

Cangrelor: A New Kind of Antiplatelet Therapy

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Antiplatelets are the cornerstone therapy for the prevention of thrombotic complication in Acute Coronary Syndrome (ACS) after Percutaneous Coronary Intervention (PCI). Aspirin in addition to thienopyridines (TDP), such as clopidogrel and prasugrel, or non-TDP, such as ticagrelor, are recommended by the current guidelines. As the antiplatelets may increase risks of bleeding, clopidogrel and ticagrelor need to be held for at least 5 days, and prasugrel needs to be held for at least 7 days prior to surgical procedures [1]. Unfortunately, premature discontinuation of antiplatelets increases risk of ischemic complications [2]. Physicians are caught in the dilemma of weighing the risks and benefits of continuing or holding antiplatelet therapy prior to surgery.

Cangrelor is a non-TDP, adenosine diphosphate (ADP) analogue available in an intravenous (IV) form. It offers the advantage of having a rapid onset and rapid offset mechanism of action. Cangrelor is administered as an IV bolus, followed by an infusion, and maximal platelet inhibition occurs within 15 minutes of initiation. After discontinuation of infusion, platelet function returns to baseline within 24 hours [3]. Efficacy of cangrelor was studied in 4 landmark trials: CHAMPION PCI, CHAMPION PLATFORM, CHAMPION PHOENIX, and BRIDGE.

CHAMPION PCI and CHAMPION PLATFORM were the first 2 trials conducted around the same time to evaluate the efficacy of cangrelor as compared to clopidogrel in patients undergoing PCI. Both were randomized, double blind, double dummy, and placebo-controlled. In the CHAMPION PCI trial, cangrelor infusion was compared to clopidogrel 600 mg Loading Dose (LD) given before PCI. In the CHAMPION PLATFORM trial, cangrelor infusion was compared to clopidogrel 600 mg LD given after PCI. Duration of therapy was 2 hours or the duration of PCI, whichever is longer, and was up to 4 hours at the discretion of the physician. Primary efficacy endpoint was a composite of death, Myocardial Infarction (MI), ischemia-driven revascularization 48 hours after PCI. Primary safety endpoint was bleeding rates up to 48 hours after PCI. After an interim analysis, CHAMPION PLATFORM trial was prematurely stopped due to the lack of superiority in the primary efficacy endpoint. When it was halted, the CHAMPION PCI investigators were able to enroll 98.6% of the expected patient population [4,5].

In both trials, the primary efficacy endpoint was not statistically significant between cangrelor and clopidogrel. In the CHAMPION PLATFORM trial, event rate was 7% for cangrelor and 8% for clopidogrel (odds ratio [OR]: 0.87; 95% Confidence Interval [CI], 0.71 to 1.07; $p=0.17$). In the CHAMPION PCI trial, event rate was 7.5% for cangrelor and 7.1% for clopidogrel (OR: 1.05; 95% CI: 0.88-1.24; $p=0.59$). Bleeding event was not significant between the 2 treatment groups based on the criteria of the Thrombolysis in Myocardial Infarction (TIMI) trial. In the CHAMPION PLATFORM trial, cangrelor patients experienced more major bleeding events (5.5% versus 3.5%; OR: 1.61, 95% CI: 1.23-2.10; $p<0.001$) and minor bleeding events (12% versus 9.3%; OR: 1.34, 95% CI: 1.12-1.59, $p=0.001$) based on the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) criteria. In the CHAMPION PLATFORM trial, cangrelor reduced the rates of stent thrombosis at 48 hours after PCI (0.2% versus 0.6%; OR: 0.31, 95% CI: 0.11-0.85, $p=0.02$), but not at 30 days (0.6%

versus 1.1%; OR: 0.53, 95% CI: 0.28-0.99, $p=0.05$). In the CHAMPION PCI trial, rates of stent thrombosis was not significant between the 2 groups at 48 hours (0.3% versus 0.3%, OR: 0.73; 95% CI: 0.33-1.59; $p=0.43$) or at 30 days (0.6% versus 0.7%; OR: 0.89, 95% CI: 0.53-1.51; $p=0.67$) [4,5].

