Meta-Analysis of the Role of Cangrelor for Patients Undergoing Percutaneous Coronary Intervention

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Inhibition of the P2Y12 receptor by an oral P2Y12 inhibitor with loading doses along with Cyclooxygenase-1 inhibition by aspirin is considered a first-line treatment strategy in patients with the acute coronary syndrome and patients undergoing percutaneous coronary intervention (PCI). Limitations associated with oral P2Y12 receptor inhibitors include a requirement for in vivo conversion (thienopyridines), delayed onset of action, suboptimal inhibition, irreversible inhibition (thienopyridines), and delayed offset. In the acute setting, therapy with potent platelet inhibitors that have a fast onset and offset is desirable to attenuate thrombotic complications. Cangrelor, an intravenous agent, is an adenosine triphosphate analog, selectively and explicitly blocking P2Y12 receptor-mediated platelet activation. Cangrelor has been studied in a series of CHAMPION trials. A patient-level, meta-analysis of all 3 phase III trials (24,910 patients), demonstrated that cangrelor significantly reduced the rate of the composite outcome of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours and 30 days compared with clopidogrel, with no significant increase in major bleeding. It is approved for clinical use in patients undergoing PCI to reduce the risk of myocardial infarction, repeat revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a $GPII_bIII_a$ inhibitor. In conclusion, patients unable to take oral medications undergoing emergent/urgent PCI and those who had recent PCI with drug eluting stent in need for urgent cardiac or noncardiac surgery are potential candidates for cangrelor. **(Am J Cardiol 2019;123:1069−1075)**

Cangrelor is a highly potent, fast acting, with rapid onset and offset, intravenously administered platelet P_2Y_{12} receptor inhibitor which directly blocks adenosine diphosphate − induced platelet aggregation and activation. (Figure 1) It provides rapid onset and sustained platelet inhibition that is quickly reversible after discontinuation of infusion.[1] In healthy volunteers, 30 mcg/kg bolus followed by 4 mcg/kg/min continuous infusion achieved 90% inhibition of platelet aggregation within 2 minutes of bolus administration, and it was maintained throughout infusion.[2,3] After termination, platelet function returned to baseline in approximately 60 minutes.[2] Plasma half-life is approximately 3 to 5 minutes.[3] Cangrelor is not a prodrug and does not require metabolic activation for antiplatelet effect. Overdosing is not associated with increased risk of major bleeding, a favorable effect attributed to short half-life and rapid offset of action, with slight increase in minor bleeding risk.[3] The cangrelor versus standard therapy to achieve optimal management of platelet inhibition (CHAMPION) program collectively demonstrated that cangrelor reduces ischemic complications up to 30 days after percutaneous coronary intervention (PCI) completed with clopidogrel or placebo without increasing Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)—defined severe/life-threatening bleeding or requirement for blood transfusions.[4]

Pharmacology and Pharmacodynamics

Cangrelor, formerly known as AR-C69931MX, is a novel nonthienopyridine adenosine triphosphate (ATP) analogue that reversibly antagonizes P_2Y_{12} receptors leading to platelet activation and aggregation.[5] Cangrelor is referred as nucleotide mimetic,[6] as its chemical structure resembles that of ATP. After being modified from ATP, the final molecule of cangrelor (2-trifluoropropylthio, N-(2-(methylthio) ethyl)-b, g-dichloromethylene ATP), has greater affinity for P_2Y_{12} receptor and higher resistance to ectonucleotidases than parent compound.[5] Another investigation suggests that through the increase in cyclic adenosine monophosphate levels,

