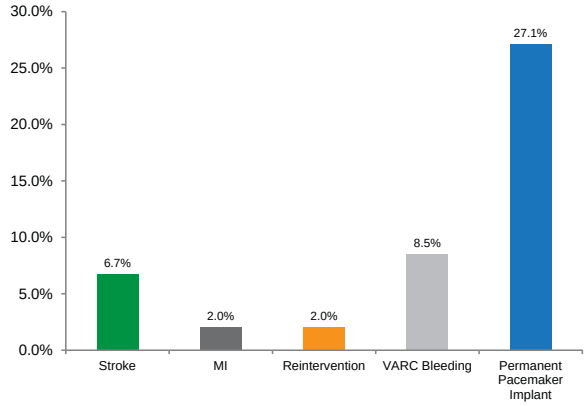
Figure 1. Major Secondary Endpoints



MI=myocardial infarction; VARC=Valve Academic Research Consortium.

SORT-OUT VI: Zotarolimus-Eluting Stent Noninferior to Biolimus-Eluting Stent

Written by Toni Rizzo

First-generation drug-eluting stents have reduced the risk of restenosis compared with bare-metal stents; however, these stents may have increased risk of stent thrombosis. Newer generation drug-eluting stents, which are constructed with biocompatible or biodegradable polymers, may have greater efficacy, safety, and device performance. The Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity trial [SORT-OUT VI; NCT01956448], presented by Bent Raungaard, MD, Aalborg University Hospital, Aalborg, Denmark, compared the efficacy and safety of a zotarolimus-eluting stent with a biolimus-eluting stent in a population-based setting.

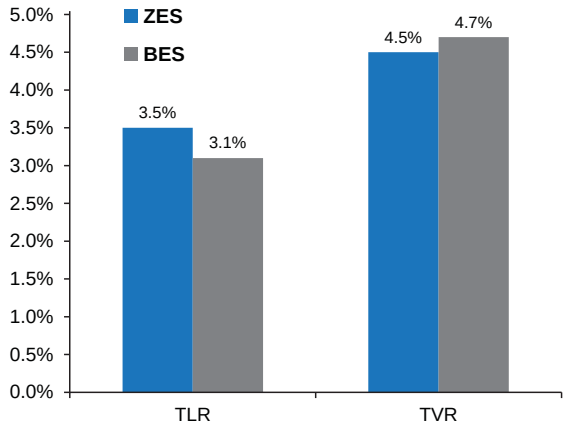
SORT-OUT VI was a prospective randomized, all-comers study designed to reflect clinical practice. A total of 2999 patients were randomized to receive either a zotarolimus-eluting permanent polymer stent (n=1502) or a biolimus-eluting biodegradable stent (n=1497). To be considered for the trial, patients had to have either stable coronary artery disease or acute coronary syndromes with ≥1 coronary lesion with a >50% diameter stenosis in a vessel with a reference diameter of 2.25 to 4.0 mm. Patients were excluded if they had a life expectancy <1 year, were allergic to aspirin, clopidogrel, prasugrel, ticagrelor, zotarolimus, or biolimus, or were not candidates for 12 months of dual antiplatelet treatment. The primary endpoint was a composite of major adverse cardiac events (MACE) defined as cardiac death, myocardial infarction (MI) or target lesion revascularization (TLR) at12 months. Patient-driven clinical event detection was used, with data accessed from the Danish Civil Registration System, National Patient Registry, and Western Denmark Heart Registry.

Most baseline patient characteristics were well balanced between the two groups. The mean subject age was 65.8 years and 76% of the patients were men. More patients receiving the biolimus-eluting stent had undergone previous percutaneous intervention (PCI; 22.0% vs 18.7%; p=0.03). In the zotarolimus-eluting stent group, more patients had >1 lesion (25.3% vs 22.1%; p=0.04) and the total stent length per patient was longer (21.0 vs 18.0 mm; p<0.01).

At 12 months, the primary endpoint of MACE had occurred in 5.3% of patients with a zotarolimus-eluting stent compared with 5.1% of those with a biolimus-eluting stent (difference, 0.2%; upper one-sided 95% CI, 1.8%; noninferiority p=0.006).

At 12 months, cardiac death had occurred in 1.5% of the zotarolimus-eluting stent group compared with 1.7% of the biolimus-eluting stent group (HR, 0.85; 95% CI, 0.48 to 1.50; p=0.58). MI was reported in 1.3% of patients in the zotarolimus-eluting stent group compared with 0.9% of patients in the biolimus-eluting stent group (HR, 1.43; 95% CI, 0.72 to 2.84; p=0.30). TLR was required in 3.5% of patients with the zotarolimus-eluting stent and 3.1% of biolimus-eluting stent (HR, 1.11; 95% CI, 0.75 to 1.65; p=0.80; Figure 1), while target vessel revascularization was required in 4.5% of patients with the zotarolimus-eluting stent and 4.7% of those with the biolimus-eluting stent (HR, 0.95; 95% CI, 0.68 to 1.32; p=0.75; Figure 1).

Figure 1. Target Lesion and Target Vessel Revascularization



BES=biolimus-eluting stent; TLR=target lesion revascularization; TVR=target vessel revascularization; ZES=zotarolimus-eluting stent.

