in those who were randomized to ticagrelor (5.8% vs 3.6%; p=0.01). This difference was not seen on repeat Holter at 30 days (2.1% vs 1.7%; p=0.52). Discontinuation due to adverse events occurred more frequently with ticagrelor compared with clopidogrel (7.4% vs 6.0%; p< 0.001).

Results from PLATO were simultaneously published online in the *New England Journal of Medicine*. In an accompanying editorial, Professor Albert Schömig, MD, Deutsches Herzzentrum, Munich, Germany, highlighted important differences between PLATO and two other pivotal antiplatelet (P2Y12 receptor antagonists) trials: CURE with clopidogrel and TRITON-TIMI 38 with prasugrel. Of the three trials, PLATO was the only one to demonstrate a reduction in all-cause mortality with more potent platelet inhibition, reducing the risk of overall mortality compared with clopidogrel by 22% (4.5% vs 5.9%; p<0.001).

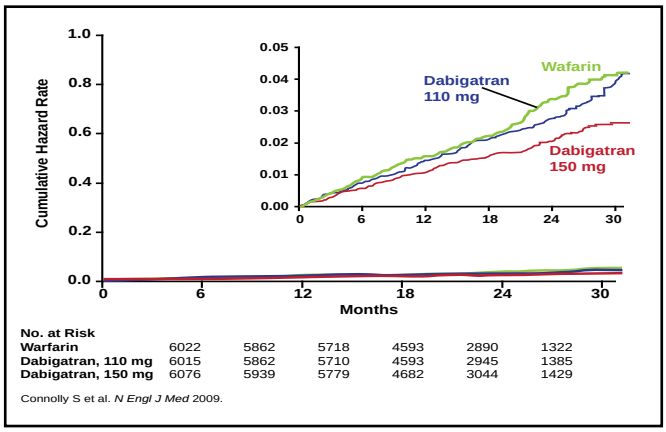
Results from the RE-LY Trial

Results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial, presented by Professor Stuart Connolly, MD, McMaster University, Hamilton, Ontario, Canada, at the European Society of Cardiology Meeting in Barcelona, Spain, show that the oral direct thrombin inhibitor dabigatran is a safe and effective alternative to warfarin for the prevention of stroke in patients with atrial fibrillation (AF).

RE-LY (NCT00262600) was a phase 3, multicenter, multinational, noninferiority trial that was conducted to compare the efficacy and safety of two different doses of dabigatran with warfarin therapy. The study enrolled 18,113 subjects (mean age 71 years; 64% men; 50% vitamin K antagonist experienced; mean $CHADS_2$ score 2.1) with electrocardiography-documented nonvalvular AF and at least one of the following: previous stroke or transient ischemic attack, left ventricular ejection fraction <40%, New York Heart Association class ≥II within 6 months before screening, and age ≥75 years (65 to 74 years for subjects with diabetes, hypertension, or coronary artery disease). Subjects were randomly assigned to receive dabigatran 150 mg (n=6076) or 110 mg (n=6015) twice daily in a blinded fashion or open-label, adjusted-dose warfarin (n=6022). Median follow-up was 2 years and complete in 99.9% (20 subjects lost to follow-up). The primary efficacy outcome was hemorrhagic/nonhemorrhagic stroke or systemic embolism, and the primary safety outcome was major hemorrhage.

Dabigatran 150 mg twice daily was superior to warfarin in reducing the primary efficacy endpoint (134 subjects; 1.11% per year versus 199 subjects; 1.69% per year; RR, 0.66; 95% CI, 0.53 to 0.82; p<0.001). The risk of major bleeding was similar (3.11% versus 3.36% per year in the dabigatran 150 mg and warfarin groups, respectively; RR, 0.93; 95% CI, 0.81 to 1.07; p=0.31). Meanwhile, dabigatran 110 mg twice daily achieved a similar rate of the primary efficacy endpoint compared with warfarin (182 subjects; 1.53% per year versus 199 subjects; 1.69% per year; RR, 0.91; 95% CI, 0.74 to 1.11; p=0.34; Figure 1), meeting the criteria for noninferiority (p<0.001 for the prespecified noninferiority margin of 1.46), while the rate of major bleeding was significantly lower (2.71% vs 3.36% per year; RR, 0.80; 95% CI, 0.69 to 0.93; p=0.003). The rate of hemorrhagic stroke was significantly (p<0.001) lower with both doses of dabigatran (0.12% and 0.10% per year dabigatran 110 mg and 150 mg, respectively) versus warfarin (0.38% per year).

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.



Overall, the mean percentage of time in the therapeutic range for subjects who were randomized to warfarin was 64%. At 2 years, study drug was discontinued in 21% of those who were randomized to dabigatran compared with 16.6% in those who were randomized to open-label warfarin. Adverse events were similar between groups except for dyspepsia, which was significantly more common with dabigatran (707 subjects [11.8%] and 688 subjects [11.3%] in the 110-mg and 150-mg dabigatran groups, respectively, versus 348 subjects [5.8%] in the warfarin group; both p<0.001 compared with warfarin). Importantly, there was no significant difference in rates of abnormal liver function tests between groups, as had been observed with a prior oral direct thrombin inhibitor (ximelagatran).

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