Clinical Effectiveness for Cangrelor in PCI Not Persuasive

The final results of the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI (NCT00305162) and CHAMPION PLATFORM (NCT00385138) trials showed no clinical benefit with cangrelor for the primary composite outcome of death, myocardial infarction (MI), and ischemic-driven revascularization (IDR) in patients who were undergoing percutaneous coronary intervention (PCI). Both studies were halted early in May of this year for futility, based on recommendations from an independent Interim Analysis Review Committee (IARC).

In CHAMPION PCI, presented by Robert A. Harrington, MD, Duke Clinical Research Institute, Durham, NC, 8877 patients (median age 62 years; 26% women) with stable angina or ACS (unstable angina (UA), ST-segment elevation or non-ST-segment-elevation myocardial infarction [STEMI; NSTEMI]) were randomly assigned in a double-blind double-dummy design to receive either intravenous (IV) cangrelor (30-µg/kg bolus 30 minutes before PCI and 4-µg/kg/min infusion continuing for 2 hours; n=4367) followed by 600 mg of placebo at the completion of the infusion or 600 mg of clopidogrel with IV placebo bolus and infusion (n=4355).

The median age was 62 years, 27% were female, 31% had diabetes, and 25% had prior MI. The presenting diagnoses were as follows: stable angina 15%, UA 25%, NSTEMI 49%, and STEMI 11%. The median time from hospitalization was 6.3 hours (range 2.6 to 27 hours), and the median duration of infusion was 2.1 hours (interquartile range [IQR] 2.0 to 2.2 hours). The primary endpoint (a composite of death from any cause, MI, and ischemia-driven revascularization or IDR) at 48 hours occurred in 7.5% of subjects in the cangrelor group versus 7.1% of subjects in the clopidogrel-only group (OR 1.05; 95% CI, 0.88, to 1.24; p=0.59). This was a modified intention-to-treat population that included patients who underwent randomization (excluding the STEMI cohort), received at least one dose of a study drug, and underwent the index PCI. Patients with STEMI were excluded from the primary efficacy analysis due to challenges in measuring reinfarction in the early hours of STEMI. There was no difference in stent thrombosis between the groups (0.2% cangrelor vs 0.3% clopidogrel; p=0.34).

Adverse events were similar in the two groups overall (26.4% cangrelor vs 25.7% clopidogrel), with the exception of dyspnea, which occurred in significantly more subjects who received cangrelor (1.0% vs 0.4% in the clopidogrel group; p=0.001). Major bleeding was similar between those who were randomized to cangrelor versus clopidogrel (ACUITY Major 3.6% vs 2.9%; p=0.06; GUSTO severe or life-threatening 0.2% versus 0.3%; p=0.82; TIMI Major 0.4% vs 0.3%; p=0.39). Only ACUITY minor bleeding (17.6% vs 15.2; p=0.003) and GUSTO mild bleeding (19.6% vs 16.9% with; p=0.001) were significantly higher in the cangrelor group. There were no differences in other bleeding categories and no increase in the need for blood transfusion.

In the CHAMPION PLATFORM trial, presented by Deepak L. Bhatt, MD, Brigham and Women's Hospital, Boston, MA, the primary endpoint and eligibility criteria were the same as in the PCI study except for the exclusion of patients with STEMI. Patients (median age 63 years; 29% female, 32% diabetics, 25% history of MI) were randomly assigned to receive cangrelor (30-µg/kg bolus and 4-µg/kg/min infusion for the duration of PCI; n=2654) or placebo (n=2641). All patients received clopidogrel 600 mg after PCI. Only 5% had stable

angina, while 35% had UA and 60% had NSTEMI. The median time from admission to PCI was 7.9 hours (IQR 3.3 to 24.1), and median duration of infusion was 2.1 hours (IQR 2.0 to 2.3).

The primary endpoint, assessed in a modified intention-to-treat cohort that consisted of all patients who underwent randomization, received at least one dose of a study drug, and underwent the index PCI, occurred in 7.0% of patients in the cangrelor group versus 8.0% of patients in the clopidogrel-only group (OR, 0.87; 95% CI, 0.71 to 1.07; p=0.17). At 48 hours, the rate of stent thrombosis was reduced with cangrelor, from 0.6% to 0.2% (OR, 0.31; 95% CI, 0.11 to 0.85; p=0.02), and all-cause mortality was reduced with cangrelor, from 0.7% to 0.2% (OR, 0.33; 95% CI, 0.13 to 0.83; p=0.02).

