CI, 1.06 to 1.51; p=0.01). There were no differences in TIMI major bleeding, fatal bleeding, intracranial hemorrhage, or coronary artery bypass graft related major bleeding between the clopidogrel doses. With high-dose compared with low-dose aspirin, there was no difference in CURRENT major bleeding; overall (2.3% vs 2.3%; p=0.90), but a trend toward more gastrointestinal bleeding (0.38% vs 0.24%; p=0.051).

Interpretation

Overall, the results of this trial are complex, due to the factorial design and presence of a statistically significant interaction between aspirin and clopidogrel dose for the primary endpoint. Double-dose clopidogrel reduced the primary endpoint in the high-dose aspirin strata by 17% but was associated with more bleeding and transfusion overall. The data that are available thus far in the postrandomization subgroup of subjects who are undergoing PCI must be interpreted with caution, given the potential for bias in such unadjusted analyses of improper subgroups. Further investigation will be important in understanding the possible reasons why double-dose clopidogrel may provide differential benefit in patients who are undergoing PCI, dependent upon the dose of aspirin administered. Additional adjusted analyses of the postrandomization PCI subgroup that account for events post-PCI are also needed. Careful consideration will be important when integrating these results into clinical practice, which likely will have bearing on future practice guidelines.

Ticagrelor Superior to Clopidogrel in Reducing MI, Stroke, and CV Death in ACS (PLATO)

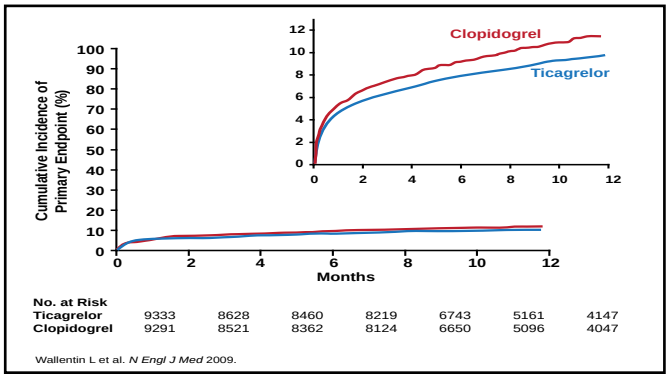
Ticagrelor significantly reduced the risk of cardiovascular (CV) events and death without increasing major bleeding compared with clopidogrel in patients with acute coronary syndrome (ACS), according to findings from the Study of Platelet Inhibition and Patient Outcomes (PLATO; NCT00391872).

Ticagrelor is an investigational oral antiplatelet agent that directly and reversibly inhibits the adenosine diphosphate receptor P2Y12. Professor Lars Wallentin, MD, PhD, Uppsala Clinical Research Center, Uppsala, Sweden, reported findings from PLATO, which was designed to evaluate whether ticagrelor is superior to clopidogrel –currently a component of standard therapy for ACS –in preventing vascular events and death in a broad population of patients.

PLATO randomized 18,624 patients who were hospitalized with ACS with or without ST-segment elevation to ticagrelor (180-mg loading dose, 90 mg twice-daily thereafter) or clopidogrel (300-mg to 600-mg loading dose, 75 mg thereafter) in a double-blinded fashion and treated for up to 12 months. All patients were treated with background therapy of aspirin 75 to 100 mg/day. The primary efficacy endpoint was a composite of CV death, myocardial infarction (MI), or stroke. The primary safety endpoint was major bleeding as defined by the trial.

At 12 months, ticagrelor reduced the primary endpoint from 11.7% to 9.8% compared with clopidogrel (HR, 0.84; p<0.001; Figure 1). Ticagrelor also reduced the rates of predefined secondary endpoints compared with clopidogrel, including MI (5.8% vs 6.9%; HR, 0.84; p=0.005) and death from vascular causes (4.0% vs 5.1%; HR, 0.79; p=0.001). However, ticagrelor did not prevent stroke (1.5% vs 1.3%; p=0.22).

Figure 1. Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy Endpoint.



There was no significant difference in the rates of trial-defined major bleeding (11.6% with ticagrelor vs 11.2% with clopidogrel; p=0.43) or TIMI major bleeding (7.9% vs 7.7%; p=0.57). Ticagrelor was associated with increased rates of major bleeding that were not related to coronary artery bypass grafting (CABG), the secondary safety endpoint (4.5% vs 3.8%; p=0.03). There was no significant difference in CABG-related bleeding (7.4% vs. 7.9%; p=0.32).

Overall adverse events were similar; however, ticagrelor was associated with more dyspnea (13.8% vs 7.8%; p<0.001). In addition, among patients who underwent Holter monitoring during the first week of treatment (n=2866), ventricular pauses ≥3 seconds were more frequently seen

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).

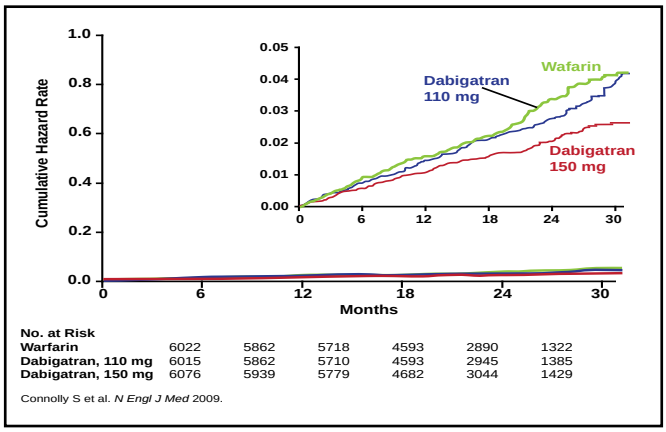
Results from the RE-LY Trial

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).