was compared with two historical control groups from the main ISAR-REACT 3 trial, including patients who were treated with a bolus dose of UFH 140 U/kg (n=2281) or with bivalirudin (n=2289) [Kastrati A et al. *N Eng J Med* 2008].

In the ISAR-REACT 3 trial, treatment with bivalirudin significantly reduced the risk of minor bleeding (6.8% vs 9.9%; p=0.0001) and major bleeding (3.1% vs 4.6%; p=0.008) compared with UFH 140 U/kg in patients who were undergoing elective PCI. However, the net clinical benefit, which accounted for death, myocardial infarction (MI), urgent target vessel revascularization (TVR), and major bleeding, was similar in the bivalirudin and UFH 140 U/kg groups at 30 days (8.3% vs 8.7%; p=0.57) [Kastrati A et al. *N Eng J Med* 2008].

In the current ISAR-REACT 3A study, the net clinical benefit at 30 days favored treatment with UFH 100 U/kg compared with UFH 140 U/kg (7.3% vs 8.7%; p=0.007). Although the 100-U/kg and 140-U/kg dosing groups were associated with similar rates of death, MI, or urgent TVR (4.4% vs 5.0%; p=0.15), the risk of major bleeding was 29% lower in the 100-U/kg dosing group (3.6% vs 4.6%; p=0.03).

In the second comparison, treatment with UFH 100 U/kg met the criteria for noninferiority compared with bivalirudin. Low-dose UFH and bivalirudin had similar rates of death, MI, or urgent TVR (4.4% vs 5.9%), as well as similar rates of major (3.6% vs 3.1%) and minor bleeding (6.2% vs 6.8%).

Findings from the ISAR-REACT 3A trial support a shift in practice for biomarker-negative patients who receive elective PCI. Reducing the UFH dose from 140 U/kg to 100 U/kg provides a superior net clinical benefit for PCI patients and is noninferior to treatment with bivalirudin, Dr. Schulz concluded.

Apixaban Reduces Stroke Risk in Patients with AF: Results from the AVERROES Trial

The oral direct factor Xa inhibitor apixaban was superior to aspirin (ASA) therapy for the reduction of stroke or systemic embolism risk in patients with atrial fibrillation (AF) who were unsuitable for vitamin K antagonist (VKA) therapy. The phase III Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES; NCT00496769) trial was terminated early at the suggestion of the Data Monitoring Committee due to clear evidence of efficacy at the predefined interim analysis in May 2010. Stuart Connolly, MD, Population Health Research Institute, Hamilton, Ontario, Canada, discussed results from the preliminary analysis of AVERROES and the clinical implications of this study.

AF presents a high risk of stroke, which can be offset by the use of VKA therapy. However, this regimen is unsuitable for many patients because of increased bleeding risk, compliance issues, and difficulties that are related to anticoagulation monitoring or control. Therefore, a safe, easy-to-use alternative to VKA therapy is warranted. Apixaban offers a possible antithrombotic solution to those who are unable to take VKA, with the added advantages of a 12-hour half-life, multiple excretion pathways (25% renal), and no routine coagulation monitoring requirements.

AVERROES was a double-blind, randomized, multicenter, international, trial that included 5600 patients with AF and at least one risk factor for stroke who were unsuitable candidates for VKA therapy. Patients were randomized to receive either apixaban (5 mg twice daily or 2.5 mg twice daily in selected patients; n=2809) or ASA (81-324 mg daily, with 91% receiving ≤162 mg daily; n=2791). The patients were well matched at baseline. The mean patient age was 70 years, and median follow-up was 1 year. The primary endpoint was the composite of stroke or systemic embolic event (SEE), and the primary safety endpoint was major hemorrhage. Secondary endpoints included a composite of stroke, SEE, myocardial infarction or vascular death, and total death.

Preliminary data revealed that the incidence of stroke or SEE was significantly lower in the apixaban group compared with the ASA group (RR, 0.46; 95% CI, 0.33 to 0.64; p<0.001). Apixaban reduced the incidence of stroke by >50% compared with ASA (1.5% for the apixaban group vs 3.3% for ASA; p<0.001), without a significant increase in major bleeding. The rate of major bleeding was similar between the two groups (hemorrhagic stroke was 0.2% for both groups). The composite secondary outcome and rate of total death also favored apixaban over ASA therapy.

Apixaban appeared to be safe and well tolerated compared with ASA, without evidence of liver toxicity. The reductions in stroke and SEE risk occurred without a significant increase in bleeding. Dr. Connolly concluded that for every 1000 patients who were treated with apixaban rather than ASA for 1 year, 18 strokes, 10 deaths, and 31 cardiovascular hospitalizations would be prevented at the cost of 2 major bleeds. These findings demonstrate that apixaban is appropriate for stroke prevention in AF patients who are unsuitable candidates for VKA therapy.