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