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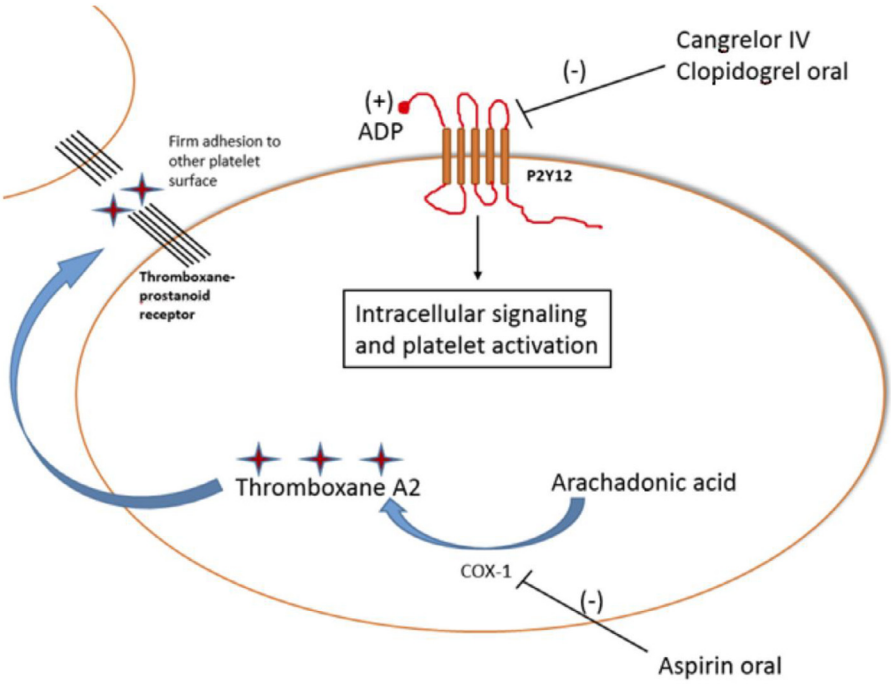

Figure 1. Mechanism of action of cangrelor and platelet inhibition.

cangrelor may exert some of its antiplatelet action, which are independent of P_2Y_{12} pathways, however, clinical implications of such an effect are yet to be determined.[7]

Pharmacokinetics

Cangrelor has a linear pharmacokinetic profile in healthy volunteers and patients with predictable plasma concentrations.[3,6] After administration of the recommended dose (30 mcg/kg bolus followed by 4 mcg/kg/min infusion), maximum plasma concentrations are reached in 2 minutes with mean volume of distribution 3.9 liters suggestive of dispersion only in intravascular compartment achieving a maximum platelet inhibition of 95% to 100% far superior than any other antiplatelet agent. In a study, intravenous infusion in healthy individuals of radiolabeled cangrelor 2 mcg/kg/min, showed 58% radioactivity recovered in urine and 35% in feces. Excretion was initially rapid, with 50% and 75% of radioactivity recovered in first 24 and 48 hours, respectively. Mean systemic clearance is 43.9 L/h and mean elimination half-life is 3.71 minutes.[3,6] Plasma protein binding is 97% to 98%. It gets rapidly deactivated in plasma via dephosphorylation to its primary nucleoside metabolite (ARC-69712XX), which has negligible antiplatelet activity.[6] Cangrelor does not need dose adjustment in the elderly or in patients with renal or hepatic impairment.[3]

To summarize, the unique pharmacodynamics properties are: (1) reaching a steady-state concentration in minutes; (2) therapeutic effects are dose-dependent in a linear pattern, and thus, have predictable effects; (3) highly potent, that is, achieving a very high degree of platelet inhibition; (4) rapid onset, short half-life, and fast offset of action, controlling the amount of side effects.

Clinical Trials, Clinical Safety and Efficacy

CHAMPION trials, for example, CHAMPION-PCI, CHAMPION-PLATFORM, and CHAMPION-PHOENIX are 3 phase III trials that compared cangrelor with either clopidogrel or placebo. The main differences between the trials related to the timing of clopidogrel administration and the loading dose of clopidogrel, differences in the population (patients with ST-segment elevation myocardial infarction [STEMI]), and in the outcome definitions.

Eligible patients were men or nonpregnant women 18 years of age or older who required PCI. In CHAMPION-PCI and CHAMPION-PHOENIX, patients with stable angina, non-ST-segment elevation ACS (NSTE-ACS), or STEMI were enrolled, whereas CHAMPION-PLATFORM did not enroll patients with STEMI. Major exclusion criteria were receipt of a P_2Y_{12} inhibitor or Abciximab at any time in the 7 days before randomization (except for CHAMPION-PCI, in which patients could be taking clopidogrel before randomization), and receipt of Eptifibatide, Tirofiban, or fibrinolytic therapy in the 12 hours before randomization.

