クロピドグレルを凌ぐticagrelorの有益性

PLATO：新たな経口抗血小板薬はクロピドグレルと比較し、急性冠症候群患者の心血管イベントを軽減する

PLATO: New oral antiplatelet agent reduces cardiovascular events when compared to clopidogrel in patients with acute coronary syndromes

急性冠症候群患者を抗血小板治験薬であるticagrelorで治療することにより、クロピドグレルと比較し、心血管（CV）イベント（CV死、心筋梗塞、または脳卒中）を有意に軽減したことがphase3 PLATO（Platelet Inhibition and Patient Outcomes：血小板抑制と患者の予後）スタディにおいて示された、とESC 2009ホットラインセッションで報告され、New England Journal of Medicineに掲載された。PLATOはticagrelorとアスピリンの併用とクロピドグレルとアスピリンの併用をhead-to-headで比較したアウトカムスタディである。全ての大陸から選出した43ヵ国893施設の患者18,624人を組み入れた。全ての患者は急性冠症候群により入院しており、3分の1はST上昇心筋梗塞であり3分の2にはST上昇がなかった。入院直後に患者らは、無作為化二重盲検試験の形で、ticagrelor（90mgを1日2回）またはクロピドグレル（1日75mg）を6～12ヵ月内服する長期抗血小板療法を開始された。その結果、ticagrelorによりクロピドグレルと比較し、CVイベントは11.7%から9.8%に減少した（p<0.001、RRR=16%）が、重大な出血は増加しなかった。このエンドポイントに関する有効性はCV死および心筋梗塞の減少によるものであり、脳卒中に関しては差がなかった。

Full Text

The presentation of the PLATO (A Study of Platelet Inhibition and Patient Outcomes) trial, showed that ticagrelor reduced the rate of cardiovascular (CV) events (CV death, myocardial infarction or stroke) from 11.7% to 9.8% compared clopidogrel (p<0.001, RRR = 16%), without an increase in major bleeding. This efficacy endpoint was driven by a statistically significant reduction in both CV death and myocardial infarction (MI) with no difference in stroke. Ticagrelor is the first antiplatelet agent to demonstrate a reduction in CV death across all major acute coronary syndromes (ACS) patient types.

For every 1,000 patients admitted to the hospital because of an ACS event, use of ticagrelor instead of clopidogrel, for up to one year, led to 14 fewer deaths, or 11 fewer MI's, or 8 fewer cases of stent thrombosis, without an increase in major bleeds. In the PLATO study, the reduction in risk of cardiovascular events appears early and the benefit over clopidogrel grows with time. Ticagrelor demonstrated a consistent benefit
across multiple secondary efficacy endpoints including CV death and total mortality; myocardial infarction; the composite of myocardial infarction, stroke, and total mortality; and a composite of cardiovascular death, myocardial infarction, stroke, transient ischemic attack, recurrent cardiac ischemia, severe recurrent cardiac ischemia, and other arterial thrombotic events.

"Ticagrelor is the first antiplatelet therapy to achieve a significant reduction in CV mortality in ACS patients versus clopidogrel and perhaps most importantly without an increase in major bleeding," commented Professor Lars Wallentin, co-chair of the PLATO Executive Committee. "PLATO has redefined what is possible in the prevention of recurrent events in patients with acute coronary syndromes."

The PLATO study confirmed the clinical safety profile of previous ticagrelor studies by showing an efficacy advantage without an increase in major bleeding. Across all the important patient subgroups (e.g. gender, weight, history of stroke/TIA) in PLATO, ticagrelor showed no difference versus clopidogrel in the incidence of major bleeding. When minor bleeding was added, ticagelor showed a small increase in PLATO defined major plus minor bleeding versus clopidogrel. At continuous ECG monitoring wile in hospital, but not at later follow-up in the outpatient setting, pauses in the heart rhythm were seen more frequent with ticagrelor. However such pauses were not associated with any symptoms or clinical consequences for the patient. Transient symptoms of dyspnoea were reported more often by patients on ticarelor but only one in 100 ticagrelor treated patients overall stopped taking study medication due to dyspnoea.

PLATO was a head-to-head outcomes study of ticagrelor plus aspirin versus the active comparator, clopidogrel plus aspirin, and was designed to establish whether ticagrelor could achieve meaningful cardiovascular endpoints in ACS patients. 18,624 patients at 893 sites in 43 countries across all continents were successfully recruited. All patients were admitted to hospital because of acute coronary syndrome, one third with ST-elevation myocardial infarction and two thirds without ST-elevation. Shortly after admission to hospital, the patients started their long-term anti-platelet treatment with either ticagrelor (90 mg twice daily) or clopidogrel (75 mg daily) in a randomized, double blind fashion for 6 - 12 months. The PLATO study was led by the Executive Committee co-chairs, Professor Lars Wallentin, Sweden (Uppsala Clinical Research Center) and Professor Robert Harrington, USA (Duke Clinical Research Institute).

The PLATO study was sponsored by AstraZeneca, which has developed and manufactures ticagrelor. Ticagrelor is the first reversibly binding oral adenosine diphosphate (ADP) receptor antagonist. It selectively inhibits P2Y12, a key target receptor for ADP. ADP receptor blockade inhibits the action of platelets in the blood, reducing recurrent thrombotic events. Ticagrelor is the first in a new chemical class, the CPTPs (cyclopentyl-triazolo-pyrimidines) and is chemically distinct from the thienopyridines, such as clopidogrel and prasugrel.

The study design of PLATO was published in the April 2009 edition of the American Heart Journal (James, S. et al. in Am. Heart J. 2009; 157: 599-605).

Conference News