

## **Cangrelor - rising from the ashes: a phoenix story**

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### **ABSTRACT**

Cangrelor is a novel intravenous antiplatelet agent that has been approved for usage in the setting of percutaneous coronary revascularization in patients with acute coronary syndrome. The drug was evaluated in three major trials namely Champion-Platform, Champion-PCI and Champion Phoenix with a total of 25,107 patients. Although there was a reduction in the incidence of ischemia driven revascularization, Q wave MI and stent thromboses in the first 48 hours among cangrelor users as compared to clopidogrel, there was no difference in the incidence of all-cause mortality or myocardial infarction. In terms of safety, cangrelor does not appear to have a higher bleeding risk. A distinct appeal with cangrelor is its unique pharmacokinetic property of having a rapid onset and offset of action. The drug would also have a niche role among patients with challenges to oral drug administration as in mechanically ventilated patients and those with severe vomiting. Although the drug managed to rise against odds in getting regulatory approval from the FDA, it remains to be seen if this could become a frontline agent among the current array of anti-platelet molecules.

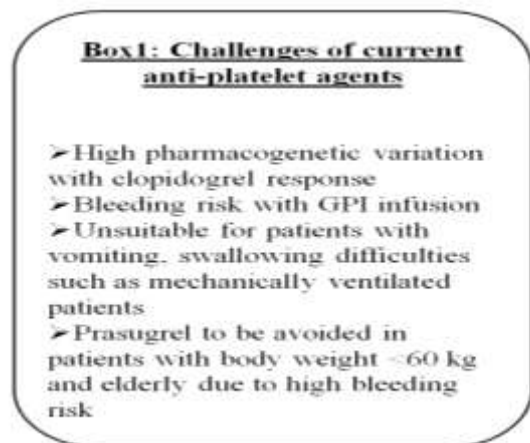
**Keywords:** Cangrelor, Clopidogrel, Novel anti-platelet, PCI, Stent thromboses

### **INTRODUCTION**

Percutaneous Coronary intervention has revolutionized the field of cardiology in the last two decades and there has been an increasing shift of coronary artery disease being treated with drug eluting stents over coronary artery bypass surgery.<sup>1</sup> The flip side of this, is that there has also been an increase in the incidence of thrombotic complications. Following a stent implantation, a patient is at a greater propensity to experience recurrent myocardial infarction, stroke, target vessel revascularization and cardiovascular death. Dual antiplatelet therapy with aspirin and clopidogrel is the current standard of care for all post stented patients for at least one year.<sup>2</sup> While these drugs have stood the test of time and found to be effective, there are certain caveats attached to them. For instance, it has been observed in the last few years that,

the gene coding the enzyme CYP2C19 which metabolizes clopidogrel is highly polymorphic. As a result of this, there is high degree of inter-individual variability in the metabolism of clopidogrel.<sup>3</sup> In patients with polymorphic enzyme, the diminished conversion of clopidogrel into its active metabolite results in therapeutic failure. Several studies have even documented presence of polymorphic CYP2C19 gene with increased risk of major adverse cardiovascular events among clopidogrel users.<sup>4</sup> Ticagrelor and prasugrel were subsequently introduced in the market as anti-platelet agents. While these drugs do not have any pharmacogenetic variation in the patient response, the delayed onset and offset of action continue to present as a challenge. In addition, prasugrel causes irreversible inhibition of P2Y<sub>12</sub> receptor.<sup>5</sup> Some patients who have been intubated and those who have severe vomiting that

pre-empt any form of oral therapy would also find the current anti-platelet agents unsuitable. These limitations with the current crop of anti-platelet agents have reignited the search for an elusive novel anti-platelet agent that can overcome these challenges [Figure 1].<sup>6</sup>



**Figure 1: Challenges of current anti-platelet agents.**

## DRUG DESCRIPTION

Cangrelor, a nonthienopyridine adenosine triphosphate analogue is an intravenous, quick acting, reversible platelet inhibitor.<sup>7</sup> Cangrelor was recently approved by US Food and Drug Administration for use in the setting of PCI. This review will focus on the efficacy and safety of Cangrelor and discuss its therapeutic status in the cardiologist's armamentarium.

