The net clinical benefit (a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding) was significantly lower with the 150-mg dose of dabigatran compared with warfarin (RR, 0.91; 95% CI, 0.82 to 1.00; p=0.04) but was not different between the two doses of dabigatran (RR, 0.98; 95% CI, 0.89 to 1.08; p=0.66) or between the 110-mg dose of dabigatran and warfarin (RR, 0.92; 95% CI, 0.84 to 1.02; p=0.10).

Further reading: Ezekowitz MD et al. *Am Heart J* 2009;157:805-810; Connolly SJ et al. *N Engl J Med* 2009;361; Gage B. *N Engl J Med* 2009;361.

Otamixaban May Reduce the Risk of Ischemic Events in Patients with NSTE-ACS

Results from the phase 2 SEPIA-ACS1 TIMI 42 (Study Program to Evaluate the Prevention of Ischemia with Direct Xa inhibition; NCT00317395) study, presented by Marc S. Sabatine, MD, MPH, Brigham and Women's Hospital, Boston, MA, provide promising data that otamixaban, an intravenous direct Factor Xa inhibitor, at intermediate doses may be associated with a lower risk of ischemic events with similar bleeding compared with the current standard of care in patients with non-ST elevation acute coronary syndromes (NSTE-ACS) [Sabatine MS et al. *Lancet* 2009].

This phase 2, randomized, double-blind, dose-ranging study enrolled patients with moderate- to high-risk NSTE-ACS in whom an early invasive strategy was planned. The primary efficacy endpoint was the composite of all-cause death, new myocardial infarction (MI), severe recurrent ischemia that required urgent revascularization, or bailout use of a glycoprotein IIb/IIIa inhibitor (GPI) through Day 7. The primary safety endpoint was TIMI major or minor bleeding that was unrelated to coronary artery bypass graft (CABG).

Three thousand two hundred forty-one patients were randomized within 24 hours of presentation with NSTE-ACS to receive a bolus infusion of otamixaban 0.08 mg/kg that was followed by infusions of 0.035, 0.070, 0.105, 0.140, or 0.175 mg/kg/hr, or to unfractionated heparin (UFH; 60-IU/kg bolus followed by an infusion of 12 IU/kg/hr) plus eptifibatide (180-µg/kg bolus followed by an infusion of 1.0-2.0 µg/kg/min). Subjects were aged a mean of 61 years; 31% was female. ST segment deviation ≥0.1 mV was present in 57%; 77% had an elevated cardiac biomarker of necrosis. Of those who were enrolled, 99% underwent angiography, 63% underwent PCI, and 4% underwent CABG. Most patients were treated with aspirin (98%) and clopidogrel (98%).

There was no significant difference in the rate of the primary efficacy endpoint across otamixaban arms; however, in all but the 0.035-mg/kg/hr arm (stopped early due to inadequate anticoagulation), the point estimate of death, second heart attack, or additional coronary complications were lower with otamixaban than with UFH+eptifibitide. Treatment with intermediate doses of otamixaban (0.105 or 0.140 mg/kg/hr) resulted in an approximate 40% reduction in the primary efficacy endpoint (RR, 0.61; 95% CI, 0.36 to 1.02 and RR, 0.58; 95% CI, 0.34 to 0.996, respectively). The benefits were driven primarily by a reduction in death or MI (RR, 0.52; 95% CI, 0.28 to 0.98 and RR, 0.56; 95% CI, 0.30 to 1.03, for the 0.105- and 0.140-mg/kg/hr doses, respectively).

Urgent revascularization and the need for GPI bailout occurred in <1% of patients. The rates of thrombotic complications in patients who underwent PCI (n=2032) were similar between the intermediate doses of otamixaban (range 2.9% to 3.5%) and the control arm (2.4%).

There was a significant dose-dependent increase in the primary safety endpoint of TIMI major or minor bleeding with otamixaban (p=0.001 for trend); however, the rates in the intermediate-dose arms (3.1% for 0.105 mg/kg/hr and 3.4% for 0.140 mg/kg/hr) were similar to that observed with UFH+eptifibitide (2.7%). The relative risk of major bleeding was higher in the highest-dose group compared with control (RR, 1.26; 95% CI, 1.06 to 3.85) but was similar in the intermediate-dose groups (RR, 1.15; 95% CI, 0.57 to 2.32 for 0.105 mg/kg/hr and RR, 1.26; 95% CI, 0.63 to 2.52 for 0.140 mg/kg/hr).

"The data show that intermediate doses of otamixaban may offer a substantial reduction in major coronary complications in patients presenting with an acute coronary syndrome, with bleeding rates comparable to current therapy," said Dr. Sabatine. "These findings will need to be tested in a large phase 3 trial to establish the definitive role of otamixaban in the treatment of acute coronary syndromes."

