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Safety, Tolerability, and Initial Efficacy of AZD6140, the First Reversible Oral Adenosine Diphosphate Receptor Antagonist, Compared With Clopidogrel, in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

Primary Results of the DISPERSE-2 Trial

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Objectives Our goal was to compare the safety and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, with clopidogrel in patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS).

Background AZD6140 achieves higher mean levels of platelet inhibition than clopidogrel in patients with stable coronary artery disease.

Methods A total of 990 patients with NSTE-ACS, treated with aspirin and standard therapy for ACS, were randomized in a 1:1:1 double-blind fashion to receive either twice-daily AZD6140 90 mg, AZD6140 180 mg, or clopidogrel 300-mg loading dose plus 75 mg once daily for up to 12 weeks.

Results The primary end point, the Kaplan-Meier rate of major or minor bleeding through 4 weeks, was 8.1% in the clopidogrel group, 9.8% in the AZD6140 90-mg group, and 8.0% in the AZD6140 180-mg group ($p = 0.43$ and $p = 0.96$, respectively, vs. clopidogrel); the major bleeding rates were 6.9%, 7.1%, and 5.1%, respectively ($p = 0.91$ and $p = 0.35$, respectively, vs. clopidogrel). Although not statistically significant, favorable trends were seen in the Kaplan-Meier rates of myocardial infarction (MI) over the entire study period (MI: 5.6%, 3.8%, and 2.5%, respectively; $p = 0.41$ and $p = 0.06$, respectively, vs. clopidogrel). In a post-hoc analysis of continuous electrocardiograms, mostly asymptomatic ventricular pauses >2.5 s were more common, especially in the AZD6140 180-mg group (4.3%, 5.5%, and 9.9%, respectively; $p = 0.58$ and $p = 0.01$, respectively, vs. clopidogrel).

Conclusions This initial experience with AZD6140 in patients with ACS showed no difference in major bleeding but an increase in minor bleeding at the higher dose with encouraging results on the secondary end point of MI. This agent is currently being studied in a large outcomes trial in 18,000 patients with ACS. (J Am Coll Cardiol 2007;50:1844–51) © 2007 by the American College of Cardiology Foundation

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Antiplatelet therapy with aspirin, thienopyridines (e.g., clopidogrel), or their combination has resulted in major reductions in cardiovascular events (1–6). This latter class inhibits platelet activation and aggregation by blocking the $P2Y_{12}$ receptor, 1 of 2 adenosine diphosphate (ADP) receptors on platelets (7). However, clopidogrel has several limitations: it is a pro-drug that requires hepatic conversion, leading to delay in onset of action, and there is wide interindividual variability in levels of platelet inhibition, with up to one-third of patients exhibiting minimal platelet inhibition (often referred to as "clopidogrel nonresponders") (8–10). At steady state, clopidogrel achieves only 30% to 40% mean inhibition of platelet aggregation response to ADP, and its active metabolite binds irreversibly to $P2Y_{12}$ receptors, such that recovery of platelet function is precluded.

AZD6140 is the first reversible oral $P2Y_{12}$ receptor antagonist in a new chemical class of antiplatelet agents termed cyclopentyl-triazolo-pyrimidines with a half-life of approximately 12 h (11,12). Distinct from the thienopyridines, this agent does not require metabolic conversion to an active form; it binds directly to the $P2Y_{12}$ receptor, and it can more completely inhibit the sustained aggregation response to ADP. A study in patients with stable atherosclerosis found a dose-dependent increase in the level of inhibition with AZD6140, with levels being significantly higher than those achieved with clopidogrel (12). The DISPERSE (Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non–ST-segment Elevation myocardial infarction)-2 trial was a randomized, double-blind, double-dummy trial conducted to assess the safety, tolerability, and initial efficacy of AZD6140 plus aspirin in comparison with clopidogrel plus aspirin in patients with non–ST-segment elevation (NSTE) acute coronary syndromes (ACS).

Abbreviations and Acronyms

ACS = acute coronary syndromes
ADP = adenosine diphosphate
CABG = coronary artery bypass grafting
CI = confidence interval
IQR = interquartile range
NSTE-ACS = non–ST-segment acute coronary syndromes
PCI = percutaneous coronary intervention

Methods

Patients. Between October 3, 2004 and April 23, 2005, patients with NSTE-ACS were entered into the trial from 152 participating sites in 14 countries (Online Appendix 1). The study protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients before the initiation of trial procedures.

Detailed entry criteria are in Online Appendix 2. Briefly, patients were eligible if they were hospitalized for NSTE-ACS within the preceding 48 h, experienced ischemic symptoms of ≥10 min duration at rest, with either biochemical marker evidence of myocardial infarction (MI) or electrocardiographic evidence of ischemia.

Study protocol. Patients received standard medical (antiischemic and antithrombotic) and interventional treatment for ACS, including aspirin at an initial dose of up to 325 mg followed by 75 to 100 mg daily with or without a glycoprotein IIb/IIIa inhibitor. Patients who had received clopidogrel before randomization were permitted in the study, but open-label clopidogrel was discontinued after randomization and replaced with study drug.

Eligible patients were randomized in a 1:1:1 double-blind fashion to receive AZD6140 90 mg twice daily, AZD6140 180 mg twice daily, or clopidogrel 300 mg followed by 75 mg once daily for up to 3 months. Patients in the AZD6140 group were subrandomized to receive or not receive an initial loading dose of 270 mg. Patients were scheduled to receive 1, 2, or 3 months of study drug, depending on when during the trial period they were enrolled. For patients undergoing percutaneous coronary intervention (PCI) within 48 h post-randomization, an additional 300 mg of clopidogrel study drug or placebo (clopidogrel for patients in the clopidogrel group or placebo for patients in the AZD6140 group) could be administered at the discretion of the treating physician. Patients returned monthly for follow-up visits, and were contacted by telephone 7 days after stopping study drug for evaluation of any adverse events.

The primary objective was to assess the safety and tolerability of the different doses of AZD6140 plus aspirin, versus clopidogrel plus aspirin, in patients with NSTE-ACS by evaluating total bleeding events (major plus minor bleeding, but excluding minimal bleeds as adjudicated by the Independent Clinical Adjudication Committee) observed within the first 4 weeks of treatment (see Online Appendix 2 for definitions). Additional objectives of the trial were to assess: 1) individual and composite incidence of MI (including silent MI), death, stroke, and severe recurrent ischemia; and 2) incidence of recurrent ischemia with AZD6140 plus aspirin and clopidogrel plus aspirin, using total duration of ischemia as detected by continuous Holter electrocardiogram monitoring (LifeCard CF, DelMar Reynolds, Irvine, California) during the first 4 to 7 days after randomization.

Statistical analyses. Statistical analyses were performed using SAS version 8.1 (SAS Institute, Inc., Cary, North Carolina), with details provided in Online Appendix 2. An independent data safety monitoring board comprising clinical experts and a statistician monitored safety data on an ongoing basis to ensure that patient safety was maintained. Comparisons between AZD6140 and clopidogrel were made using the Cox proportional hazards model (time-to data), Fisher exact test (count data), and the t test (continuous data). The Thrombolysis In Myocardial Infarction (TIMI) study group has a copy of the database and has independently confirmed the data presented here.