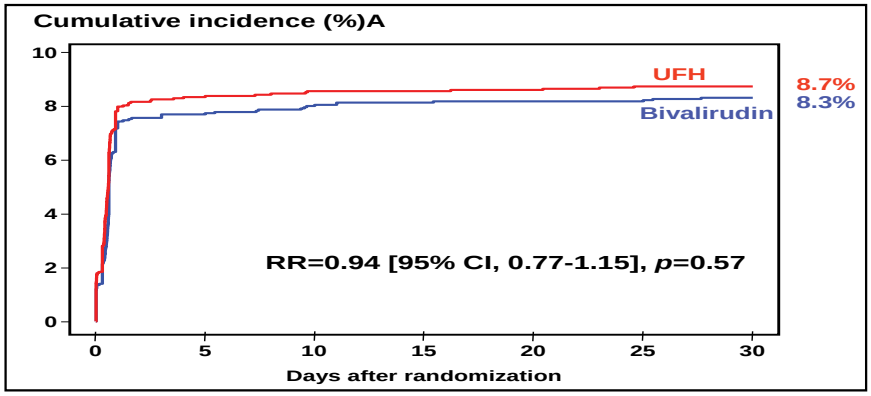
Bivalirudin Not Superior to Unfractionated Heparin in Patients Receiving 600 mg Clopidogrel Prior to PCI

Bivalirudin failed to show a superior "net clinical benefit" compared with unfractionated heparin (UFH) in patients undergoing percutaneous coronary intervention (PCI) in the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment 3 (ISAR-REACT 3) trial. However, bivalirudin reduced the rate of major and minor bleeding events in this patient population.

In the ISAR-REACT 3 trial, 4570 patients with biomarker-negative stable or unstable angina were randomly assigned to treatment with bivalirudin (n=2289) or UFH (n=2281) prior to scheduled PCI. All patients received clopidogrel 600 mg at least 2 hours before PCI and at least 325 mg oral or intravenous aspirin. Bivalirudin was administered as a 0.75 mg/kg loading dose followed by 1.75 mg/kg/hr infusion. Patients in the UFH group received a 140 U/kg bolus followed by placebo infusion.

Following PCI, patients received clopidogrel 75-150 mg/day until discharge (≤3 days) and 75 mg/day for at least 1 month after balloon angioplasty or implantation of bare-metal stents and for at least 6 months after implantation of drug-eluting stents. All patients received aspirin 80-325 mg/day indefinitely. At 30 days, the cumulative incidence of death, myocardial infarction, urgent target vessel revascularization, and major bleeding (the primary endpoint) in the bivalirudin and UFH groups was 8.3% and 8.7%, respectively (RR 0.94; p=0.57; Figure 1).

Figure 1. Net Clinical Benefit of Bivalirudin and UFH.



Despite similarities in net clinical benefit, bivalirudin showed a clear advantage over 140 U/kg UFH with regard to risk of bleeding. Compared with those in the UFH group, bivalirudin-treated patients had a significantly lower rate of major bleeding (3.1% vs 4.6%; p=0.008) and minor bleeding (6.8% vs 9.9%; p=0.0001).

"Bleeding is important to patient outcomes," said Harvey White, MD, Auckland City Hospital, Auckland, New Zealand. "Strikingly, bivalirudin reduced TIMI major bleeding by 50 percent."

Still, "ISAR-REACT 3 was powered for its primary endpoint, so conclusions should focus on the primary endpoint," said lead study author Adnan Kastrati, MD, Technische Universität,

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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.

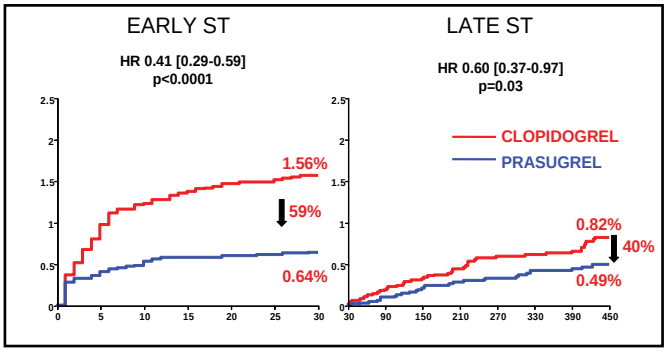
Advantage of Prasugrel Over Clopidogrel Holds Across Range of Patient- and Procedure-Related Factors

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