All the 3 trials were double-blind, double-dummy, and randomized. Therefore, all patients received an intravenous and an oral study drug. In all trials, the intravenous study drug was administered as a bolus (30 μg/kg of cangrelor or matching placebo), followed by an infusion (4 μg/kg/min of cangrelor or matching placebo). The bolus and infusion were to be administered as soon as possible after randomization after confirmation of suitable anatomy in patients with stable angina or NSTE-ACS. In patients with STEMI, intravenous study drugs could be administered before the coronary anatomy was known. The infusion was to be continued for at least 2 hours or until the conclusion of the index PCI, whichever was longer. At the end of the infusion,

patients in the cangrelor group received 600 mg of clopidogrel. The comparator group differed between the 3 studies. In CHAMPION-PCI, the comparator group was given 600 mg clopidogrel at the start of PCI; in CHAMPION-PLATFORM, clopidogrel 600 mg was given at the end of PCI; and in CHAMPION-PHOENIX clopidogrel 300 mg or 600 mg, as by site standard of care, was to be administered either at the start or at the end of PCI.

Cangrelor Efficacy

A pooled analysis of all 3 clinical trials namely, CHAMPION-Platform, CHAMPION-PCI, and CHAMPION-Phoenix, with respect to the clinical efficacy outcomes, are shown in Table 3. This included a total of 24,910 patients. At 48 hours, cangrelor alleviated the odds of the primary composite quadruple outcome by 19% (3.8% for cangrelor vs 4.7% for control; OR 0.81, 95% CI 0.71 to 0.91, p = 0.0007). Cangrelor decreased the odds of the key secondary outcome of stent thrombosis by 41% (0.5% for cangrelor vs 0.8% for control; OR 0.59, 95% CI 0.43 to 0.80, p = 0.0008) and also reduced the odds of the secondary triple composite outcome (death, myocardial infarction, and ischemia-driven revascularization) by 19% (3.6% in the cangrelor arm vs 4.4% in the control arm; OR 0.81, 95% CI 0.71 to 0.92, p = 0.0014) as well as the composite of death, Q-wave myocardial infarction, and stent thrombosis (0.8% vs 1.3%, 0.63, 95% CI 0.49 to 0.81, p = 0.0002). When the 48-hour primary composite outcome included the combination of death, Q-wave myocardial infarction, and ischemia-driven revascularization, the benefit of cangrelor remained, with a 32% reduction (0.8% in the cangrelor arm vs 1.2% in the control arm; OR 0.68, 95% CI 0.52 to 0.87, p = 0.0022). Cangrelor also alleviated the odds of ischemia-driven revascularization by 29% (0.5% vs 0.7%; OR 0.71, 95% CI 0.52 to 0.98, p = 0.0363) and myocardial infarction by 15% (3.1% vs 3.6%; OR 0.85, 95% CI 0.74 to 0.97, p = 0.0182) at 48 hours. There was no significant reduction in death at 48 hours, although the number of deaths was lower in patients who received cangrelor (0.3% vs 0.4%; OR 0.73, 95% CI 0.47 to 1.15, p = 0·1694).[8]

Analysis of the efficacy outcomes at 30 days postrandomization was consistent with the primary efficacy results. The reductions seen at 48 hours were maintained at 30 days for the primary composite quadruple outcome (5.3% vs 6.1%; OR 0.87, 95% CI 0.78 to 0.97, p = 0.0099), for stent thrombosis (0.9% vs 1.3%; 0.69, 0.54 to 0.88, p = 0.0027), and the secondary triple composite efficacy outcome (5.1% vs 5.7%; 0.88, 0.79 to 0.98, p = 0.0218) as well as for the composite of death, Q-wave myocardial infarction and stent thrombosis (1.9% vs 2.4%; OR 0.81, 95% CI 0.68 to 0.96, p = 0.0139).[8]

The benefit of cangrelor on the primary efficacy outcome at 48 hours was reproducible across all the subgroups, including patients with bio marker elevations at baseline, diabetes mellitus, and age ≥75. The benefits were reproducible irrespective of the clinical presentation as STEMI, NSTE-ACS, or stable angina; cangrelor was associated with a sustained reduction in the primary efficacy composite at 48 hours in patients undergoing PCI for STEMI (OR 0.84, 95% CI 0.55 to 1.27, p = 0.4104), NSTE-ACS (0.82, 0.68 to 0.99, p = 0.0421), or stable angina (0.77, 0.64 to 0.93, p = 0.0053), with no interaction between treatment effect and clinical presentation. Analysis of clopidogrel loading dose and timing indicated that cangrelor also alleviated the primary quadruple outcome at 48 hours in patients treated with a clopidogrel 600 mg loading dose (3.5% vs 4.4%; OR 0.80; 95% CI 0.70 to 0.92, p = 0.0013) or in those who received clopidogrel at the start of PCI (4.1% vs 4.9%; 0.83, 0.70 to 0.97, p = 0.0212). The benefit of cangrelor on the key secondary outcome of stent thrombosis at 48 hours was also consistent across all the subgroups.[8]

