Low response to clopidogrel linked to increased risk of cardiac death after PCI

JUNE 25, 2010 | Sue Hughes

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Strasbourg, France - In patients undergoing PCI, a low response to **clopidogrel** assessed by the vasodilator-stimulated-phosphoprotein (VASP) flow cytometry test is an independent predictor of cardiovascular death, a new study shows [**1**]. The deleterious impact of a low response to clopidogrel was significantly higher in patients who received a drug-eluting stent.

The study, published in the June 2010 issue of *JACC: Cardiovascular Interventions*, was conducted by a group led by **Dr Soraya El Ghannudi** (University of Strasbourg, France).

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Senior author **Dr Olivier Morel** (University of Strasbourg) commented to **heartwire**: "Our main message is that if your platelets are not correctly inhibited, your risk of cardiac death increases after PCI."

He added: "There are many studies now that have shown an association between low platelet inhibition and cardiac events, but this is one of the largest studies and one of the few to have shown a relation between low platelet inhibition and cardiac death. These are really definitive data."

The current study used the VASP test to measure platelet inhibition. Although it is not available as a bedside test and blood samples must be sent to a specialized laboratory for measurement, Morel told **heart*wire*** that this test has advantages over some other tests in that it is selective for the P2Y12 receptor and so is a good indicator of responsiveness to clopidogrel; it is not sensitive to IIb/IIIa blockers; and it is convenient in that it uses whole blood, so the sample does not need to be centrifuged. In addition, the test can be done any time within 48 hours of the blood sample being taken.

Morel said: "We believe the VASP test is the most reliable test for platelet inhibition with regard to thienopyridine use. Light-transmission tests may be best if you want to look for hyperreactive platelets in general, as these cover several different pathways of platelet aggregation. The VASP test looks only at the activation of the P2Y12-receptor pathway, but as this is the pathway used by clopidogrel to block platelet activation, it is ideal for testing responsiveness to clopidogrel."

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Morel uses the VASP test in his clinical practice, and for patients showing a low response on the normal clopidogrel dose, he would either raise the clopidogrel dose or switch to **prasugrel**. "We normally test 12 hours after the clopidogrel loading dose. If patients are

low responders, we would give another clopidogrel bolus or prasugrel and repeat the test after another 12 to 24 hours."

In the paper, the researchers explain that the VASP test is a new assay specific to the P2Y12 adenosine-diphosphate-receptor pathway. In this test, platelet activation is expressed as platelet-reactivity index (PRI), and low responders to clopidogrel were defined as having a PRI >60%.

In the study, 461 unselected patients undergoing urgent or planned PCI were classified as low responders or responders to clopidogrel, depending on their PRI as measured by the VASP test. The patients were followed for a mean of nine months.

The median value of the PRI in the 277 clopidogrel responders was 41.37, and in the 184 low responders it was 73.15. There was a significantly higher proportion of diabetic and obese patients in the low-responder group.

At follow-up, the rate of dual antiplatelet therapy was equivalent between groups. Results showed that cardiac mortality rates and stent thrombosis rates were higher in patients classified as low responders to clopidogrel.

Cardiac events in low responders and responders to clopidogrel

Outcome	Low responders to clopidogrel (%)	Responders to clopidogrel (%)	p
Total death	9.6	3.3	0.005
Cardiac death	7.9	2.2	0.004
STEMI	1.7	1.8	1.00
NSTEMI	6.2	4.4	0.39
TLR	10.1	8.7	0.62
Stent thrombosis	8.3	3.3	0.018
MACE	19.7	13.1	0.06

MACE= major adverse cardiovascular events; TLR= target lesion revascularization

Low response to clopidogrel was one of four factors identified by multivariate analysis as independent predictors of cardiac death. The others were reduced creatinine clearance, use of a drug-eluting stent, and raised CRP.

Independent predictors of cardiac death

Factor	HR for cardiac death (95% CI)
Creatinine clearance	0.95 (0.93-0.98)

Drug-eluting stent	5.73 (1.40-23.43)
CRP	1.01 (1.001-1.02)
Low response to clopidogrel	4.00 (1.08-14.80)

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Worse with drug-eluting stents

The authors note that the deleterious impact of a low response to clopidogrel on cardiovascular death was significantly higher in patients implanted with drug-eluting stents. While they say this result should be taken with great caution, given the inherent limitation of registry data, the limited size of the cohort, and the possible contribution of unmeasured confounding factors, they also point out that this finding supports the view that the delayed endothelium healing after drug-eluting-stent placement requires a more robust and sustained platelet inhibition than after a bare-metal stent. "Altogether, these data strongly suggest that the evaluation of platelet responsiveness to clopidogrel could be useful for the management of patients treated with drug-eluting stents," they say.

What to do for these patients

In an accompanying editorial [2], **Drs Sotirios Tsimikas** (University of California, San Diego) and **Gregor Leibundgut** (University Hospital Basel, Switzerland) report that several randomized trials are under way to give answers on what to do about low responses to clopidogrel. These include **GRAVITAS**, **DANTE**, **ARCTIC**, and **TRIGGER-PCI**, which will randomize patients with low responsiveness to clopidogrel to standard doses of clopidogrel, higher doses, or other agents.

They conclude: "Ultimately, for selected patients, particularly those at high risk of thrombotic events, it is possible that data derived from platelet-function testing might be useful in improving patient outcomes. The resolution of these issues in the next few years will ultimately allow clinicians to effectively individualize and prescribe optimal antiplatelet therapies in patients with ACS and particularly those undergoing PCI."

The study authors do not declare any financial conflicts. Tsimikas has served as consultant to AstraZeneca.

Sources

1. Ghannudi SE, Ohlmann P, Meyer N, et al. Impact of P2Y12 inhibition by clopidogrel on cardiovascular mortality in unselected patients treated by percutaneous coronary angioplasty. *JACC Cardiovasc Interv* 2010; 3:648-656.
2. Tsimikas S and Leibundgut G. Post-thienopyridine platelet response, cardiovascular outcomes, and personalized therapy: *En attendant Godot*. *JACC Cardiovasc Interv* 2010; 3:657-659.