieve optimal Management of Platelet InhibitiON) were initiated, the CHAMPION-PCI and CHAMPION-PLATFORM studies (Table 1) [51, 52]. Despite its promise, the results of both studies failed to demonstrate that cangrelor was superior to clopidogrel in terms of the primary composite endpoints at both 48 hours and at 30 days [51, 52]. Discouraging trends in results led to premature termination of both studies. However, some positive results were obtained from the reduction of secondary endpoints, such as death, stent thrombosis or Q-wave myocardial infarction, along with no excess in severe bleeding. It was also identified that many patients had one or even no cardiac markers assessed, or had increasing cardiac markers, before PCI resulting in an inability to detect PCI-related MI beyond clinical judgement. Hence, this may explain the relatively better results of cangrelor in patients with stable angina, in whom cardiac markers prior to PCI tend to be normal [51, 52]. The plausibility of inadequate MI definition being a source for poor cangrelor results in CHAMPION-PCI and CHAMPION-PLATFORM was made higher when a retrospective analysis used the Universal MI definition to yield a lower number of PCI-related MI events [53].

Taking this into account, a third phase III study, the CHAMPION PHOENIX trial, was designed and executed, involving 11,145 patients undergoing urgent or elective PCI, to prospectively evaluate whether cangrelor reduces ischaemic complications of PCI; cangrelor significantly reduced the rate of primary efficacy end point as compared to clopidogrel (adjusted odds ratio with cangrelor, 0.78; 95% confidence Interval [CI], 0.66 to 0.93; P = 0.005) consistently across many prespecified groups, with no significant increase in severe bleeding [31]. In a pooled analysis of patient-level data including all the CHAMPION studies, it was then shown that cangrelor provided a 19% relative risk reduction for the primary endpoint (odds ratio 0·81, 95% CI 0·71–0·91, p=0·0007) and impressive 41% reduction in stent thrombosis with no difference in major bleeding but an acceptable increase in mild bleeding [54].

After finally proving its efficacy and feasibility of use, cangrelor became available as a treatment option [5]. However, studies are yet to be conducted to investigate its use and advantage compared to other more potent and rapid-acting oral $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor, agents that have already been shown to be superior to clopidogrel.

Regulatory situation

Cangrelor has been approved by the Food and Drug Administration and the European Medicines Agency for use in patients undergoing PCI, provided that other oral $P2Y_{12}$ inhibitors have not been administered prior to the PCI procedure or are not desirable for use (Table 2).

Expert commentary

The efficacy of platelet $P2Y_{12}$ inhibition in the prevention and management of arterial thrombosis is well proven and supported by the results of the CHAMPION PHOENIX study of initial treatment with cangrelor compared to clopidogrel in patients undergoing PCI. Cangrelor currently offers unique

properties as a selective, potent $P2Y_{12}$ inhibitor with immediate onset of action following bolus administration and the most rapid offset of action of any antiplatelet therapy used in cardiological practice. These properties make it an attractive option in high-risk patients undergoing PCI who either have not received prior loading with an effective oral $P2Y_{12}$ inhibitor or have received opiates that may delay absorption of the oral therapy by several hours. Understanding the negative interaction between cangrelor and thienopyridines is critical to avoiding the hazard of acute stent thrombosis if both classes of drug are administered. Cangrelor offers an advantage over intravenous GPIIb/IIIa antagonists in PCI patients through targeting the same pathway as the oral $P2Y_{12}$ inhibitors rather than an additional pathway and theoretically this should attenuate bleeding hazard although comparative studies are required. The properties of cangrelor make it an ideal agent for bridging patients up to the time of surgery or in particularly hazardous circumstances of high ischaemic risk with ongoing bleeding, these being areas that require further research.

Five year view

Cangrelor will become established in clinical practice as an option for managing high-risk patients undergoing PCI, for balancing ischaemic and bleeding risk in patients undergoing surgery or in life-threatening situations as a consequence of high thrombotic and bleeding risks. Easy transition from cangrelor to ticagrelor will make this a common combination for high-risk PCI patients. Cangrelor will further displace the use of GPIIb/IIIa antagonists in PCI such that these will eventually be rarely used.