The rates of ACUITY minor and GUSTO mild bleeding were higher in the cangrelor group (ACUITY 12.0% vs 9.3%; p=0.001; GUSTO 16.0% vs 11.7%; p<0.001), primarily driven by an increase in groin hematomas. There was no increase in the need for transfusion, even among high-risk groups. Dyspnea was more common in the cangrelor group (1.4%) compared with clopidogrel only (0.5%; p=0.002). Other adverse events were similar between the two groups.

While these two trials of this IV-reversible ADP antagonist were stopped early due to futility (low likelihood to show a statistically significant difference in the primary endpoint), there were some intriguing findings. Cangrelor was associated with a similar to slightly higher bleeding risk compared with clopidogrel 600 mg pre-PCI in CHAMPION PCI but offered a much quicker onset and offset of action. Compared with clopidogrel that was given post-PCI (as in CHAMPION PLATFORM), cangrelor was associated with a reduction in mortality and in stent thrombosis but caused more groin hematomas. The short time from hospital admission to PCI and definition of MI may have limited the ability to detect a reduction in procedure-related MI in both trials. Specific populations may benefit from this agent, and additional carefully designed investigations are warranted.

Additional reading:

- Harrington RA et al. Platelet Inhibition with Cangrelor in Patients Undergoing PCI. *N Engl J Med* 2009;361. Published online 15 November 2009.
- Bhatt DL et al. Intravenous Platelet Blockade with Cangrelor during PCI. *N Engl J Med* 2009;361. Published online 15 November 2009.
- Kastrati A & Ndrepepa G. Cangrelor — A Champion Lost in Translation. *N Engl J Med*. Published online 15 November 2009.

Results of the PLATelet Inhibition and Patient Outcomes (PLATO) Trial

In a late-breaking clinical trial that was presented at the American Heart Association 2009 Scientific Sessions in Orlando, FL, Philippe Gabriel Steg, MD, Hôpital Bichat-Claude Bernard, Paris, France, reported that ticagrelor, the first reversible oral P2Y12 receptor antagonist, was superior to clopidogrel in terms of preventing cardiovascular (CV) death, myocardial infarction (MI), or stroke in patients who presented with ST-segment elevation myocardial infarction (STEMI) and for whom PCI was planned, without causing a significant increase in major bleeding.

In this prespecified subset analysis of the larger PLATO trial (NCT00391872), presented earlier this year at the European Society of Cardiology Meeting, 8430 patients with STEMI who presented within the previous 24 hours and were planned for primary percutaneous coronary intervention (PCI) were randomly assigned to receive either 180 mg ticagrelor during PCI and stenting, followed by a maintenance dose of 90 mg twice daily, or a 300- to 600-mg loading dose of clopidogrel, followed by a maintenance dose of 75 mg daily for 6 to 12 months. In addition, all patients received daily aspirin. Patients who were previously treated with clopidogrel, either as a prerandomization loading dose or as chronic therapy (~46%), did not receive a loading dose of the study drugs. Patients were excluded if they received fibrinolytic therapy within 24 hours prior to randomization.

The primary endpoint, a composite of CV death, MI, or stroke at 12 months, was significantly reduced in those who were randomized to ticagrelor versus clopidogrel (9.3% vs 11.0%; HR, 0.85; 95% CI, 0.74 to 0.97; p=0.02). Components of the primary endpoint were also reduced with ticagrelor, including a statistically significant reduction in MI (4.7% vs 6.1%; p=0.01) and a trend toward a lower rate of CV (4.5% vs 5.4%; p=0.09). However, there was a trend toward an increased rate of stroke (1.6% vs 1.0%; p=0.07) with ticagrelor. As was observed in the main trial result, all-cause mortality was significantly reduced from 6.0% for those on clopidogrel to 4.9% for ticagrelor (HR, 0.82; 95% CI, 0.68 to 0.99; p=0.04) among patients with STEMI. Stent thrombosis (ARC definite, definite or probable, and all ARC categories) was significantly reduced (2.5% vs 3.6% for definite or probable, HR, 0.69; 95% CI, 0.52 to 0.92; p=0.01) in the patients who were treated with ticagrelor.