

Pre-treatment with prasugrel—more risk, no benefit: ACCOAST

September 1 2013

In patients with non-ST-elevation acute coronary syndrome (NSTEMI-ACS), pre-treatment with the P2Y₁₂ antagonist prasugrel prior to catheterization, significantly increases the risk of life-threatening bleeding without reducing the risk of major ischemic events, according to the results of the ACCOAST (A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction) trial.

The findings point to a "[paradigm shift](#)" away from pre-treatment in such [patients](#) which will not only be "hard to believe and destabilizing for many [cardiologists](#), but may also be difficult to implement since the routine use of pre-treatment has been anchored for so long," said the study's lead investigator Gilles Montalescot, from the ACTION study group at the Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtrière, in Paris, France.

Current ESC and ACCF/AHA guidelines recommend that pre-treatment with P2Y₁₂ inhibitors should be added to aspirin as soon as possible before catheterization and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding, explained Dr. Montalescot.

This strategy has been accepted for years based on the results of observational, subgroup and non-randomized analyses performed with the older drug clopidogrel,

But newer P2Y₁₂ [receptor antagonists](#) such as prasugrel are more potent

and have a faster onset of action, which makes these drugs well-adapted to PCI.

"With the rapid onset of action of the oral and intravenous P2Y12 inhibitors and the modern era of short delays between [hospital admission](#) and catheterization, the risk of an ischemic complication before catheterization is extremely low, suggesting that there is no longer a need for pre-treatment in NSTEMI-ACS patients to prevent ischemic complications while waiting for catheterization," he said. "Moreover, there is also no benefit of pre-treatment on peri-PCI complications. Together, our findings suggest use of prasugrel should be considered only after the coronary anatomy has been defined."

Enrolment for ACCOAST was suspended by an independent data monitoring committee on November 16, 2012 when a planned interim analysis showed that pre-treatment with prasugrel was associated with an increased risk of major and life-threatening bleeding, although no increased rate of mortality.

The phase 3, randomized, double blind, event-driven study conducted in 171 centers and 19 countries in Europe, Canada, Israel and Turkey, randomized 4033 patients to either pre-treatment with prasugrel or placebo at the time of NSTEMI-ACS diagnosis (n=2037) followed by prasugrel given selectively after the coronary angiogram to patients with a confirmed indication for PCI (n=1996). Patients in both arms also received aspirin and standard of care.

Patients were to be scheduled to undergo coronary angiography/PCI within 48 hours from randomization.

Patients In the pre-treatment arm received a 30-mg loading dose (LD) of prasugrel at the time of randomization and, if PCI was indicated, an additional 30-mg at the time of PCI, while patients in the no pre-

treatment arm got a placebo dose at randomization, and, if PCI was indicated, a 60-mg LD of prasugrel at the time of PCI.

Ultimately, PCI was performed in 68.7% of subjects, while in the 7 days post-randomization coronary artery bypass surgery (CABG) was chosen for 6.2% and medical management for 25.1%.

For the primary endpoint, a composite of cardiovascular death, [myocardial infarction](#), stroke, urgent revascularization or GPIIb/IIIa bailout at 7 and 30 days post-randomization, there was no significant difference between the pre-treatment and no pre-treatment groups (10.0% vs 9.8%, $p = 0.812$, and 10.8 vs 10.8, $p = 0.976$, respectively).

However, the rate of all major bleeding, according to Thrombolysis in Myocardial Infarction (TIMI) criteria was almost double in the pre-treatment group at both 7 days (2.6% vs 1.4%, $p = 0.006$), and 30 days (2.9% vs 1.5%, $p = 0.002$).

At 7 days, major and life-threatening TIMI bleeding not related to CABG procedures were increased by three-fold and six-fold respectively (1.33% vs 0.45%, $p = 0.003$; and 0.83% vs 0.15%, $p = 0.002$).

There was however, no excess of fatal or intracranial hemorrhage with pre-treatment.

ACCOAST is the first randomized study of pre-treatment versus no pre-treatment in NSTEMI ACS before scheduled catheterization, said Dr. Montalescot. While the study looked specifically at prasugrel, the results, when considered alongside another recent study of pre-treatment with [clopidogrel](#) (JAMA. 2013;309(14):1461) are potentially applicable to the global concept of pre-treatment with a P2Y₁₂ inhibitor.

Provided by European Society of Cardiology

Citation: Pre-treatment with prasugrel—more risk, no benefit: ACCOAST (2013, September 1)
retrieved 25 April 2024 from

<https://medicalxpress.com/news/2013-09-pre-treatment-prasugrelmore-benefit-accoast.html>

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