Prasugrel compared with high-dose Clopidogrel in acute coronary syndrome.
The randomized, double-blind ACAPULCO study.
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Background:

The TRITON-TIMI 38 study compared prasugrel (60 mg loading and 10 mg/day maintenance) to clopidogrel (300 mg loading and 75 mg/day maintenance) in patients with moderate-to-high-risk acute coronary syndrome (ACS) at 15 months. The primary composite endpoint of cardiovascular death, myocardial infarction and stroke was significantly lower in the prasugrel group than in the clopidogrel group (9.9% vs 12.1%, $p<0.001$). There was no significant higher risk of major bleeding in the prasugrel group in patients not meeting any of these 3 criterion: age≥75 years, weight<60 kg, or a history of stoke or transient ischemic attack.

Reported in the European congress 2009, the CURRENT-OASIS 7 study showed that a higher dose of clopidogrel (600 mg loading followed by 150mg/day for 1 week and then 75 mg/day maintenance vs 300 mg loading followed by 75 mg/day) in patients undergoing PCI for ACS was associated with a decrease in the rate of the 30 day composite endpoint of cardiovascular death, myocardial infarction and stroke (4.5% vs. 3.9%, $p=0.036$). There was no significant difference in terms of major bleeding between the groups (1.04% for clopidogrel high dose vs. 0.95% for low dose, $p=0.5$).

The clinical impact of high-dose clopidogrel (600 mg, as used in the CURRENT-OASIS 7 study) compared to prasugrel, however, remains unclear.

The PRINCIPLE-TIMI 44 study showed that high dose clopidogrel (600 mg loading followed by 150mg/day) resulted in less inhibition of platelet aggregation than prasugrel (60 mg loading followed by 10 mg/day) in patients with stable coronary disease.

In ACS, however, platelet reactivity is enhanced; whether the results of the PRINCIPLE-TIMI 44 study could be extrapolated from stable to ACS patients is questionable. The ACAPULCO study was designed to address this issue.

Methods:

This study is a prospective, randomized, cross-over study of patients with acute coronary syndrome or unstable angina, all receiving a clopidogrel loading dose of 900 mg. Patients treated with clopidogrel 150 mg/day were then compared to those treated with prasugrel 10 mg/d. After receiving prasugrel or clopidogrel for 14 days, patients were switched to the other drug for 14 days. The primary endpoint was the maximum platelet aggregation (MPA with 20 micromoles of ADP) as assessed by light transmission aggregometry at 14 and 28 days.

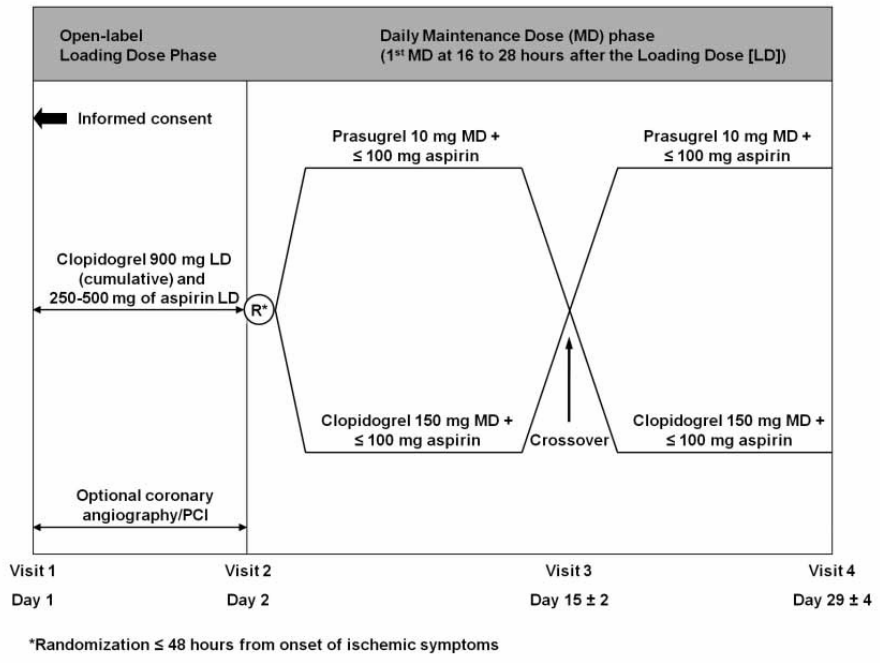

Figure courtesy from Dr. Montalescot

Results:

Of 51 patients enrolled, 37 underwent PCI. Mean MPA (mixed data from pre-crossover, visit 3 and post-crossover phase, visit 4) was 26.2% for the prasugrel group and 39.1% for the clopidogrel group ($p<0.001$). Patients were judged as thienopyridine non-responders (defined as a MPA under 50%) in 2% of the cases with prasugrel and 26% with clopidogrel.

Conclusion:

Compared even to a higher dose of clopidogrel as used in the TRITON-TIMI 38 and CURRENT-OASIS 7 studies, prasugrel resulted in higher overall platelet inhibition in the setting of ACS. More specifically, a prasugrel 60 mg loading dose is more results in lower platelet reactivity than a clopidogrel 900 mg loading dose; and a prasugrel 10 mg maintenance dose results in lower platelet reactivity than a clopidogrel 150 mg maintenance dose. Whether this information translates to a clinical benefit requires further study.

Commentary:

Dr. Belle discussed the results of the trial with the senior author, Dr. Montalescot from Paris, France. The transcription of this interview follows.

Dr Belle: Dr. Montalescot, congratulations for this work and all your papers regarding this topic. Do you think that the stronger and faster effect of prasugel could be related to the dose of clopidogrel which could be to low? Could we imagine performing the same study as ACAPULCO with a higher dose of Clopidogrel (maybe 300 or 600 mg daily) and find a dose of Clopidogrel that has the same degree of platelet inhibition as prasugrel?

Pr Montalescot: Few studies have evaluated MD doses higher than 150mg. We know from small series of patients that higher MD doses would increase the level of inhibition.

In patients with a poor response to clopidogrel, higher doses up to 300 mg daily have been tested with some effect in some patients to overcome resistance (A Pena et al Circulation 2009)

Dr Belle: In the setting of non ST elevation ACS, the CURE study reported a very early clinical benefit of clopidogrel following admission. The ACC/AHA 2007 guidelines recommend an immediate Clopidogrel loading dose of 300-600 mg before diagnostic coronary angiography for patients with ACS. In the TRITON-TIMI 38 study, however, patients scheduled for PCI received the thienopyridine loading dose only when the coronary anatomy was known.

For our practice, we now have 3 types of management strategies for thienopyridines.

- 60 mg loading dose of Prasugrel upon admission and before coronary angiography, anticipating a higher bleeding risk with patients referred for CABG or for patients with a different diagnosis.
- thienopyridine naïve until angiography, and then giving prasugrel at the time of PCI.
- 600 mg loading dose of clopidogrel followed by 150 mg daily maintenance until angiography and switching to prasugrel at the time of PCI for patients eligible for it.

What would be your optimal strategy for thienopyridine therapy at this time?

Dr. Montalsecot: The first option is adequate for primary PCI of STEMI and was actually tested this way in the TRITON study.

The second option is already what is recommended for clopidogrel in the American guidelines in NSTE-ACS, but the European guidelines recommend to pre-treat these patients with clopidogrel before knowing the coronary status. We have no data for prasugrel and this is being currently tested in the randomized double blind ACCOAST trial.

The third option has not been tested clinically and is not currently being tested in any clinical trial. This is where ACAPULCO sheds some light on what we can expect in terms of platelet inhibition level.