Based on the results of the CHAMPION trials, cangrelor failed to show an advantage over clopidogrel in the primary efficacy endpoints, but was able to show a reduction in the rates of stent thrombosis. The CHAMPION PHOENIX trial was conducted to compare cangrelor with clopidogrel in the rates of ischemic complications. This trial was a double blinded double dummy and randomized patients to cangrelor or clopidogrel. Cangrelor patients received cangrelor infusion, followed by clopidogrel 600 mg LD at the end of the infusion. Clopidogrel patients received placebo infusion, along with clopidogrel 300 mg or 600 mg LD, at the discretion of the investigators. The primary efficacy end point was the composite rate of death from any cause, MI, ischemia-driven revascularization, or stent thrombosis in the 48 hours after PCI. Key secondary endpoint was the rate of stent thrombosis at 48 hours. Primary safety endpoint was the occurrence of non-Coronary Artery Bypass Graft (CABG) related bleeding according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria at 48 hours. Primary efficacy composite endpoint was significantly lower in the cangrelor group (4.7% vs. 5.9%; OR: 0.78; 95% CI: 0.66 to 0.93; $p=0.005$). However, when considering the individual endpoints, only the rates of MI (3.8% versus 4.7%; OR: 0.80, 95% CI: 0.67-0.97; $p=0.02$) and of stent thrombosis at 48 hours was also lower in the cangrelor group (0.8% vs. 1.4%; OR: 0.62, 95% CI: 0.43 to 0.90; $p=0.01$). At 30 days, the rate of the composite efficacy end point remained significantly lower in the cangrelor group than in the clopidogrel group (6% vs. 7%; OR: 0.85, 95% CI: 0.73 to 0.99; $p=0.03$), and the rates of stent thrombosis were lower in the cangrelor group (1.3% vs. 1.9%; odds ratio, 0.68; 95% CI, 0.50 to 0.92; $P=0.01$). Rates of primary safety endpoint were not significant between the 2 groups (0.16% for cangrelor, 0.11% for clopidogrel; OR: 1.5; 95% CI: 0.53 to 4.22; $p=0.44$). Significantly higher rates of dyspnea occurred with cangrelor (1.2% vs. 0.3%, $P<0.001$) [6].

As cangrelor has a short half-life, its role in patients who had clopidogrel therapy held while awaiting surgery was explored in the BRIDGE trial. This was a 2 phase clinical trial. Phase 1 was to determine the optimal dose of cangrelor to achieve maximal platelet inhibition. Phase 2 was a randomized, double blinded, placebo controlled trial to assess whether the cangrelor dose determined in phase 1 was able

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to obtain platelet reactivity of less than 240 P2Y₁₂ Reaction Units (PRU) during preoperative period of non emergent open heart surgery. Patients were randomized to receive cangrelor or placebo infusion. Study drug was initiated after discontinuation of TDP and continued for up to 1-6 hours prior to open heart surgery. Time lapse between discontinuation of TDP and initiation of surgery was at the discretion of individual physicians. The primary efficacy end point of phase 2 was the proportion of patients with PRU <240 PRU during study drug infusion prior to surgery. Primary safety endpoint was the rates of CABG-related bleeding. Additional endpoints included rates of combined ischemic endpoint of death, MI, stroke or need for urgent revascularization from randomization up until discontinuation of drug infusion, and up to 30 days after CABG surgery. Median time from discontinuation of study drug to the initiation of surgical procedure was 3.2 hours for both treatment groups. Primary efficacy endpoint was significant higher for cangrelor (98.8% versus 19%, p<0.001). CABG-related bleeding rates were not significant (11.8% for cangrelor, 10.4% for placebo; relative risk: 1.1; 95% CI: 0.5-2.5; p=0.76). Combined ischemic endpoints occurred in 2.8% of the cangrelor group and in 4% of the placebo group. No statistical analysis was conducted on the ischemic endpoints [7].

After decades of having only oral ADP receptor antagonists available, cangrelor is the first IV ADP receptor blocker available. In the CHAMPION PLATFORM and the CHAMPION PCI trials, occurrence rates of the primary efficacy endpoint were not significant when comparing cangrelor to clopidogrel. The CHAMPION PLATFORM showed a reduction in rates of stent thrombosis at 48 hours, but not at 30 days post PCI. The CHAMPION PHOENIX trial was able to show reduction rates in primary efficacy endpoint and in stent thrombosis with cangrelor at 48 hours and at 30 days. The difference in the results may be due to the discrepancy in the patient population used for analysis. The first 2 CHAMPION trials conducted analysis of the primary efficacy endpoint based on the Modified Intention-To-Treat (MITT) population, while the CHAMPION PHOENIX trial conducted analysis based on the Intention-To-Treat (ITT) population. If the CHAMPION PHOENIX were to utilize the MITT population, the results may be different from its current findings. Additionally, when considering the individual primary endpoints, only the rates of MI and stent thrombosis were significant at 48 hours. At 30 hours, no information was presented on the rates of death, revascularization or MI. Therefore, cangrelor may be effective in reducing rates of stent thrombosis, but it may not have any mortality benefit.

The role of cangrelor in the perioperative period prior to surgery remains uncertain at this time. The BRIDGE trial only showed that cangrelor maintained platelet inhibition during the period that clopidogrel or prasugrel was held. However, the rates of ischemic complications were secondary endpoints with no statistical analysis performed. Therefore, no definitive clinical recommendations can be made.

All the CHAMPION studies conducted have compared cangrelor to clopidogrel. Future studies should be conducted to evaluate the clinical efficacy of cangrelor in the perioperative period when clopidogrel, prasugrel, or ticagrelor were held for surgery. However, as cangrelor is only to be administered as an IV infusion, whether or not patient

can safely receive cangrelor in the outpatient setting is questionable. If patients were to be admitted as an inpatient or an outpatient infusion clinic solely for the purpose of administering cangrelor, the costs associated needs to be assessed. Additionally, all the CHAMPION trials initiated cangrelor after the coronary anatomy is known and patients are undergoing PCI. Efficacy of cangrelor in ACS prior to diagnostic angiography is unknown. Based on current data, the potential role for cangrelor may be in ACS patients who were vomiting, or who were unable to swallow tablets.

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