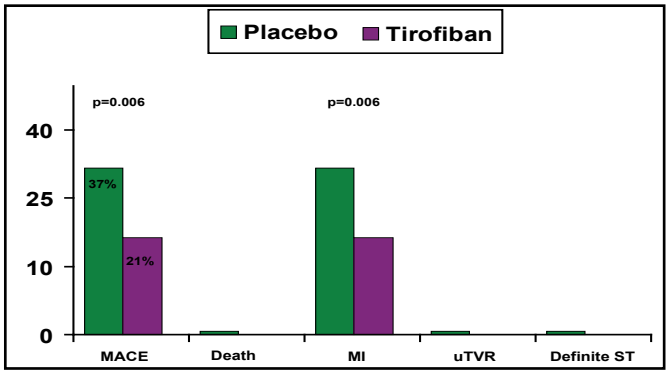
At 30 days, the MACE rate was significantly lower in patients who were treated with add-on tirofiban (21%) versus those who were treated with standard care only (37%; p=0.006), with the difference being driven almost entirely by the rate of MI (Figure 1).

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

edema (5 vs 10). Moreover, there was no evidence of altered cardiac rhythms, hypotension, or thrombotic risk that was associated with FX06.

Based on these initial findings, Prof. Atar believes that FX06 may have a role as a cardioprotective adjunct to PCI, although any positive trends need to be explored in a larger trial and he suggests that future trials focus on the outcomes of cardiac death and new-onset heart failure, which are known complications of STEMI.

Intensive Lipid-Lowering Therapy with Simvastatin/Ezetimibe Combination Does Not Affect the Progression of Aortic Valve Stenosis: Results From the SEAS Study

Results from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis; NCT00092677) study indicate that intensive LDL-cholesterol (LDL-C)-lowering with the combination of simvastatin 40 mg and ezetimibe 10 mg does not affect the progression of aortic valve stenosis, but can reduce the risk of cardiovascular ischemic events in subjects with mild-to-moderate asymptomatic aortic stenosis (AS), when compared with placebo.

AS is a relatively common disease among elderly people and, if left untreated, can progress to death from heart failure or cardiac arrest. The standard treatment is valve replacement. There are no pharmacological therapies to prevent or treat this condition. Several studies have indicated that the cellular mechanism that is involved in the progression of AS may be similar to that of atherosclerosis [Rajamannan NM et al. *Circulation* 2002; 2003; 2005; *Nat Clin Practi Cardiovasc Med 2007*]; however, the results of one small prospective study that examined the effect of lipid-lowering on the progression of AS failed to find any effect [Cowell SJ et al. *N Engl J Med* 2005].

The objective of the SEAS study was to evaluate the effect of long-term, intensive cholesterol-lowering on clinical and echocardiographic outcomes in subjects with AS. The primary study endpoint was major cardiovascular events, a composite that consisted of death from cardiovascular causes, aortic valve replacement, congestive heart failure (CHF) resulting from the progression of AS, nonfatal myocardial infarction (MI), hospitalization for unstable angina, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and nonhemorrhagic stroke. Key secondary outcomes included aortic valve events (eg, aortic valve replacement surgery, CHF due to aortic valve stenosis, or death from cardiovascular causes); ischemic events (death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, CABG, PCI, or hemorrhagic stroke), progression of AS as seen by echocardiography, and drug safety.

The study population included 1873 men and women aged 45 to 85 years (mean 67 years) with asymptomatic, echocardiographically confirmed mild-to-moderate aortic valve stenosis (mean aortic valve area of 1.28±0.47 cm^2, with a mean and peak gradient of 23 and 39 mm Hg, respectively) and no other condition that was an indication for lipid-lowering therapy. After a diet run-in period of 4 weeks, subjects were randomly assigned to receive a combination of 40 mg simvastatin + 10 mg ezetimibe (n=944) or placebo (n=929). Subjects were followed for a minimum of 4 years; the median follow-up period was 52.2 months.

At Week 8, combination treatment with simvastatin/ezetimibe resulted in a 61% decrease from baseline LDL-C levels (140±36 mg/dL to 53±23 mg/dL) compared with no change in the placebo group.

The SEAS study found no difference between the simvastatin/ezetimibe and placebo groups for the primary endpoint (HR 0.96; 95% CI, 0.83 to 1.12; p=0.59) or for the secondary outcome measures that were associated with aortic valve disease events (HR 0.97; 95% CI, 0.83 to 1.14; p=0.73). In contrast, significantly fewer subjects in the combination group experienced ischemic cardiovascular events versus those in the placebo group (148 [15.7%] vs 187 [20.1%]; HR 0.78, 95% CI, 0.63 to 0.97; p=0.024; Figure 1), a difference that primarily was driven by a lower incidence of CABG in the combination group (69 [7.3%] vs 100 [10.8%]; HR 0.68; 95% CI, 0.50 to 0.93; p=0.015; Figure 2). There was no difference between the two groups in any of the other components of the secondary endpoint.

Figure 1. Kaplan-Meier Curve for Secondary Outcome of Ischemic Cardiovascular Events.