Analysis of data from CHAMPION trial suggest that cangrelor is generally a safe and well-tolerated drug. Although, cangrelor can cause a significant inhibition of the platelet P_2Y_{12} signaling pathway, it can be administered for a short period of time and has rapid offset of action. Reduction in ischemic events obtained by cangrelor are not hampered by an excessive risk of major bleeding or blood transfusion.[1,9,10] Cangrelor did not increase the risk of GUSTO severe bleeding, GUSTO moderate bleeding, or the need for blood transfusion but did increase ACUITY major bleeding (4.2 vs 2.8%; p < 0.001). However, when excluding hematomas >5 cm in diameter, the absolute difference in ACUITY major bleeds was small but still statistically significant (1.3 vs 1.0%; p = 0.007). In the cangrelor group used in the pooled analysis of the 3 CHAMPION trials, the rates of minor bleeding were increased, whichever criteria was applied.[8] Cangrelor overdose (defined as an increase of >20% in the bolus dose or the infusion) was not associated with an increase in bleeding complications in the CHAMPION trials.[11]

Adverse Reactions

Most common adverse reaction observed with cangrelor is bleeding and the risk of bleeding was more than clopidogrel.[12,13] Coronary artery dissection, coronary artery perforation, and dyspnea were the most common reasons for discontinuation. Other noncardiac side effects are hypersensitivity, decreased renal functions, and dyspnea.[13] Most common hypersensitivity reactions observed were anaphylactic reactions, anaphylactic shock, angioedema, stridor, and bronchospasm. Worsening of renal functions was observed in patients who were having creatinine clearance of <30 ml/min.[13] However, cangrelor is not cleared through kidney and does not required any dose adjustment in patients with kidney disease. Significant active bleed and hypersensitivity is a contraindication to cangrelor use. In Tables 1 and 2 we have described the adverse event noted in various CHAMPION trials.

Cangrelor on Background of Bivalirudin[14]

A total of 11,145 patients were randomized in the CHAMPION PHOENIX trial. Two hundred and three did not undergo PCI or receive the study drug, resulting in a modified intention to treat study population of 10,942 patients. Bivalirudin was used during PCI in 2,059 of these patients (18.8%), formulating the present analysis cohort. Analysis of champion Phoenix trial data at 48 hours after randomization showed a significant

Table 1
The CHAMPION trials and important results*

Name of Trial	Primary outcome	Stent Thrombosis at 48 hours (Cangrelor vs. Placebo)	Major limitation
CHAMPION PLATEFORM n = 5362 n = 5301 mITT	Cangrelor: 185/2654 (7%) Comparator: 210/2641(8%), P = 0.17	0.2% vs 0.6%, P = 0.02	Did not utilize universal definition of MI
CHAMPION PCI n = 8877 n = 8667 mITT	Cangrelor: 290/3889 (7.5%) Comparator: 276/3865 (7.1%), P = 0.59	0.6% vs 0.7%, P = 0.7	Did not utilize universal definition of MI
CHAMPION PHOENIX n = 11145 n = 10942 mITT	Cangrelor: 257/5470 (4.7%) Comparator: 322/5469 (5.9%), P = 0.005	0.8% vs. 1.4%, P =0.01	

mITT = modified intention to treat, GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy, TIMI = Thrombolysis In Myocardial Infarction.

* All the studies included in this table were double blind, placebo controlled, double dummy trials. Primary outcomes for all the studies were composite of death, myocardial infarction or stent thrombosis at 48 hours.

