Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study


Summary

Background Variation in and irreversibility of platelet inhibition with clopidogrel has led to controversy about its optimum dose and timing of administration in patients with acute coronary syndromes. We compared ticagrelor, a more potent reversible P2Y12 inhibitor with clopidogrel in such patients.

Methods At randomisation, an invasive strategy was planned for 13 408 (72.0%) of 18 624 patients hospitalised for acute coronary syndromes (with or without ST elevation). In a double-blind, double-dummy study, patients were randomly assigned in a one-to-one ratio to ticagrelor and placebo (180 mg loading dose followed by 90 mg twice a day), or to clopidogrel and placebo (300–600 mg loading dose or continuation with maintenance dose followed by 75 mg per day) for 6–12 months. All patients were given aspirin. The primary composite endpoint was cardiovascular death, myocardial infarction, or stroke. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00391872.

Findings 6732 patients were assigned to ticagrelor and 6676 to clopidogrel. The primary composite endpoint occurred in fewer patients in the ticagrelor group than in the clopidogrel group (569 [event rate at 360 days 9·0%] vs 685 [10·7%]; p=0·0025). There was no difference between ticagrelor and clopidogrel groups in the rates of total major bleeding (691 [11·6%] vs 689 [11·5%]; 0.99 [0·89–1·10]; p=0.8803) or severe bleeding, as defined according to the Global Use of Strategies To Open occluded coronary arteries, (198 [3·2%] vs 185 [2·9%]; 0.91 [0·74–1·12]; p=0·3785).

Interpretation Ticagrelor seems to be a better option than clopidogrel for patients with acute coronary syndromes for whom an early invasive strategy is planned.

Funding AstraZeneca.

Introduction

Clopidogrel, a thienopyridine, in addition to aspirin is recommended for prevention of myocardial infarction and stent thrombosis in patients with acute coronary syndromes with or without ST elevation.1-4 It is a prodrug that undergoes hepatic conversion, therefore leading to delayed onset of action and substantial variability between individuals in levels of platelet inhibition. Up to a third of patients are low responders who have inadequate levels of inhibition.5 Prasugrel, another thienopyridine, is metabolised differently and results in higher levels of inhibition than does clopidogrel, without any low responders;4 the increased inhibition further reduces the risk of myocardial infarction and stent thrombosis when started at the time of percutaneous coronary intervention (PCI) in patients with acute coronary syndromes, albeit with an increased risk of bleeding.6 Because both thienopyridines are irreversible platelet inhibitors, patients need to produce new platelets to regain normal platelet function. To avoid the risk of severe bleeding, treatment has to be stopped for 5–7 days before coronary artery bypass graft (CABG) or other surgery can be undertaken. Because of these properties, the early initiation of thienopyridines in patients with acute coronary syndromes is quite variable and controversial.1

Ticagrelor, a reversible and direct-acting oral P2Y12-receptor antagonist, provides greater and more consistent platelet inhibition than does clopidogrel, with more rapid onset and offset of action.2,3 In the PLATElet inhibition and patient Outcomes (PLATO) trial, reversible long-term P2Y12 inhibition with ticagrelor was better than that with clopidogrel for the prevention of cardiovascular and total death, myocardial infarction, and stent thrombosis, without any increase in the rates of major bleeding in a broad population of patients with acute coronary syndromes who were started on treatment as soon as possible after hospital admission.2 We therefore compared ticagrelor with clopidogrel in patients with acute coronary syndromes who were planned to undergo an invasive strategy.

Methods

Patients

The details of the study design, patient population, and outcome definitions have been reported by James and
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death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, transient ischaemic attack, or other arterial thrombotic event; components of the primary endpoint; all-cause mortality; and stent thrombosis. Deaths from vascular causes were those resulting from cardiovascular and cerebrovascular events, or any other death for which there was no clearly documented non-vascular cause. Myocardial infarction was defined in accordance with the universal definition.\textsuperscript{13} Stent thrombosis was established from medical records in accordance with the Academic Research Consortium criteria.\textsuperscript{14}

The primary safety endpoint was PLATO-defined total major bleeding as previously described.\textsuperscript{12,13} An independent central adjudication committee, unaware of the group assignments, adjudicated all primary and secondary endpoints, and major and minor bleeding events. Major bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) definition was recorded from the electronic case-report form, using a cutoff for haemoglobin of at least 50 g/L, but did not necessarily require clinical evidence of excessive bleeding after CABG. Severe bleeding, as defined according to the Global Use of Strategies To Open occluded coronary arteries (GUSTO),\textsuperscript{15} was also established from specific questions on the electronic case-report form, and was defined as fatal, intracranial, or intrapericardial bleeding with cardiac tamponade, or development of hypovolaemic shock or severe hypotension caused by bleeding and requiring pressor support or surgery. These events were specified by the investigators on a specific form for bleeding.

**Statistical analysis**

The analysis was a prespecified stratum of the whole trial, and based on the investigator’s response in the interactive randomisation process, just before the patient was randomly assigned—ie, concerning this patient, do you intend to use an invasive strategy with coronary angiography followed by revascularisation based on the coronary anatomy, or a non-invasive strategy?

The outcome in relation to the clopidogrel loading dose was analysed according to the amount of open-label clopidogrel given to the patient 24 h before randomisation, allowing categorisation into subgroups that were given at least 600 mg or less than 600 mg. It was also analysed in comparison with the intended total amount of clopidogrel given to the patient before randomisation to 24 h after first dose of investigational product—ie, open-label clopidogrel before randomisation or as investigational product (active and placebo).

The Cox proportional hazards model was used to analyse the primary and secondary endpoints. The proportional hazards assumption was assessed with a model of time to event with randomised treatment. All analyses were by intention to treat, and were done with SAS (version 9.2). A p value of 0·05 was regarded as significant for the overall treatment differences.

Investigators were expected to indicate intention for an invasive strategy in about two-thirds of patients randomly

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**Figure 3:** Cumulative Kaplan-Meier estimates of time to myocardial infarction (A) or cardiovascular death (B) in patients intended to undergo an invasive strategy.

**Figure 4:** Cumulative Kaplan-Meier estimates of time to all-cause mortality in patients intended to undergo an invasive strategy.
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Death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, transient ischaemic attack, or other arterial thrombotic event; components of the primary endpoint; all-cause mortality; and stent thrombosis. Deaths from vascular causes were those resulting from cardiovascular and cerebrovascular events, or any other death for which there was no clearly documented non-vascular cause. Myocardial infarction was defined in accordance with the universal definition.\textsuperscript{13} Stent thrombosis was established from medical records in accordance with the Academic Research Consortium criteria.\textsuperscript{14}

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