Munich, Germany. Dr. Kastrati cautioned that because the dose of UFH (140 U/kg) was higher in ISAR-REACT 3 than that used in other recent PCI trials and the dose (70-100 U/kg) recommended in current PCI guidelines in the absence of GP IIb/IIIa inhibitors [Smith.*Circulation* 2006], it was not clear how much of an effect the higher UFH dose had on the observed ischemic or bleeding event rates in the trial.

Dr. White noted that the ISAR-REACT 3 results should not be generalized to patients with higher ischemic risk, such as those with elevated troponin levels, acute MI, or recent CABG. Furthermore, the findings are not applicable to patients who have not received 600 mg clopidogrel ≥2 hours before PCI, he concluded.

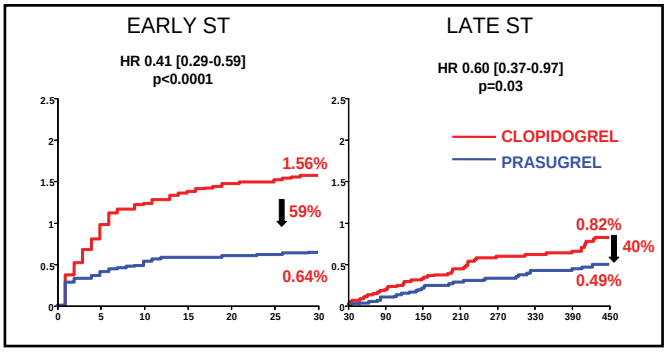
Advantage of Prasugrel Over Clopidogrel Holds Across Range of Patient- and Procedure-Related Factors

The advantage of prasugrel over clopidogrel in preventing stent thrombosis has been found to be maintained regardless of the time since the stenting procedure, the type of stent, or the ARC definition of thrombosis. The TRITON-TIMI 38 stent analysis showed that the drug led to a highly significant reduction in stent thrombosis over a broad array of clinical and procedural characteristics.

The patients who were included in the stent analysis represented a subset of patients from the main TRITON-TIMI 38 trial, which included patients with moderate-to-high-risk acute coronary syndrome who were scheduled for PCI. In that trial, 6461 patients received only bare-metal stents (BMS), and 5743 patients received only drug-eluting stents (DES). The patients were randomly assigned to antiplatelet therapy with either clopidogrel (300 mg loading dose before PCI, followed by a maintenance dose of 75 mg daily for one year) or prasugrel (loading dose of 60 mg, followed by 10 mg daily for one year). The findings of that study showed that prasugrel was associated with a 52% reduction in stent thrombosis (2.4% compared with 1.1% for clopidogrel; p<0.0001).

Stephen D. Wiviott, MD, Brigham and Women's Hospital, Boston, MA, reported that the stent analysis portion of TRITON-TIMI 38 demonstrated rates of stent thrombosis for the 2 drugs that were similar to the rates in the main trial. Overall, prasugrel reduced early (within 30 days)stent thrombosis by 59% (0.64% vs 1.56%; p<0.0001) and late stent thrombosis by 40% (0.49% vs 0.82%; p=0.03); (Figure 1). The frequency of definite or probable stent thrombosis associated with prasugrel was significantly lower in the BMS arm (1.27% vs 2.41%; HR 0.52; p=0.0009), as well as in the DES arm (0.84% vs 2.31%; HR 0.36; p<0.0001).

Figure 1. Comparison of Early and Late Definite/ Probable Stent Thrombosis (Any stent n=12844).



The rates of stent thrombosis associated with the 2 drugs were also consistent across the various ARC definitions of stent thrombosis. Prasugrel was associated with a 0.9% rate of definite stent thrombosis, a 1.1% rate of definite or probable thrombosis, and a 1.5% rate of definite, probable, or possible thrombosis. All of these rates were significantly lower (p<0.0001) than those for clopidogrel (2.0%, 2.3%, and 2.7%, respectively).

In discussing the balance of efficacy and safety, Dr. Wiviott noted that prasugrel prevented stent thrombosis in 12 of 1000 patients and prevented adverse events other than stent thrombosis (cardiovascular disease, myocardial infarction, and stroke) in 15 of 1000 patients. The drug was associated with major bleeding in 5 of 1000 patients.

"What TRITON-TIMI showed with respect to the prevention of stent thrombosis was clinically very important. Now we need to find ways to determine which patients are best suited for which therapies," said. Dr. Wiviott.

Bavarian Reperfusion Alternatives Evaluation-3 Trial

For patients with acute ST-elevation myocardial infarction (STEMI) who undergo primary coronary intervention (PCI), the addition of abciximab does not enhance the clinical benefits that are provided by pretreatment with high-dose clopidogrel, according to the findings of the Bavarian Reperfusion Alternatives Evaluation-3

(BRAVE-3) trial. Moreover, abciximab increases the risk of adverse clinical outcomes, suggesting that it should not be added to standard antiplatelet therapy in this patient population.