Rosuvastatin Only Minimally Effective in Reducing AF in Patients with HF

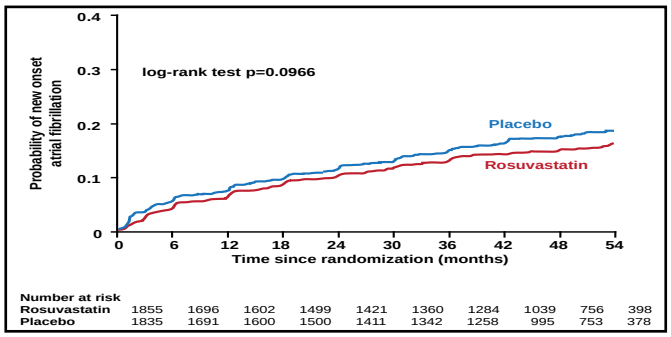
Professor Aldo Maggioni, MD, ANMCO Research Center, Florence, Italy, presented data from a post hoc analysis of the GISSI-HF (Effect of rosuvastatin in patients with chronic heart failure; NCT00336336) study, showing only modest evidence of a reduction in atrial fibrillation (AF) in heart

failure (HF) patients who were treated with rosuvastatin. The aim of the subanalysis was to assess the effect of n-3 PUFA and rosuvastatin compared with placebo in patients with chronic HF who were not in AF at study entry.

GISSI-HF was a double-blind, placebo-controlled trial in patients with chronic HF. Patients were randomized to daily treatments of n-3PUFA (1 g) or placebo (n=6975), and to rosuvastatin (10 mg) or placebo (n=4574). Patients were followed for nearly 4 years. Primary endpoints were all-cause mortality or cardiovascular (CV) hospitalizations. The study comprised men and women aged 18 years or older with clinical evidence of HF New York Heart Association class II-IV. Left ventricular ejection fraction (LVEF) was measured within 3 months of enrollment. AF occurrence was defined as the presence of AF on the electrocardiogram (ECG) that was performed at each visit during the trial, AF as a cause of worsening HF, hospital admission, or as an event during hospitalization.

Of the patients without AF at baseline, a total of 15.0% developed AF during a median follow-up of 3.7 years. AF occurred in 16% of the placebo and 13.9% of rosuvastatin patients with a 13.2% RRR and 2.1% absolute risk reduction. This difference was not significant when an unadjusted analysis (p=0.097; Figure 1) or multivariable analysis that adjusted just for clinical variables (p=0.067) was performed. However, it became significant when an adjustment was made for clinical variables and laboratory examinations (p=0.039) and for clinical variables, laboratory examinations, and background therapies (p=0.038).

Figure 1. Kaplan-Meier Curves for Time to New Onset of AF.



Maggioni A et al. *Eur Heart J* 2009. By permission of Oxford University Press.

Patients who experienced AF during the study were significantly (p≤0.03) older (aged >70 years) and had higher BMI, systolic blood pressure, heart rate, NYHA class, and percent LVEF than those who did not experience an AF. They also had significantly (p<0.05) higher frequencies of prior admission for HF, previous stroke, history of hypertension, pacemaker, history of paroxysmal AF, chronic obstructive pulmonary disorder, and more drug treatment.

Although this post hoc analysis showed some evidence of rosuvastatin's superiority over placebo in reducing the occurrence of AF, it should be noted that the trial was not powered to assess the effect of rosuvastatin on AF occurrence. The effect of a statin treatment that is conducted for a longer period of time or in a larger population of patients should be evaluated to confirm the findings of our study.

The discussant, Professor Harry Crijns, MD, Maastricht University Medical Centre, Maastricht, The Netherlands, agreed that rosuvastatin was not very effective in preventing incidence of AF in this study and suggested that there are a number of unanswered questions, including "whether statins prevent AF progression and reduce the burden of AF" and "whether prevention of AF by statins improves CV morbidity/mortality."

Full article available at: http://eurheartj.oxfordjournals.org/cgi/content/full/ehp357.

New Data from the RECORD Study

Two analyses from the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) study [NCT00379769; Home PD et al. *Lancet* 2009] of cardiovascular (CV) outcomes in patients who were treated with rosiglitazone were presented at the European Society of Cardiology 2009 Annual Congress. The first evaluated rates of CV death or CV hospitalization, and the second evaluated rates of coronary events.

The first analysis showed no difference in the primary endpoint of CV hospitalization or CV death but did demonstrate increased rates of heart failure (HF) that led to hospitalization or death in subjects who were randomized to rosiglitazone plus metformin or a sulfonylurea (RSG) compared with a control group that was treated with a combination of metformin and a sulfonylurea.

Professor Michel Komajda, MD, Université Pierre et Marie Curie, France, Paris, presented the results of the post hoc analysis, showing that over the 5.5 years of follow-up in the RECORD study, subjects in the RSG group experienced similar rates of the primary endpoint (HR, 0.99; 95% CI, 0.85 to 1.16; p=0.93) compared with those on control, meeting the criteria for noninferiority. There were, however, significantly more fatal/nonfatal HF events in the RSG group (61 events in the RSG group vs 29 in the control group; HR, 2.10; 95% CI, 1.35 to 3.27; p = 0.001). The HF event rates for the two groups began to diverge early and continued to diverge throughout the trial.