Table 2
Safety of cangrelor compared to clopidogrel across the CHAMPION TRIALS*

	GUSTO MILD BLEEDING Event rate (Cangrelor vs. Placebo)	Acuity Major Bleeding Event rate (Cangrelor vs. Placebo)	Acuity Minor Bleeding Event rate (Cangrelor vs. Placebo)	Dyspnea Event rate (Cangrelor vs. Placebo)
CHAMPION PLATFORM	16% vs 11.7%, P <0.001	5.5% vs 3.5%, P = <0.001	12% vs 9.3%, P = 0.001	1.4% vs. 0.5%, P = 0.002
CHAMPION PCI	19.6% vs 16.9%, P = 0.001	No difference	17.6% vs 15.2%, P = 0.003	1% vs. 0.4%, P = 0.001
CHAMPION PHOENIX	Not available	4.3% vs 2.5%, P < 0.001	11.8% vs 8.6%, P < 0.001	1.2% vs. 0.3%, P < 0.001

* There was no difference in GUSTO severe or life-threatening or moderate bleeding and TIMI major or minor bleeding event in all 3 trials.

(32%) reduction in the risk of primary efficacy endpoint of death, Myocardial Infarction (MI), Ischemia-driven Revascularization (IDR), or stent thrombosis compared with clopidogrel (4.7% vs 6.7%, odds ratio [OR]: 0.68 [95% confidence interval (CI): 0.47 to 0.99], p = 0.047). The number needed to treat with cangrelor to prevent 1 primary endpoint was 50. The need for rescue glycoprotein II_bIII_a inhibitors was also lower with cangrelor compared with clopidogrel (1.4% vs 3.1%, OR: 0.44 [95% CI: 0.24 to 0.84]; p = 0.010). The rate of stent thrombosis at 48 hours was nonsignificantly lower in the cangrelor group than in the clopidogrel group (0.7% vs 1.4%, OR: 0.48, 95% CI: 0.19 to 1.18; p = 0.10), also a trend for decreased stent thrombosis with cangrelor in the first 2 hours compared with clopidogrel (0.59% cangrelor vs 1.44% clopidogrel; log-rank p = 0.057). MI was also reduced with cangrelor compared with clopidogrel (3.6% vs 5.6%, OR: 0.63, 95% CI: 0.42 to 0.96; p = 0.032). The composites of death or MI (p = 0.036) and death, MI, or stent thrombosis (p = 0.039) were also significantly reduced. In terms of bleeding risk, there were no significant differences in GUSTO severe or moderate bleeding, TIMI major or minor bleeding, ACUITY major bleeding, or the need for blood transfusions in patients treated with cangrelor compared with clopidogrel.[14]

In the HORIZONS-AMI trial[15] in STEMI patients undergoing primary PCI, bivalirudin use compared with heparin plus $GPII_bIII_a$ inhibitors resulted in similar ischemic events, significantly less bleeding and thrombocytopenia, and lower mortality rates at 30 days and 3 years.[1] However, patients treated with bivalirudin also had a higher rate of acute stent thrombosis. In the HORIZONS-AMI trial, bivalirudin was given as a short infusion and clopidogrel as a loading dose of 600 mg was only given in 60% of patients. One mechanism which could explain this is rapid clearance of the drug after discontinuation which was supported in EUROMAX trial. A second possible mechanism relating to an increase in acute stent thrombosis in STEMI patients is inadequate platelet inhibition.[16]

The CHAMPION phoenix trial concluded that in patients receiving bivalirudin, cangrelor alleviated the frequency of MI and acute stent thrombosis, successfully, compared with clopidogrel, without significantly increasing major bleeding or blood transfusions.

Cangrelor has also been studied in BRIDGE trial (maintenance of platelet inhibition with cangrelor after discontinuation of thienopyridines in patients undergoing surgery).[17]This double-blinded study evaluated the use of cangrelor with placebo in 210 patients with ACS or patients treated with a coronary stent who had received a thienopyridine and were awaiting CABG (within 48 hours to 7 days of randomization). Patients were randomized to receive a cangrelor "bridge" intravenous infusion or placebo infusion. The primary outcome of the BRIDGE trial was levels of platelet reactivity measured by the Verify Now P_2Y_{12} test (Accriva, San Diego, CA); specifically, the percentage of patients who maintained platelet reactivity of <240 platelet reactivity units for all blood samples analyzed during study drug infusion before CABG. The main safety endpoint was excessive CABG-related bleeding. For the primary endpoint, a greater proportion of patients treated with cangrelor had low levels of platelet reactivity throughout the

