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.

Safety results were similar to the overall trial. There was no significant difference in the risk of PLATO major, TIMI major, or fatal bleeding between treatment groups. Episodes of dyspnea were more common with ticagrelor (13.8%) compared with clopidogrel (7.8%). The difference was statistically significant (p<0.0001) and led to significantly (p=0.002) more ticagrelor patients who discontinued treatment.

Ticagrelor differs from thienopyridines, such as clopidogrel, in a number of important ways. It is *not* a prodrug and thus does not require hepatic activation—instead, it directly inhibits the adenosine diphosphate (ADP) receptor P2Y12 (purinoceptors), which is involved in platelet activation. Ticagrelor has a rapid onset of action and can completely inhibit the sustained aggregation response to ADP; yet, it is reversible, wherein functional recovery of circulating platelets occurs within 48 hours of treatment cessation. Because patients with STEMI who undergo primary PCI require urgent and effective blockade of the P2Y12 platelet receptor and are at a greater risk of side effects from inconsistent platelet inhibition, the pharmacokinetic profile of ticagrelor is well suited for treating such patients.

One drawback, mentioned by the discussant of this trial, Lisa K. Jennings, PhD, University of Tennessee Health Science Center, Memphis, TN, was the need for twice-daily dosing due to ticagrelor's reversible binding properties and 12-hour half-life. This might cause problems for patients who are not fully compliant. In balance, however, the significant reduction in all-cause mortality and in clinically important cardiac events, without increased bleeding, makes this new agent a promising new addition to oral antiplatelet therapy for patients with STEMI who are undergoing PCI.

Primary PCI at Hospitals without On-Site Cardiac Surgery Increases Risk of Repeat Vascularization

According to a new analysis of data from the Massachusetts Data Analysis Center (MASS-DAC) registry, patients who are undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) face similar risks of death and MI but higher rates of repeat revascularization when treated at hospitals without on-site cardiac surgery (non-SOS) capabilities compared with hospitals with cardiac surgery capabilities (SOS).

If it can be performed quickly (within 90 minutes of initial medical contact), primary PCI is the preferred method of reperfusion in patients with STEMI, according to current American Heart Association/American College of Cardiology guidelines. However, most patients with STEMI present to hospitals without SOS, where primary PCI is generally discouraged (eg, in Massachusetts). With limited access to immediate PCI, many patients with STEMI either are treated with fibrinolytic therapy or face potential delays in treatment in transfer to PCI centers.

Allowing primary PCI in hospitals without SOS could greatly expand access to timely PCI for STEMI patients. In 1997, the Massachusetts Department of Health initiated a pilot program for primary PCI at non-SOS hospitals. Ather Anis, MD, Boston University Medical Center, Boston, MA, presented findings from the MASS-DAC analysis, comparing outcomes of primary PCI in hospitals depending on the availability of SOS.

Of a total of 6139 patients in the MASS-DAC registry with STEMI who underwent PCI between 2005 and 2007, there were 3018 patients with complete data who were not transferred and were treated at centers with (n=2041) and without (n=977) cardiac surgery capabilities. Demographic, clinical, and angiographic variables were included in multivariate analyses, with propensity score-matching to minimize confounding. The primary outcomes were 30-day and 1-year all-cause mortality, MI, repeat revascularization, and target vessel revascularization.

Patients who were treated at non-SOS hospitals were more frequently white, covered by HMO insurance, and had multivessel disease. All-cause mortality was similar in centers with and without cardiac surgery capabilities at 30 days (4.5% vs 5.7%; p=0.22) and at 1 year (9.4% vs 8.6%; p=0.51). Although there was a trend toward increased risk of MI at 30 days at non-SOS hospitals (4.35% vs 2.82%; p=0.05), the risk of MI was similar at 1 year (6.7% vs 5.1%; p=0.11).

Target vessel revascularization rates were also similar at 30 days (6.3% vs 5.0%; p=0.21) and at 1 year (10.9% vs 9.7%; p=0.39). However, repeat revascularization rates were significantly higher in non-SOS centers through 30 days (14.9% vs 7.6%; p<0.0001) and 1 year (21.0% vs 14.7%; p<0.0001).

This observational analysis suggests that primary PCI may be safely performed in patients who present with STEMI to non-SOS hospitals, with no differences observed in 30-day or 1-year mortality. Dr. Anis noted, however, that "STEMI patients undergoing primary PCI at hospitals without on-site cardiac surgery had a slightly higher incidence of