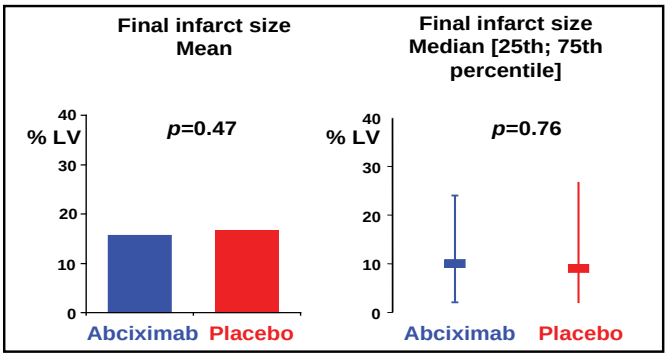
"Therapy without abciximab would certainly be more cost-effective and reduce the risk of bleeding complications," said lead author Julinda Mehilli, MD, Deutsches Herzzentrum, Technical University, Munich, Germany.

Prior studies in primary PCI suggested that antiplatelet therapy with intravenous glycoprotein IIb/IIIa inhibitors improved clinical outcomes in patients with acute STEMI, Dr. Mehilli said. Given the trend toward greater benefit with more robust platelet inhibition, BRAVE-3 was designed to evaluate whether the intravenous glycoprotein inhibitor abciximab reduces infarct size in patients with acute STEMI undergoing PCI following pretreatment with 600 mg clopidogrel, a dose that is higher than currently recommended in STEMI treatment guidelines.

BRAVE-3 enrolled 800 patients with acute STEMI who presented within 24 hours of symptom onset. After pretreatment with clopidogrel (600 mg), aspirin (500 mg), and unfractionated heparin (UFH) (5000 IU), patients were randomly assigned to therapy with abciximab (n=401) or placebo (n=399). Following PCI, all patients received additional treatment with clopidogrel 75 mg twice daily for 3 days, clopidogrel 75 mg once daily for at least 4 weeks, and aspirin 200 mg once daily indefinitely.

Abciximab did not provide additional reduction of the infarct size (the primary endpoint), which was expressed as a percentage of the left ventricle and measured 5-7 days after randomization. The final mean infarct size was similar in patients treated with abciximab and placebo (15.7% vs 16.6%, respectively; p=0.47; Figure 1).

Figure 1. Infarct Size Following Primary PCI With and Without Abciximab.



In the first 30 days following PCI, abciximab did not increase the rate of TIMI major bleeding compared with placebo (1.8% in both groups). However, abciximab did increase the rates of TIMI minor bleeding and thrombocytopenia

In summary, these findings suggest that abciximab on a background of 600 mg clopidogrel did not reduce infarct size in patients with STEMI undergoing primary PCI.

Two Studies Explore Ways to Improve Clinical Outcomes in STEMI

The findings of 2 studies have helped to identify ways to improve clinical outcomes of patients with ST-segment elevation myocardial infarction (STEMI) undergoing fibrinolysis or percutaneous coronary intervention (PCI). These studies provide answers about the role of thrombus aspiration before primary PCI and the role and optimal timing of routine PCI after fibrinolysis.

Thrombectomy typically is performed before primary PCI in patients with STEMI only when the clot is large. However, the TAPAS trial demonstrated that thrombus aspiration before PCI, regardless of the clot size, resulted in improved myocardial perfusion and better clinical outcomes. TAPAS was a single-center study that involved consecutive patients with STEMI who were randomly assigned to either manual aspiration of the thrombus and PCI (535 patients) or conventional PCI (536 patients). The primary measure of reperfusion was determined by the myocardial blush grade (MBG), and an MBG of 0 or 1 (defined as absent or minimal myocardial blush) was the primary endpoint.

Felix Zijlstra, MD, PhD, Thoraxcentre, University Medical Centre, Groningen, The Netherlands, reported that fewer patients who had thrombus aspiration compared with conventional PCI had an MBG of 0 or 1 (17% vs 26%; p<0.001). Thrombus aspiration also led to a significantly higher rate of complete resolution of ST-segment elevation, another measure of myocardial reperfusion (57% vs 44%; p<0.001). Through 30 days, thrombus aspiration tended to reduce the risk of death (RR 0.52; p=0.07), reinfarction (RR 0.40; p=0.11), target-vessel revascularization (RR 0.77; p=0.34), and major adverse cardiac events (RR 0.72; p=0.12). At one year, the rate of the composite endpoint (death and reinfarction) was significantly lower among patients who had thrombus aspiration (Figure 1). In addition, MBG was found to be a good predictor of clinical outcome; the one-year mortality rate was significantly lower for patients with an MBG of 3 than for patients with a MBG of 0/1 (3.7% vs 11%; p=0.001).