Table 3
Clinical efficacy outcomes at 48 h and at 30 days of CHAMPION trials

Clinical efficacy outcomes at 48 h and at 30 days of CHAMPION trials				
	n/N (%) of patients		Cangrelor vs Clopidogrel	
	Cangrelor (n = 12475)	Clopidogrel (n = 12435)	OR (95% CI)	p
48 hours (primary)				
Death/MI/IDR/ST	473/12459 (3.8%)	579/12422 (4.7%)	0.81 (0.71−0.91)	0.0007
ST	62/12459 (0.5%)	105/12422 (0.8%)	0.59 (0.43−0.80)	0.0008
Death	33/12459 (0.3%)	45/12422 (0.4%)	0.73 (0.47−1.15)	0.1694
MI	387/12459 (3.1%)	453/12422 (3.6%)	0.85 (0.74−0.97)	0.0182
IDR	66/12459 (0.5%)	92/12422 (0.7%)	0.71 (0.52−0.98)	0.0363
Q-wave MI	19/12459 (0.2%)	36/12422 (0.3%)	0.53 (0.30−0.92)	0.0211
Death/MI/IDR	446/12459 (3.6%)	543/12422 (4.4%)	0.81 (0.71−0.92)	0.0014
Death/Q-wave MI/IDR	102/12459 (0.8%)	150/12422 (1.2%)	0.68 (0.52−0.87)	0.0022
Death/MI/ST	450/12459 (3.6%)	550/12422 (4.4%)	0.81 (0.71−0.92)	0.0011
Death/Q-wave MI/ST	103/12459 (0.8%)	162/12422 (1.3%)	0.63 (0.49−0.81)	0.0002
Death/MI	414/12459 (3.3%)	495/12422 (4.0%)	0.83 (0.73−0.95)	0.0054
Death/IDR	92/12459 (0.7%)	130/12422 (1.0%)	0.70 (0.54−0.92)	0.0098
Death/ST	89/12459 (0.7%)	140/12422 (1.1%)	0.63 (0.48−0.82)	0.0007
30 Days				
Death/MI/IDR/ST	657/12407 (5.3%)	748/12357 (6.1%)	0.87 (0.78−0.97)	0.0099
ST	113/12407 (0.9%)	162/12357 (1.3%)	0.69 (0.54−0.88)	0.0027
Death	137/12407 (1.1%)	141/12357 (1.1%)	0.97 (0.76−1.23)	0.7832
MI	418/12407 (3.4%)	487/12357 (3.9%)	0.85 (0.74−0.97)	0.0165
IDR	153/12407 (1.2%)	178/12357 (1.4%)	0.85 (0.69−1.06)	0.1555
Q-wave MI	31/12407 (0.2%)	51/12357 (0.4%)	0.60 (0.39−0.95)	0.0257
Death/MI/IDR	631/12407 (5.1%)	710/12357 (5.7%)	0.88 (0.79−0.98)	0.0218
Death/Q-wave MI/IDR	287/12407 (2.3%)	323/12357 (2.6%)	0.88 (0.75−1.04)	0.1269
Death/MI/ST	586/12407 (4.7%)	681/12357 (5.5%)	0.85 (0.76−0.95)	0.0049
Death/Q-wave MI/ST	238/12407 (1.9%)	293/12357 (2.4%)	0.81 (0.68−0.96)	0.0139
Death/MI	538/12407 (4.3%)	609/12357 (4.9%)	0.87 (0.78−0.98)	0.0266
Death/IDR	277/12407 (2.2%)	301/12357 (2.4%)	0.91 (0.78−1.08)	0.2895
Death/ST	224/12407 (1.8%)	268/12357 (2.2%)	0.83 (0.69−0.99)	0.0405

IDR = ischemia-driven revascularization; MI = myocardial infarction; OR = odds ratio; ST = stent thrombosis.
A patient who did not complete the scheduled follow-up and had no event was not counted in the denominator.

treatment period (98.8 vs 19.0%; $p < 0.001$). Excessive CABG-related bleeding was not significantly different between the cangrelor and placebo groups. Although this study was small and underpowered for hard outcomes such as death, MI, or stent thrombosis, the results support consideration of cangrelor for bridging patients who require discontinuation of an oral thienopyridine before surgery. However, cangrelor is not currently approved for this indication.

