group had a significant 59% reduction in Lp-PLA$_2$ activity compared with those in the placebo group (62 vs 153 µmol/min^{-1}/L^{-1}; p<0.001). Other inflammatory biomarkers, including oxidized phospholipid/apolipoprotein B, did not change significantly. However, in a post hoc analysis, a higher proportion of patients in the darapladib group achieved hsCRP levels <1 mg/L compared with placebo (62% vs 45%; p=0.008).

The IBIS-2 trial was not powered to evaluate the effects of darapladib on cardiovascular outcomes, and no differences were observed. A safety analysis showed no differences in serious adverse events or clinical outcomes between the treatment groups, although there was a slightly higher systolic blood pressure, measured noninvasively (+3.0 mm Hg. 95% CI +0.3 to +5.7 mm Hg; p=0.031), in patients who were treated with darapladib.

In summary, IBIS-2 failed to show that Lp-PLA$_2$ inhibition improves plaque stability, as measured by IVUS palpography. However, analyses of the IBIS-2 secondary endpoints suggest that necrotic core expansion occurs despite optimal medical therapy, even in the absence of an overall change in plaque size. In addition, treatment with darapladib appears to halt this process in patients with established coronary disease. This trial was relatively small, and patients were followed for only 12 months; thus, future clinical trials will be required to evaluate whether Lp-PLA$_2$ inhibition, by stopping expansion of the necrotic core, can prevent recurrent cardiovascular events in high-risk patients.

Promise and Problems Emerge for Oral Investigative Factor Xa Drug in Treating Acute Coronary Syndrome

Treatment with investigative apixaban, an oral factor Xa inhibitor, shows promise as add-on protection against recurrent ischemic cardiovascular (CV) events among acute coronary syndrome (ACS) patients who already are on standard antiplatelet therapy, including aspirin and clopidogrel. But dose-dependent bleeding remains an unresolved problem.

Investigators from the APPRAISE-1 (A Phase 2, Placebo-Controlled, Randomized, Double-Blind, Parallel Arm, Dose-Ranging Study to Evaluate Safety and Efficacy of Apixaban in Patients with a Recent Acute Coronary Syndrome; NCT00313300) trial reported their findings in Munich at the European Society of Cardiology Congress 2008.

"The addition of apixaban to standard antiplatelet therapy for 6 months after onset of ACS resulted both in dose-dependent increases in bleeding and in a trend toward a reduction in clinically important ischemic events," said principal investigator John Alexander, MD, Duke Clinical Research Institute and Duke Heart Center, Durham, NC.

Dr. Alexander noted that one of the most challenging problems in treating ACS patients is finding a drug combination that inhibits clot formation without increasing the risk of serious bleeding. APPRAISE-1 is the first trial of an oral drug that targets factor Xa, a key enzyme in blood coagulation.

APPRAISE-1 was a phase 2 study that aimed at defining the optimal dose of apixaban regarding safety and efficacy in patients with a recent onset ACS. The study took place in 2 phases.

Phase A enrolled 547 patients who manifested ACS within the prior 7 days. Subjects were randomized to placebo (n=184), apixaban 2.5 mg BID (n=179), or apixaban 10 mg QD (n=184). Following the safety review of phase A, the enrollment was continued in phase B, reaching a study total of 1715 subjects. Those who were enrolled after the safety review were randomized to placebo (n=427), apixaban 2.5 mg BID (n=138), apixaban 10 mg QD (n=134), apixaban 10 mg BID (n=248), and apixaban 20 mg QD (n=221).

The primary safety outcome was major bleeding, as measured with the International Society of Thrombosis and Hemostasis (ISTH) scale, or clinically relevant non-major (CRNM) bleeding. The secondary efficacy outcome was a composite of CV death, myocardial infarction (MI), severe recurrent ischemia, and ischemic stroke.

During phase B of the trial, the higher apixaban dosing groups (10 mg BID and 20 mg QD) were discontinued due to unacceptably increased rates of total bleeding.

The index event was ST-elevation MI in 67% of patients. Investigators reported that the incidence of major or CRNM bleeding was 5.7% for apixaban 2.5 mg BID (n=315), 7.9% for apixaban 10 mg QD (n=315), and 3.0% for placebo (n=599). Bleeding at both apixaban dosages was higher compared with placebo (2.5 mg BID: HR 1.78; 95% CI, 0.91 to 3.48; p=0.09; and 10 mg QD: HR 2.45; 95% CI, 1.31 to 4.61; p=0.005; Figure 1). The absolute rates of bleeding were higher in patients on clopidogrel (7.0% for apixaban 2.5 mg BID, 9.1% for apixaban 10 mg QD, and 3.1% for placebo) compared with aspirin (2.4% for apixaban 2.5 mg BID, 4.1% for apixaban 10 mg QD, and 2.7% for placebo).

For the combined secondary efficacy endpoint outcome of CV death, MI, severe recurrent ischemia, or ischemic stroke, investigators reported incidence rates of 7.6% for apixaban 2.5 mg BID (n=317), 8.7% for apixaban 10 mg QD

(n=318), and 6.0% for placebo (n=611). These findings suggested a trend toward efficacy versus placebo (2.5 mg BID: HR 0.73; 95% CI, 0.44 to 1.19; p=0.21; and 10 mg QD: HR 0.61; 95% CI, 0.35 to 1.04; p=0.07), but the difference did not reach statistical significance (Figure 2).