Key issues

- The platelet $P2Y_{12}$ receptor remains the most attractive target beyond cyclo-oxygenase 1 in antiplatelet therapy for cardiovascular disease
- Cangrelor is a novel reversibly-binding platelet $P2Y_{12}$ inhibitor with rapid onset and offset of action
- Initial treatment with cangrelor reduces the risk of thrombotic complications of PCI compared to initial treatment with clopidogrel
- Cangrelor blocks the binding of thienopyridine active metabolites to $P2Y_{12}$ and so great care must be taken if transitioning from cangrelor to clopidogrel or prasugrel
- Cangrelor offers an attractive option for 'bridging' high-thrombotic-risk patients to surgery after discontinuation of oral antiplatelet therapy
- Cangrelor is likely to displace use of GPIIb/IIIa antagonists in PCI

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Table 1. Characteristics (based on Steg et al [54]) and results of the three CHAMPION studies

	CHAMPION-PCI[52]			CHAMPION-PLATFORM[51]			CHAMPION PHOENIX[31]		
Number of patients (modified intention to treat)	8,667			5,301			10,942		
Patient Population	70% troponin elevated at baseline Previous chronic clopidogrel allowed Placebo or clopidogrel control (all patients received 600 mg) loaded at the start of PCI PCI for STEMI, NSTEMI, UA (ECG changes + pain + age/diabetes) or stable angina (capped at 15%)			70% troponin elevated at baseline $P2Y_{12}$ inhibitor naïve only Placebo or clopidogrel control (all patients received 600 mg) loaded at the end of PCI PCI for NSTEMI, UA (ECG changes + pain + age/diabetes) or stable angina (capped at 15%)			35% troponin elevated at baseline $P2Y_{12}$ inhibitor naïve only Placebo or clopidogrel (300 mg or 600 mg) loaded at the start or at the end of PCI PCI for stable angina, NSTE-ACS or STEMI		
Comparator	Clopidogrel 600 mg administered at the beginning of PCI			Clopidogrel 600 mg administered after PCI			Clopidogrel 300 or 600 mg (per local standard of care) administered before or after PCI according to physician choice		
Endpoint	Primary: death/MI/IDR at 48 h			Primary: death/MI/IDR at 48 h			Primary: death/MI/IDR/ST at 48 h		
MI definition	Cardiac markers alone used to define PCI-related MI			Cardiac markers alone used to define PCI-related MI			Use of Universal Definition of MI: cardiac markers + clinical criteria to define PCI-related MI		
Stent thrombosis (ST) definition	Angiographic evidence of ST associated with IDR			Angiographic evidence of ST associated with IDR			*Either* definite ST as per ARC definition, for post PCI events *or* intraprocedural ST for events occurring during PCI		
Primary efficacy endpoint	Cangrelor	Clopidogrel	OR (95% CI)	Cangrelor	Placebo	OR (95% CI)	Cangrelor	Clopidogrel	OR (95% CI)
	7.5%	7.1%	1.05 (0.88-1.24)	7.0%	8.0%	0.87 (0.71-1.07)	4.7%	5.9%	0.78 § (0.66-0.93)
Safety endpoints	Cangrelor	Clopidogrel	OR (95% CI)	Cangrelor	Placebo	OR (95% CI)	Cangrelor	Clopidogrel	OR (95% CI)
GUSTO Mild	19.6%	16.9%	1.2 § (1.07-1.34)	16.0%	11.7%	1.44 (1.23-1.69)	NA	NA	NA
Moderate	0.9%	0.8%	1.21 (0.76-1.90)	0.8%	0.5%	1.54 (0.76-3.09)	0.4%	0.2%	1.69 (0.85-3.37)
Severe	0.2%	0.3%	0.91 (0.39-2.14)	0.3%	0.2%	1.5 (0.53-4.21)	0.2%	0.1%	1.5 (0.53-4.22)
TIMI Minor	0.8%	0.6%	1.39 (0.84-2.30)	0.8%	0.6%	1.37 (0.72-2.62)	0.2%	0.1%	3.0 (0.81-11.10)
Major	0.4%	0.3%	1.36 (0.68-2.71)	0.2%	0.3%	0.44 (0.14-1.44)	0.1%	0.1%	1.0 (0.29-3.45)
Haemodynamic compromise	0.2%	0.3%	0.82 (0.34-1.97)	0.3%	0.2%	1.40 (0.44-4.40)	NA	NA	NA
Any blood transfusion	1.1%	1%	1.09 (0.72-1.67)	1%	0.6%	1.62 (0.87-3.03)	0.5%	0.3%	1.56 (0.83-2.93)