Pharmacological Transition Between Cangrelor and Oral Antiplatelet Agents: Prasugrel, Clopidogrel, Ticagrelor

Transition from cangrelor to an oral P_2Y_{12} receptor inhibitors is necessary to continue long-term antiplatelet therapy. There have been some concerns regarding the gap in platelet inhibitions, when transition occurs, which could be of paramount importance in some clinical settings like stent placement.[18] As of now, no randomized clinical trial has examined the efficacy and safety of cangrelor in patients receiving prasugrel or ticagrelor, although pharmacodynamic studies have explored the optimal transition strategy from cangrelor to thienopyidines (clopidogrel and prasugrel) or ticagrelor in patients with stable CAD.

Thienopyridines are prodrugs that require hepatic conversion into active metabolites, which have short half-lives, to irreversibly bind the P2Y12 receptor and inhibit platelet function.[8] A pharmacodynamic study examining the transition from cangrelor to thienopyidines (clopidogrel and prasugrel) showed a transient recovery in platelet reactivity in the first hour after stopping cangrelor infusion.[19] The study concluded that to maintain platelet inhibition after discontinuation of cangrelor, prasugrel 60 mg should be administered immediately after or 30 minutes before stopping the cangrelor infusion and clopidogrel 600 mg immediately after stopping the cangrelor infusion.[19,20]

Ticagrelor is a reversible, direct acting agent and has no interaction with cangrelor.[8,21] A study evaluating the transition from cangrelor to ticagrelor observed no significant increase in platelet reactivity after cangrelor was stopped,[21] irrespective of time of ticagrelor commencement. Therefore, ticagrelor 180 mg can be administered anytime during the cangrelor infusion or immediately after the cangrelor infusion ends.

Role of Cangrelor in Current Era

Cangrelor is approved by FDA for prevention of periprocedural myocardial infarction in patients who have not been treated with a P_2Y_{12} platelet inhibitor and not been

given a $GPII_bIII_a$ inhibitor.[12] European Society of Cardiology proposed use of cangrelor in patients who have not received an oral P_2Y_{12} receptor antagonist before PCI and in whom oral therapy with P_2Y_{12} receptor antagonist is not feasible or desirable.[22] Cangrelor can be a good option to use in patients who are unable to take oral medications. Approximately 5% to 6% of patients with STEMI experience resuscitated cardiac arrest and 64 % of these patients are unconscious during initial evaluation.[23] These patients and any other patients unable to take oral medications like (vomiting or sedated patients) would be suitable candidates for intravenous antiplatelet therapy with cangrelor. Also, an early reduced pharmacodynamic effect of prasugrel and ticagrelor has been reported in these patients.[24] Role of cangrelor is also suggested in reducing the risk of thrombotic events after PCI in stable CAD patients considered for ad hoc PCI.[25] Clopidogrel has been used in these types of situations, but several hours delay to achieve adequate antiplatelet effect with clopidogrel makes cangrelor a better option in this scenario.[25] Bridging therapy in patients treated with antiplatelet agents to reduce the risk of thrombotic events in the interval between drug cessation and surgery may also be a role for cangrelor in the future, although it is not currently labeled as an indication. In preparation for surgery, P_2Y_{12} inhibitors are typically discontinued 5 to 7 days before surgery to minimize bleeding risk during the procedure.[26,27] The latter practice can especially put patients who have undergone recent drug-eluting stenting at a high risk for stent thrombosis (especially in the setting of ACS) if antiplatelet therapy is interrupted. It should be kept in mind that cangrelor has not been adequately studied in head-to-head comparisons with more potent P_2Y_{12} inhibitors like ticagrelor and prasugrel. Whether cangrelor adds clinical benefit to patients treated with these agents is entirely unknown. However, in ACS patients who cannot take oral medications or bridging therapy, cangrelor is still likely to be beneficial.

In conclusion, intravenous antiplatelet agents will have an important therapeutic role with increasing complexity of PCI in high-risk patients. Limitations in the pharmacodynamic effects of all oral P_2Y_{12} inhibitors (especially in ACS) are well-described. Inadequate platelet inhibition has been associated with periprocedural thrombotic events in numerous studies. Intravenous agents obviate these limitations. Patients unable to take oral medications undergoing emergent/urgent PCI are ideal candidates for cangrelor use. Cangrelor has potential role in bridging therapy in patients who had recent PCI with DES in need for urgent cardiac or noncardiac surgery.

Disclosures

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