who were taking aspirin (0.8% of subjects in the aspirin group vs 0.5% of subjects in the placebo group).

Table 1. Primary and Secondary Outcome Events.

Endpoint	No. of Events		HR (95% CI)
	Aspirin 100 mg	Placebo	
Primary Endpoint			
Composite of initial fatal/nonfatal coronary event or stroke or revascularization	181	176	1.03 (84, 1.27)
Secondary Endpoint			
Vascular event	288	290	1.00 (0.85, 1.17)
All-cause mortality	176	186	0.95 (0.77, 1.16)

Commenting on the use of ABI as a screening method, Prof. Fowkes said, "Although the AAA trial was not to test screening, the results would suggest that using the ABI as a tool to screen individuals free of cardiovascular disease in the community is unlikely to be beneficial if aspirin is the intervention to be used in those found to be at higher risk. Other more potent antiplatelets might be considered, but only if increased effectiveness in avoiding ischemic events is not matched by increased bleeding."

In his discussion of the AAA study, Professor Carlo Patrono, MD, University of Rome, Rome, Italy, compared the results with those of the Antithrombotic Trialists' collaborative meta-analysis of aspirin trials [ATT Collaboration. *Lancet* 2009], in which treatment with aspirin resulted in a 12% proportional reduction in serious vascular events in individuals at low to moderate risk. Prof. Patrono suggested lack of statistical power, perhaps amplified by poor compliance, as the primary cause of the null response of the AAA trial.

Results from CURRENT-OASIS 7

The Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial was a 2×2 factorial, open-label, randomized trial to determine optimal clopidogrel and aspirin dosing in subjects with acute coronary syndrome (ACS) within 24 hours of ischemic symptoms. Subjects were randomly assigned to either double-dose clopidogrel for 7 days (600-mg loading dose, followed by 150 mg daily on Days 2 to 7, then 75 mg daily to Day 30) or the standard-dose regimen (300-mg loading dose, followed by 75 mg daily). The second randomization was to open-label, high-dose (300-325 mg) or low-dose (75-100 mg) aspirin daily for 30 days. The primary outcome was a composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke to Day 30. The primary safety outcome was major bleeding. The results were presented by Professor Shamir Mehta, MD, McMaster Clinic, Hamilton, Ontario, Canada.

Primary Analysis

A total of 25,087 subjects were enrolled, including 71% with UA/NSTEMI and 29% with STEMI. PCI was performed at the discretion of the treating physician in 70% of the trial cohort. The primary analysis for this 2x2 factorial trial showed a significant interaction for the primary endpoint between high-dose and low-dose aspirin and double-dose and standard-dose clopidogrel groups (p=0.043). Subjects who were randomized to high-dose aspirin had lower rates of the primary endpoint on double-dose clopidogrel compared with standard-dose clopidogrel (3.8% vs 4.6%; RR, 0.83; 95% CI, 0.70 to 0.99; p=0.036). This difference was not seen with double-dose versus standard-dose clopidogrel in the low-dose aspirin strata (4.5% vs 4.2%; RR, 1.07; 95% CI, 0.91 to 1.27; p=0.42). For the aspirin dose comparison, there was no difference in rates of the primary endpoint between high-dose and low-dose aspirin (4.2% vs 4.4%; HR, 0.96; 95% CI, 0.85 to 1.08; p=0.47). On pooling subjects across aspirin strata, there was no difference in the primary endpoint between double-dose and standard-dose clopidogrel (4.2% vs 4.4%; HR, 0.95; 95% CI, 0.84 to 1.07; p=0.37).

PCI Subgroup Analyses

In a postrandomization (improper subgroup) analysis of the pooled cohort that examined patients who were undergoing PCI only (17,232 subjects), there were lower rates of the primary endpoint with double-dose compared with standard-dose clopidogrel (3.9% vs 4.5%). In patients who were not undergoing PCI, the rate of the primary endpoint did not favor double-dose clopidogrel (4.9% vs 4.2%). The main reduction in events with double-dose clopidogrel among subjects who were undergoing PCI was for MI (2.0% vs 2.6%), with no difference in the rate of CV death. Definite or probable stent thrombosis was also lower with double-dose clopidogrel (1.6% vs 2.3%).

Safety Analysis

The primary safety endpoint of CURRENT major bleeding was increased with double-dose clopidogrel (2.5% vs 2.0%; HR, 1.25; 95% CI, 1.05 to 1.47; p=0.01), with an associated increased need for transfusion (2.2% vs 1.8%; HR, 1.26; 95%

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)

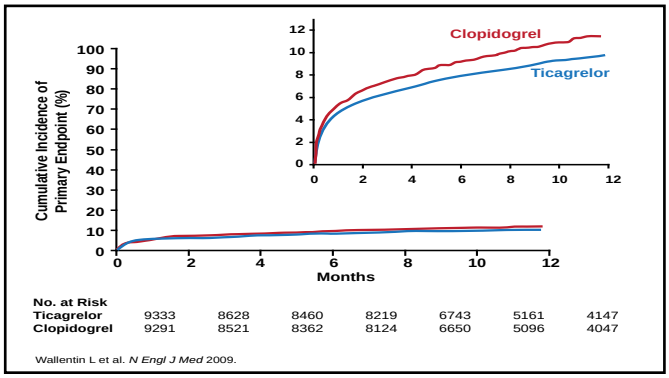
Ticagrelor significantly reduced the risk of cardiovascular (CV) events and death without increasing major bleeding compared with clopidogrel in patients with acute coronary syndrome (ACS), according to findings from the Study of Platelet Inhibition and Patient Outcomes (PLATO; NCT00391872).

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