ACS=acute coronary syndrome. ARC=Academic Research Consortium. ECG=electrocardiogram. IDR=ischaemia-driven revascularisation. MI=myocardial infarction. NSTE-ACS=non-ST-elevation acute coronary syndromes. NSTEMI=non-ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention. ST=stent thrombosis. STEMI=ST-segment elevation myocardial infarction. UA=unstable angina. UDMI=universal definition of myocardial infarction. OR = odds ratio. CI=confidence interval. NA=not available.
§ statistically significant difference

Table 2

Approved by	Indication
European Medicines Agency	Kengrexal (cangrelor), co-administered with acetylsalicylic acid (ASA), is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral $P2Y_{12}$ inhibitor prior to the PCI procedure and in whom oral therapy with $P2Y_{12}$ inhibitors is not feasible or desirable
Food and Drug Administration	Kengreal [cangrelor] is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients in who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor

Figures

Figure 1

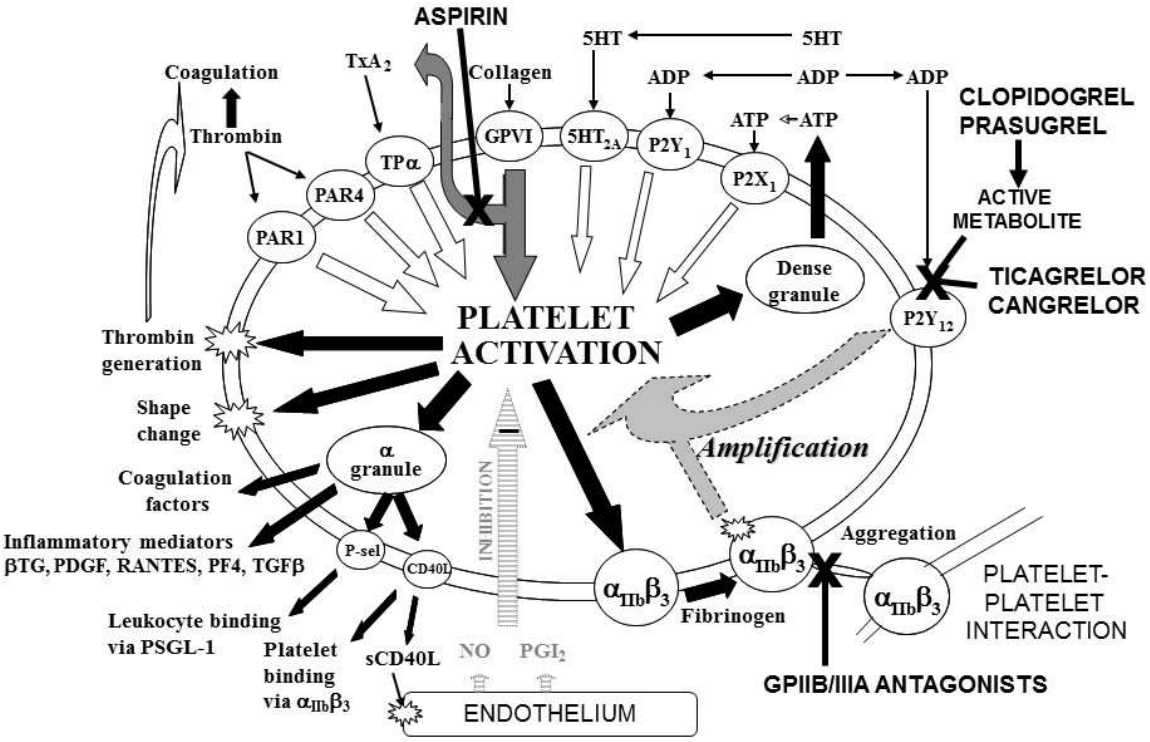

Figure 2