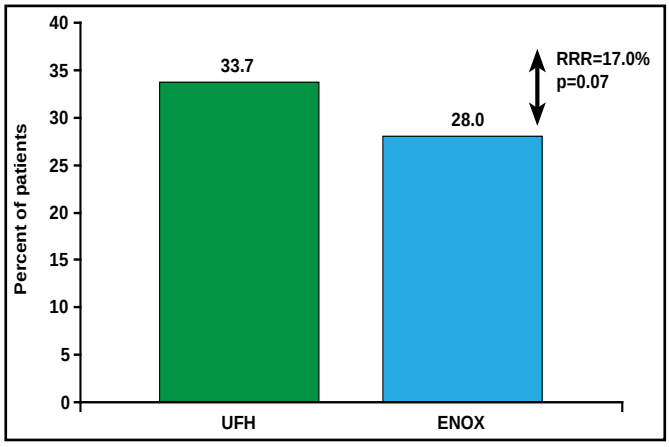
The Acute STEMI Treated with primary PCI and intravenous enoxaparin Or UFH to Lower ischemic and bleeding events at short- and Long-term follow-up study (ATOLL; NCT00718471) was an investigator-driven study that was designed to compare intravenous (IV) enoxaparin and IV UFH in patients who were undergoing primary PCI for STEMI. The study population comprised patients aged ≥18 years who presented within 12 hours of symptom onset. A total of 910 patients from 43 sites were randomly assigned to receive IV enoxaparin (n=450; 0.5 mg/kg; same dose with or without GPIIb/IIIa inhibitors) or IV-UFH (n=460; 50-70 IU/kg with GPIIb/IIIa inhibitors; 70-100 IU without GPIIb/IIIa inhibitors) before coronary angiography. All subjects received aspirin (160-500 mg/day according to local practice) and clopidogrel (300-900 mg as loading dose according to local practice). Approximately 18% of subjects were aged over 75 years.

The primary study endpoint was the composite of all-cause mortality at 30 days, complications of MI at 30 days (eg, resuscitated cardiac arrest, recurrent myocardial infarction/acute coronary syndrome (MI/ACS), urgent revascularization), procedure failure (eg, definite stent thrombosis), and non-CABG major bleeding during hospitalization. The main safety endpoint was major bleeding during hospitalization (STEEPLE definitions). The main secondary endpoint was the composite of all-cause mortality, recurrent MI/ACS, or urgent revascularization at 30 days.

At 30 days, the primary endpoint of death, MI, procedural failure, or noncoronary artery bypass grafting major bleeding was reduced but did not reach statistical significance—28% of subjects received enoxaparin and 33.7% received UFH (relative risk reduction 17%; 95% CI, 0.68 to 1.01; p=0.07; Figure 1).

Figure 1. Primary Endpoint.



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For the main secondary endpoint, there was a significant (p=0.01) 41% reduction with enoxaparin (11.3% for UFH vs 6.7% for enoxaparin). All results for the other secondary endpoints favored enoxaparin IV (Table 1).

Table 1: Other Secondary Endpoints.

Endpoint	Enoxaparin	UFH	p value
Death or complications of MI	7.8%	12.4%	p=0.02
Death, reinfarction, urgent revascularization	5.1%	8.5%	p=0.04
All-cause death	3.8%	6.3%	p=0.08
Death or resuscitated cardiac arrest	4.0%	7.0%	p=0.05
Death, complication of MI or major bleeding	10.2%	15%	p=0.03

The main safety endpoint occurred in 4.9% of patients who were on enoxaparin and 4.5% of patients who were on UFH (nonsignificant).

Commenting on the ATOLL study results, Harvey White, MD, Auckland City Hospital, Auckland, New Zealand, noted, "The ATOLL trial investigators have shown that enoxaparin is safe for patients undergoing primary PCI and likely has a clinically relevant effect in reducing ischemic complications compared with unfractionated heparin. They have moved us closer to the goal of further improving the outcomes of patients suffering an ST-elevation myocardial infarction."

ISAR-REACT 3A: Low-Dose UFH Better for Elective PCI

Unfractionated heparin (UFH), at a dose of 100 U/kg, is preferable to standard higher-dose treatment in patients who are undergoing elective percutaneous coronary intervention (PCI), according to new findings from the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment 3A (ISAR-REACT 3A; NCT00735280) trial.

Although 140 U/kg has been the standard dose for UFH in interventional cardiology for decades, physicians have started to use lower doses of UFH to decrease the risk of bleeding, said Stefanie Schulz, MD, Deutsches Herzzentrum, Munich, Germany. Dr. Schulz presented results of the ISAR-REACT 3A trial, which confirmed the benefits of lower-dose UFH in patients who are undergoing elective PCI.

In the ISAR-REACT 3A trial, 2505 biomarker-negative patients who were undergoing elective PCI were treated with a bolus dose of UFH 100 U/kg without activated clotting time (ACT) monitoring. This treatment group

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.