### Mode of action of cangrelor

Cangrelor is a direct acting P<sub>2</sub>Y<sub>12</sub> antagonist that has a reversible action. ADP is released from damaged blood vessels, RBC and it binds to P<sub>2</sub>Y<sub>1</sub> and P<sub>2</sub>Y<sub>12</sub> receptor that are present in great abundance on the platelets. This binding triggers and completes the platelet aggregation. Binding of Cangrelor to P<sub>2</sub>Y<sub>12</sub> receptor prevents ADP induced platelet aggregation.<sup>8</sup> The difference between Cangrelor and other anti-platelet agents is the swift onset and offset of action seen with the former due to its intravenous route of administration.<sup>9</sup>

### Efficacy

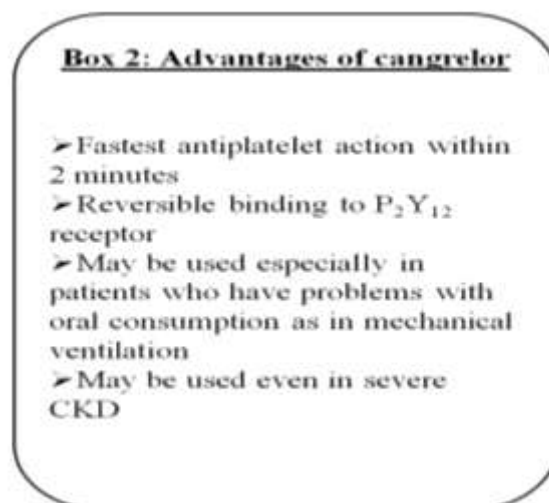
The phase 3 clinical trials that evaluated the efficacy and safety of cangrelor include CHAMPION-PCI (C-PCI), CHAMPION-PLATFORM (C-PLATFORM) and CHAMPION-PHOENIX (C-PHOENIX). The C-PCI and C-PLATFORM began around the same time in 2006 and had similar end points of death, MI and ischemia driven revascularization at 48 hours. The control used was 600 mg clopidogrel, before PCI in C-PCI study and after PCI in C-PLATFORM study. Both these studies used patients with more aggressive coronary artery disease, i.e. Acute Coronary syndrome. However the trials were stopped

midway as futility analysis revealed cangrelor to have no superiority to clopidogrel with respect to the primary end point. (OR- 1.05, p=0.59 & OR-0.87, P=0.87).<sup>10</sup>

However cangrelor did show reduced risk of stent thromboses than clopidogrel. This finding prompted the sponsor to initiate another study C-PHOENIX., which was designed to circumvent the limitations of the earlier studies. Intra procedural stent thromboses and periprocedural MI were included as primary end points besides death, MI and ischemia driven revascularization.<sup>11</sup> The study allowed flexibility in clopidogrel dosages - 300 or 600 mg as per the discretion of the operator. Besides STEMI and NSTEMI, patients with stable angina were also included in significant numbers unlike the earlier studies. Cangrelor was found to achieve better outcomes than clopidogrel at 48 hours with respect to the primary end points. (OR- 0.79, p=0.005 & 95% CI- 0.67, 0.93).<sup>12-14</sup>

### Safety

The bleeding potential of cangrelor has not been a cause for great concern from the studies carried out till date. Nevertheless, when cangrelor was combined with GPI there was a significant increase in the bleeding episodes, a risk that was similar to clopidogrel. The drug did not show increased bleeding risk when combined with clopidogrel. Unlike ticagrelor and prasugrel, intra cranial bleeding has not been a feared complication with cangrelor treatment. Nevertheless, these are still early days in the development history of the drug and more post marketing studies are definitely warranted to unravel the bleeding risk of this drug. Dyspnea was one of the common adverse effects seen among users of cangrelor. (1% vs 0.4%, p=0.001)<sup>12</sup>



**Table 2: Advantages of cangrelor.**

## Pharmacokinetics

The drug has a rapid onset of action and the maximal antiplatelet effect is obtained within 2 minutes of an IV bolus. The drug is deactivated in the plasma by dephosphorylation and the plasma half-life is 3 to 6 minutes. The platelet function resumes to normal state within one hour of cessation of infusion. The recommended bolus dosage is 30 mcg/kg IV and the dose used for IV infusion is 4 micrograms/kg/min. Cangrelor does not require dosage modification in renal and hepatic disease [Table 2].<sup>15</sup>

