(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.

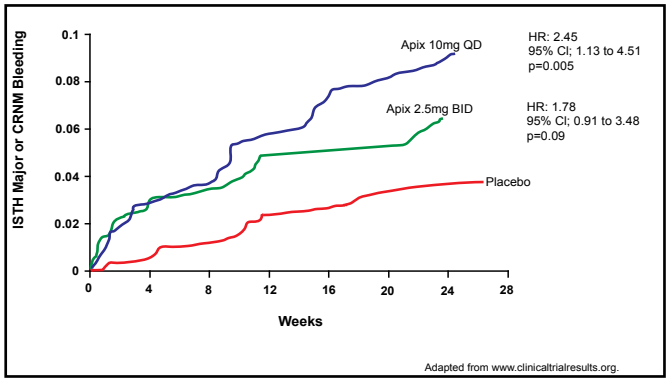
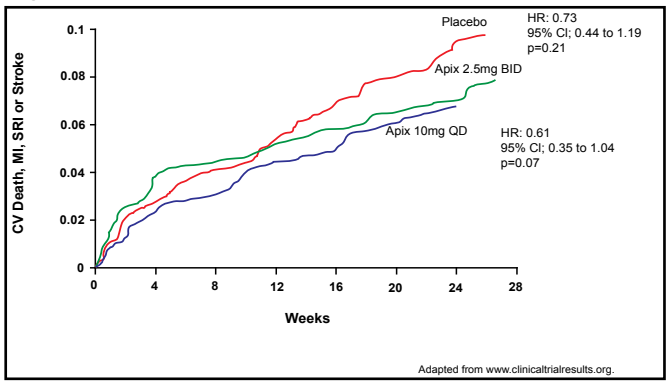


Figure 2. Ischemic Outcome.



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.

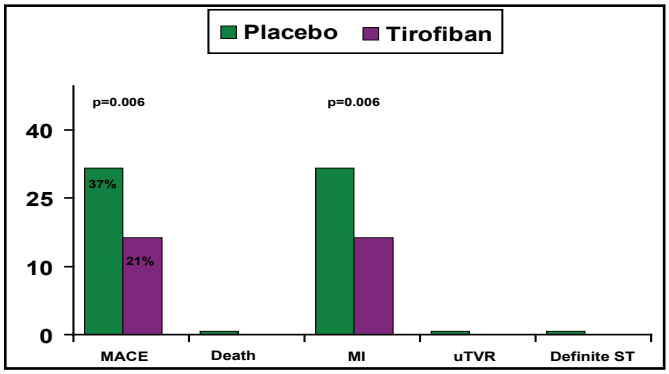
The main purpose of this study was to assess, in poor responders to oral antiplatelet therapy, whether tirofiban in addition to standard antiplatelet therapy can reduce the incidence of MI after elective coronary angioplasty compared with standard therapy alone.

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.

At 30 days, the MACE rate was significantly lower in patients who were treated with add-on tirofiban (21%) versus those who were treated with standard care only (37%; p=0.006), with the difference being driven almost entirely by the rate of MI (Figure 1).

Figure 1. 30-Day Outcomes Efficacy Endpoints.



CK-MB levels were lower in patients who were treated with add-on tirofiban but were significantly different from placebo only for those who had levels >1X ULN (RRR 62%; p=0.001). Safety results were similar in both groups. There was no major bleeding. The rate of minor bleeding was very low (p=0.99) and did not differ between the two groups.

A recently published study [Bonello L. *J Am Coll Cardiol* 2008] demonstrated that administration of additional clopidogrel (600 mg every 24 hours for 1 to 3 doses), guided by the vasodilator-stimulated phosphoprotein index, is an effective method to reduce MACE following PCI in patients with clopidogrel resistance. Further studies are needed to compare these 2 successful strategies (additional clopidogrel vs high-bolus dose tirofiban) to manage patients who have a poor response to antiplatelet therapy who are undergoing PCI. Given the difference in timing that is required to achieve an adequate antiplatelet effect, consideration of the clinical circumstances may dictate which strategy is preferred.

Positive Trends in FIRE Hint at Protection From Reperfusion Injury

FX06, a fibrin-derived peptide, may reduce myocardial necrosis that is associated with successfully reperfused acute ST-segment elevation myocardial infarction (STEMI), according to results from the FX06 In Reperfusion (FIRE) trial. The FIRE trial showed only modest trends in favor of FX06 but suggests possible protection from reperfusion injury.

FX06 employs a novel mechanism for targeting acute inflammation, a common response to myocardial reperfusion and a possible cause of reperfusion injury. By inhibiting the binding of fibrin to cadherin, FX06 increases the vascular endothelium barrier function and obstructs the migration of leukocytes, thereby creating a blockage in the inflammatory cascade.

The exploratory phase 2 FIRE trial (NCT00326976) was designed to evaluate whether FX06 limits infarct size following primary percutaneous coronary intervention (PCI) for acute STEMI. Within 6 hours of the onset of STEMI symptoms, 234 patients were randomly assigned to receive intravenous FX06 400 mg (n=114) or placebo (n=120) at the time of reperfusion. The extent of muscle damage that was induced by reperfusion was assessed by cardiac magnetic resonance imaging (MRI).

Dan Atar, MD, Aker University Hospital, University of Oslo, Oslo, Norway, reported findings from the FIRE trial. When assessing myocardial damage, Prof. Atar and colleagues focused on the total infarct zone. This region contains the necrotic core zone (the infarct itself), the microvascular obstruction zone that is embedded within the necrosis, and an area of edema that surrounds the infarct. The primary endpoint was total infarct size 5 days after PCI, evaluated as the late enhancement zone.

Data from FIRE favored FX06, but the trial failed to meet its primary endpoint. While FX06 reduced the total infarct size by 21%, this difference between the FX06 and placebo groups was not statistically significant (21.68 g vs 27.34 g; p=0.21). However, FX06 significantly reduced the necrotic core zone by 58% compared with placebo (1.77 g vs 4.2 g; p=0.019, ie, the true infarction).

Although following PCI, FX06 also reduced the levels of cardiac necrosis biomarkers relative to placebo, including troponin I at 24 hours (-10%) and 48 hours (-17%) and CK-MB at 90 minutes (-16%), the decrease in biomarker release between treatment groups was not statistically significant.

The short-term benefits of FX06 did not appear to be maintained. At 4 months, there were no longer any significant differences between FX06 and placebo in total infarct size (15.37 g vs 19.32 g; p=0.36) or scar mass (1.79 g vs 2.84 g; p=0.16). This finding could be explained by shrinking of the scar. Left ventricular ejection fraction also was similar in the FX06 and placebo groups at Day 5 (46.7% vs 46.6%) and at 4 months (49.1% vs 48.9%).

FX06 did not increase the rate of serious adverse events (SAEs) compared with placebo. A similar number of patients in the FX06 and placebo groups suffered from cardiac death (2 vs 5), cardiac SAEs (21 vs 29), and the composite of cardiac death and new-onset heart failure or pulmonary