Figure 1. ISTH Major or CRNM Bleeding.

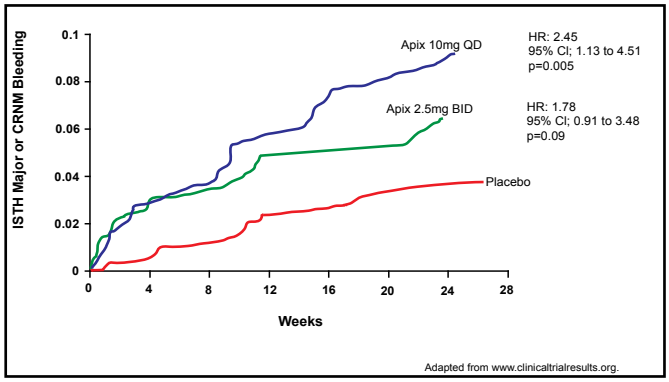
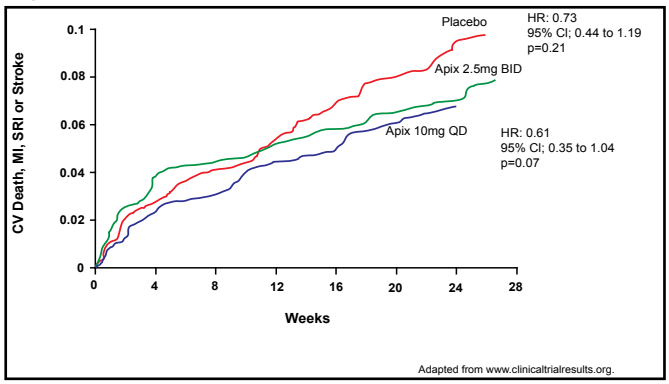


Figure 2. Ischemic Outcome.



Dr. Alexander said that while the clinical findings in APPRAISE-1 were inconclusive regarding efficacy, apixaban at 5 mg and 10 mg daily appears to be promising for ACS patients and warrants further clinical investigation in large, well-controlled trials.

Tirofiban Significantly Reduces Myocardial Damage After PCI Compared With Standard Antiplatelet Therapy

Results from the 3T/2R study (NCT00398463) demonstrated that the addition of tirofiban to standard therapy decreased the rate of myocardial infarction (MI) and resulted in a lower rate of major cardiovascular events (MACE) 30 days after percutaneous coronary intervention (PCI) compared with standard antiplatelet therapy alone in poor responders to aspirin or clopidogrel.

Individual response to aspirin or clopidogrel varies considerably among patients. Prior studies have shown that patients who have a poor response to or are resistant to one or both of these medications are at higher risk for subsequent cardiovascular events, particularly after PCI. Adjunctive inhibition of platelet glycoprotein (GP) IIb/IIIa receptors has been shown to reduce the overall risk of death or nonfatal MI 30 days after PCI [Topol EJ et al. *N Engl J Med* 2001]. Tirofiban is a highly selective, short-acting inhibitor of fibrinogen binding to platelet GP IIb/IIIa that inhibits *ex vivo* platelet aggregation in response to a variety of agonists.

The main purpose of this study was to assess, in poor responders to oral antiplatelet therapy, whether tirofiban in addition to standard antiplatelet therapy can reduce the incidence of MI after elective coronary angioplasty compared with standard therapy alone.

This was a randomized, double-blind, multicenter, placebo-controlled, proof-of-concept study in patients aged 18 to 75 years who were scheduled to undergo elective PCI for silent ischemia, stable angina, or low-risk non-ST-segment elevation acute coronary syndrome who were determined (using VerifyNow™ Aspirin and P2Y12 point-of-care assays) to be poor responders to aspirin or clopidogrel. Aspirin poor response was defined as aspirin reaction units (ARU) >550, and clopidogrel resistance as <40% platelet inhibition. The primary study endpoint was troponin I/T elevation >3X ULN in one or more blood samples within 48 hours after PCI. Secondary endpoints included CK-MB mass elevation >1X, 3X, or 5X ULN; MACE; or stent thrombosis based on ARC classification. All patients received heparin or bivalirudin, aspirin, and 300 mg (6 hours before PCI) or 600 mg (2 hours before PCI) clopidogrel. Patients in the tirofiban arm (n=132) also received tirofiban 25 µg/kg (high-bolus dose regimen), administered as a 3-minute bolus followed by a 14 to 24-hour 0.15-µg/kg/min infusion. A full discussion of the rationale and study protocol has already been published [Valgimigli M et al. *Cardiovasc Drugs Ther* 2008].

A total of 263 of 1277 patients who were scheduled for elective PCI met criteria for inclusion in the study. Within 48 hours after PCI, troponin I/T values >3X ULN were found in 35.1% of patients who were treated with standard care versus 20.4% of the patients who were treated with standard care plus tirofiban (relative risk reduction [RRR] 42%; 95% CI, 12 to 61; p=0.009). Similar benefit for add-on treatment with tirofiban was seen in both aspirin and clopidogrel poor responders separately.