## The twisting tales of cangrelor's drug development

Cangrelor has had a chequered drug development history with an intriguing tale of events over the last few years. Initially with the failure of cangrelor in two large trials, it certainly looked as if the drug was not going to see the light of the day. But the results of the C-PHOENIX trial offered a life line for the sponsor and it looked set to receive approval from the regulators. However the CRDAC had voted against approval of the drug in 2014, citing various reasons and it looked as if the last rites of the drug had been completed. Yet the story did not conclude and like the phoenix bird in Greek mythology that is said to rise from the ashes, the drug has come back to life and is currently an approved drug in the US market. The regulators in 2014 had raised several concerns about the C-PHOENIX study some of which were inclusion of intra-procedural stent thromboses and peri-procedural MI that were identified solely by biomarker elevation without clinical correlation, the delayed timing of the administration of clopidogrel in the control arm, the non-utilization of other more faster acting P2Y<sub>12</sub> inhibitors such as ticagrelor and prasugrel and restriction of GPI. However a reanalysis of the CHAMPION PHOENIX data and a suitable response from the sponsors helped the drug to gain regulatory approval in April 2015.<sup>11</sup>

<b>Box 3: Disadvantages of cangrelor</b>
<ul style="list-style-type: none"> <li>➤ Never proven to have superiority over clopidogrel</li> <li>➤ may give rise to a potentially decreased antiplatelet window for a transient period- Short time exists between offset of action of the drug and the time taken for the oral antiplatelet to work during transition from cangrelor to oral anti-platelets</li> </ul>

**Table 3: Disadvantages of cangrelor.**

## Unanswered questions with cangrelor

It is not known at the moment if cangrelor therapy can be safely switched over to prasugrel. The best strategy of using these drugs in succession need to be identified. It is also not known if cangrelor could better the efficacy of ticagrelor or prasugrel as all earlier studies with cangrelor, had used clopidogrel as the comparator drug. There could be a potential period between switching of the anti-platelet drugs, when there is sub-optimal antiplatelet action owing to the time taken for the oral antiplatelet agents to begin their action [Table 3]. A cost benefit analysis on the use of cangrelor in real world practice is also needed for the drug to receive greater patronage.

## CONCLUSION

Stent thrombosis, recurrent myocardial infarction and death still remain a major matter of concern among patients who undergo PCI. Cangrelor is an intravenous antiplatelet agent, with a fast onset and offset of action, that could offer the much needed therapeutic advantage especially in those patients who have serious barriers to consuming oral antiplatelet drugs, as seen in intubated patients and in those who are not fit candidates for GPI infusion. Although the drug has been approved by the FDA over a month ago albeit with much reluctance, it remains to be seen if this molecule would secure favour with the cardiologist and become one of the primary antiplatelet agent of choice in the setting of PCI.

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## REFERENCES

1. Klein LW. Are drug-eluting stents the preferred treatment for multivessel coronary artery disease? *J Am Coll Cardiol.* 2006;47(1):22-6.
2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35(37):2541-619.
3. Kubica A, Kozinski M, Grzesk G, Fabiszak T, Navarese EP, Goch A. Genetic determinants of platelet response to clopidogrel. *J Thromb Thrombolysis.* 2011;32(4):459-66.
4. Jeong YH, Tantry US, Kim IS, Koh JS, Kwon TJ, Park Y, et al. Effect of CYP2C19\*2 and \*3 loss-of-function alleles on platelet reactivity and adverse clinical events in East Asian acute myocardial infarction survivors treated with clopidogrel and aspirin. *Circ Cardiovasc Interv.* 2011;4(6):585-94.

5. Franchi F, Rollini F, Park Y, Angiolillo DJ. Novel Antiplatelet Agents: The Current State and What Is Coming Down the Pike. *Prog Cardiovasc Dis*, 2015
6. Rafeedheen R, Bliden KP, Liu F, Tantry US, Gurbel PA. Novel antiplatelet agents in cardiovascular medicine. *Curr Treat Options Cardiovasc Med.* 2015;17(6):383.
7. Cattaneo M. The clinical relevance of response variability to antiplatelet therapy. *Hematol Educ Program Am Soc Hematol Am Soc Hematol Educ Program.* 2011;2011:70-5.
8. Michelson AD. Advances in antiplatelet therapy. *Hematol Educ Program Am Soc Hematol Am Soc Hematol Educ Program.* 2011;2011:62-9.
9. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J.* 2009;30(16):1964-77.
10. FDA Briefing document for the Cardiovascular & Renal Drugs Advisory Committee- Cangrelor-Maryland, USA. 2015:1-25.
11. Lhermusier T, Baker NC, Waksman R. Overview of the 2014 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting regarding cangrelor. *Am J Cardiol.* 2015;115(8):1154-61.
12. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med.* 2009;361(24):2318-29.
13. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, et al. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med.* 2009;361(24):2330-41.
14. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med.* 2013;368(14):1303-13.
15. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA.* 2010;304(16):1821-30.

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