

Comparison of Ticagrelor with Clopidogrel in Patients with a Planned Invasive Strategy for Acute Coronary Syndromes (PLATO): a Randomized Double-Blind Study

BACKGROUND

- Antiplatelet therapy is essential treatment for acute coronary syndromes (ACS). Clopidogrel has a delayed onset of action and there can be substantial variability between individuals in levels of platelet inhibition.
- Ticagrelor is the first reversible and direct-acting oral P2Y₁₂-receptor antagonist and provides quicker and more consistent platelet inhibition compared to clopidogrel.

OBJECTIVE

- To determine if ticagrelor is superior to clopidogrel for the prevention of vascular events (death, MI, or stroke) in patients with ACS (with or without ST-elevation) with a planned invasive procedure, achieved with a clinically acceptable bleeding rate and overall safety profile.

METHODS

- **Design:** Multi-center, randomized, double-blind, double-dummy, parallel trial; Duration: 6 – 12 months
- **Inclusion Criteria:**
 - For patients with non-ST-elevation ACS, at least two of the following: ST-segment depression or transient elevation of ≥ 1 mm in ≥ 2 contiguous leads; positive biomarker indicating myocardial necrosis; or one of the following risk indicators: age ≥ 60 years; previous MI or CABG; coronary artery disease with $\geq 50\%$ stenosis in ≥ 2 vessels; previous ischemic stroke, hospital-based diagnosis of TIA, $\geq 50\%$ carotid stenosis, or cerebral revascularization; diabetes mellitus; peripheral artery disease; or chronic renal dysfunction
 - For patients with ST-elevation MI: persistent ST-segment elevation of ≥ 0.1 mV in ≥ 2 contiguous leads or new left bundle branch block, and the need for primary PCI
- **Exclusion Criteria:** contraindication to clopidogrel, treatment with fibrinolytic drugs within 24 hours before randomization, need for oral anticoagulant drugs, an acute complication of PCI (index event), PCI done after the index event but before first dose of study drug, increased risk of bradycardic events, and concomitant use of strong CYP3A inhibitors or inducers
- **Primary Outcome Measures:** the composite of death from vascular causes, MI, or stroke; and PLATO-defined total major bleeding
- **Secondary Outcome Measures:** the composite of all-cause mortality, MI, or stroke; death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic events; components of the primary endpoint; all-cause mortality; and stent thrombosis
- A total of 13,408 patients with a planned invasive procedure
 - 6732 in the ticagrelor group: ticagrelor (dosing below) + placebo clopidogrel + aspirin
 - Patients received a loading dose (LD) of 180 mg followed by a maintenance dose (MD) of 90 mg twice daily
 - 6676 in the clopidogrel group: clopidogrel (dosing below) + placebo ticagrelor + aspirin
 - Patients received a LD of 300 mg followed by a MD of 75 mg daily
- Power 80% with an alpha level of 0.05 to detect a 15% reduction of relative risk with ticagrelor (13.5% after adjustment for dilution effect of patient discontinuation). This was calculated to be sufficient for a sample size of 13,500.

- Data handling method was intent-to-treat.

RESULTS

- 1433 patients in the clopidogrel group and 1538 in the ticagrelor group prematurely discontinued the study drug. Reasons for dropout included unwillingness to continue the study drug, an adverse event, or another reason.
- **Primary Outcome Measures:** the composite endpoint occurred in a smaller proportion of patients in the ticagrelor group than in the clopidogrel group [ticagrelor 569 (9.0%) vs. clopidogrel 668 (10.7%); $p=0.0025$]; the rates of PLATO-defined total major bleeding did not differ between groups [ticagrelor 689 (11.5%) vs. clopidogrel 691 (11.6%); $p=0.8803$]
- **Secondary Outcome Measures:** Rates of death resulting from cardiovascular causes and of MI were lower in the ticagrelor group than in the clopidogrel group, whereas stroke rates did not differ [ticagrelor 595 (9.4%) vs. clopidogrel 701 (11.2%); $p=0.0016$]. Rate of definite stent thrombosis and stenosis were reduced in the ticagrelor group [ticagrelor 132 (2.8%) vs. clopidogrel 179 (3.8%); $p=0.0068$]. The rates of death from non-cardiovascular causes in both groups were not significantly different [ticagrelor 252 (3.9%) vs. clopidogrel 311 (5.0%); $p=0.0103$].
- **Authors' Conclusion:** Ticagrelor produces significant and clinically relevant reductions in cardiovascular and total deaths, MI, and stent thrombosis, without an increase in risk of major bleeding, and allows great flexibility in the management of all types of patients with ACS. Specifically, use of ticagrelor instead of clopidogrel for 1 year in 1000 patients with ACS with a planned invasive procedure at the start of therapy would lead to 11 fewer deaths, 13 fewer heart attacks, and six fewer cases of stent thrombosis without an increase in the rates of major bleeding or transfusion.

STRENGTHS

- Large study with good design (i.e., randomized, double-blind, double-dummy, parallel-group)
- Includes currently recommended doses of clopidogrel and initiation of therapy before PCI
- The trial reflects the full spectrum of ACS patients managed in different real-world clinical settings

LIMITATIONS

- Bias due to investigators' affiliation with AstraZeneca
- Potential unblinding
- Reasons for patient dropout are vague and inconclusive
- Non-reported non-compliance could have skewed the results for any of the treatment groups; compliance was not addressed
- It is unknown if adverse effects were statistically analyzed because none were reported

CONCLUSION

- Although results show that ticagrelor leads to improved outcomes with a reduction in the risk of death, MI, and stent thrombosis, without an increase in the risk of bleeding in patients with ACS with a planned invasive procedure, and has the benefit of reversible platelet inhibition compared to clopidogrel, ticagrelor is unlikely to replace clopidogrel as first line therapy.
 - Results did not show an advantage of ticagrelor compared to clopidogrel for CABG-related bleeding.
 - Clopidogrel will be available as a generic in the near-future.

- Future Research
 - Areas for further research include the mechanisms of mortality benefit and the use of ticagrelor in unplanned or emergent invasive procedures.

Reference: Cannon, CP, et al. "Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomized double-blind study." *Lancet*. 2010 Jan 23; 375 (9711): 283 - 93. Epub 2010 Jan 13.

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