Definite stent thrombosis was reported in 0.6% of patients with the zotarolimus-eluting stent compared with 0.4% of patients with the biolimus-eluting stent (HR,

1.29; 95% CI, 0.48 to 3.47; p=0.61). Definite or probable stent thrombosis occurred in 0.8% of patients with the zotarolimus-eluting stent compared with 0.5% of patients with the biolimus-eluting stent (HR, 1.73; 95% CI, 0.68 to 4.38; p=0.25).

The results of the SORT-OUT VI trial demonstrate that both zotarolimus-eluting stents and biolimus-eluting stents are associated with similar rates of cardiac death, MI, or TLR. The zotarolimus-eluting stent met the criteria for noninferiority compared to the biolimus-eluting stent in patients treated with PCI.

Prehospital Bivalirudin Improved Outcomes Versus Heparin in Patients With Myocardial Infarction

Written by Toni Rizzo

The HORIZONS AMI trial showed that bivalirudin therapy in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous intervention (PCI) reduced mortality and bleeding for up to 3 years compared with heparin plus a glycoprotein IIb/IIIa inhibitor [Stone GW et al. *N Engl J Med* 2008]. According to Philippe Gabriel Steg, MD, Universite Paris-Diderot, Paris, France, who presented the results of the European Ambulance Acute Coronary Syndrome Angiography Trial [EUROMAX; Steg PG et al. *N Engl J Med* 2013], several issues remain, including the role of bivalirudin in the ambulance for patients triaged to primary PCI; the potential for reducing the risk of acute stent thrombosis with a prolonged bivalirudin infusion post-PCI; and the impact of contemporary practice (frequent use of radial arterial access and novel oral P2Y12 inhibitors) on the efficacy and safety of bivalirudin.

The objective of the EUROMAX trial was to examine whether bivalirudin, initiated in patients with STEMI while being transported in the ambulance for primary PCI, was superior to heparin and provisional use of glycoprotein IIb/IIIa inhibitors.

Patients with STEMI who presented within 12 hours after the onset of symptoms and were scheduled for primary PCI (n=2218) were randomized in the ambulance or at a non-PCI hospital to treatment with bivalirudin (0.75 mg/kg bolus followed by 1.75 mg/kg/hour infusion; n=1089) or to unfractionated heparin with or without a glycoprotein IIb/IIIa inhibitor (n=1109). To address prior concerns for increased acute stent thrombosis seen in patients treated with bivalirudin in the HORIZONS AMI trial, bivalirudin infusion in EUROMAX was continued post-PCI for at least 4 hours. Bailout use of a glycoprotein IIb/IIIa inhibitor was also allowed in the bivalirudin group if needed. During the course of the trial, the primary endpoint was changed. The original primary endpoint was the composite endpoint of death, reinfarction, or major bleeding. After a change in the study protocol, the primary and secondary endpoints were switched so that the primary endpoint was the composite of all-cause mortality or major bleeding at 30 days and the key secondary endpoint was mortality, reinfarction, or major bleeding at 30 days. The change in the primary endpoint was made in order to reduce the necessary sample size and occurred while the investigators were still unaware of study outcomes. Major bleeding was defined as intracranial, retroperitoneal, or intraocular bleeding; access-site hemorrhage requiring radiologic or surgical intervention; a reduction in the hemoglobin level of more than 4 g/dL (2.5 mmol/L) without an overt source of bleeding or a reduction in the hemoglobin level of more than 3 g/dL with an overt source of bleeding; reintervention for bleeding; or use of any blood-product transfusion that was not related to coronary artery bypass surgery.

Baseline characteristics were similar between the two groups, with the exception of diabetes (bivalirudin, 11.7% vs heparin, 15.3%; p<0.05) and prior MI (bivalirudin, 7.4% vs heparin, 10.2%; p<0.05). The primary endpoint occurred in 5.1% of patients treated with bivalirudin compared with 8.5% of those treated with heparin (RR, 0.60; 95% CI, 0.43 to 0.82; p=0.001).

The secondary endpoint occurred in 6.6% of the bivalirudin group versus 9.2% of the heparin group (RR, 0.72; 95% CI, 0.54 to 0.96; p=0.02). There was no significant difference between the bivalirudin and heparin groups in cardiac deaths (2.5% vs 3.0%; RR, 0.83; 95% CI, 0.50 to 1.38; p=0.48) and noncardiac deaths (0.5% vs 0.1%; RR, 5.09; 95% CI, 0.60 to 43.51; p=0.12). Major bleeding was reported in 2.6% of the bivalirudin groups versus 6.0% of the heparin group (RR, 0.43; 95% CI, 0.28 to 0.66; p<0.001). The composite endpoint of death, reinfarction, ischemia-driven reinfarction, stroke, and major bleeding was reported in 7.8% of the bivalirudin group compared with 10.6% of the heparin group (RR, 0.73; 95% CI, 0.56 to 0.96; p=0.02). The benefits of bivalirudin were consistent across the reported subgroups.

The rate of definite stent thrombosis within 24 hours was higher in the bivalirudin group (1.1%) compared with the heparin group (0.2%; RR, 6.11; 95% CI, 1.37 to 27.24; p=0.007).

The EUROMAX trial had several limitations, including its open-label design. Additionally, the trial was not powered to assess 30-day mortality.

This trial showed that in patients with STEMI who were being transported for primary PCI, the initiation of bivalirudin prior to hospital admission reduced the primary endpoint of death or bleeding and the secondary endpoint of death, bleeding, or reinfarction when compared with heparin. However, the rate of acute stent thrombosis was higher with bivalirudin compared with heparin-treated patients. The investigators attributed the benefits of bivalirudin to the