



New Frontiers in

## CARDIOLOGY

### New Focus on Predictability of Antiplatelet Response Generated by P2Y<sub>12</sub> Inhibition Trials

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**Stockholm** - Individual variability of response to ASA and clopidogrel has shifted attention from the potency of antiplatelet agents to their predictability. Several large clinical trials have demonstrated that newer antiplatelet agents reduce risk of major adverse cardiovascular (CV) events relative to clopidogrel-based strategies, but this is only partially due to greater potency. The newer agents largely avoid the individual variability in effect of clopidogrel that is driven by genetic polymorphism. The relative absence of variability further reduces the risk of suboptimal antiplatelet effect and the life-threatening CV events that follow. The differences are best illustrated in trials conducted in acute coronary syndromes, where both the short- and long-term risks are closely linked to the ability of subduing platelet reactivity. In new data presented here at the ESC, the greater efficacy of the newer agents is shown to be largely dependent on avoiding variability in antiplatelet effect.

Relative to clopidogrel, the newer antiplatelet agents ticagrelor and prasugrel have been shown to significantly reduce the risk of thrombotic events in patients with acute coronary syndrome (ACS). Although clopidogrel, ticagrelor and prasugrel all act by inhibiting the P2Y<sub>12</sub> receptor, their mode of action, metabolism and pharmacodynamics differ. The more favourable metabolism of prasugrel and the direct-acting agent ticagrelor—and potentially of other emerging P2Y<sub>12</sub> receptor inhibitors such as cangrelor and elinogrel—results in a more rapid onset of action, greater potency, or both relative to clopidogrel. However, their most important advantage may be consistency of effect.

“The P2Y<sub>12</sub> receptor is the right target because it plays a major role in amplification of platelet responses regardless of the stimulus, but the substantial inter-individual variability with the prodrug clopidogrel stems from the steps needed to form its active metabolite,” explained Dr. Robert Storey, Department of Cardiovascular Science, University of Sheffield, UK. The variability in response to clopidogrel “is frequently the result of an inadequate generation of the active metabolite, which is in part genetically determined.”

#### Genetic Aspects

The significance of genetic polymorphisms affecting clopidogrel metabolism has been newly highlighted in an important genetic

substudy of the PLATO (PLATElet inhibition and patient Outcomes) trial, which initially demonstrated a cardiovascular (CV) mortality benefit for ticagrelor relative to clopidogrel in ACS patients (Wallentin et al. *N Engl J Med* 2009;361:1045-57). In the new substudy presented here at the ESC and published simultaneously (Wallentin et al. *Lancet* 2010; epub ahead of print August 29), the event rate was 50% higher at 30 days (5.7% vs. 3.8%;  $P=0.028$ ) in those clopidogrel patients with a loss-of-function allele for CYP2C19, which is the major enzyme of hepatic metabolism of clopidogrel, relative to those without. Ticagrelor was not affected by any genetic polymorphisms and was more effective than clopidogrel at protecting against events, irrespective of the presence or absence of polymorphisms (Table 1).

The study further showed that CYP2C19 polymorphisms were not alone in mediating variability in clopidogrel response. The risks of clopidogrel relative to ticagrelor were also influenced by gain-of-function CYP2C19 alleles; polymorphisms in other isoenzymes that influence clopidogrel metabolism such as CYP3A4, CYP3A5 and CYP2C9; and polymorphisms in ABCB1, a glycoprotein involved in transport of clopidogrel.

For the ABCB1 genotype, event rates for the primary outcome were consistently lower with ticagrelor vs. clopidogrel for all genotype groups (interaction  $P=0.39$ , 8.8% vs. 11.9%; HR 0.71; 95% CI, 0.55-0.92 for the high-

expression genotype). The primary outcome (composite of CV death, myocardial infarction (MI) or stroke up to 12 months) occurred less often in the ticagrelor group (8.6%) vs. the clopidogrel group (11.2%), irrespective of CYP2C19 genotype (HR 0.77; 95% CI, 0.60-0.99;  $P=0.0380$ ) in patients with any loss-of-function allele, and in 8.8% vs. 10.0% (HR 0.86; 95% CI, 0.74-1.01;  $P=0.0608$ ) in those without any loss-of-function allele (interaction  $P=0.46$ ), reported lead investigator of the PLATO substudy Prof. Lars Wallentin, Professor of Medicine, Uppsala University, Sweden. Patients on clopidogrel who had any gain-of-function CYP2C19 allele had a higher frequency of major bleeding (11.9%) than did those without any gain-of-function or loss-of-function alleles (9.5%;  $P=0.022$ ), but the interaction was not significant between treatment and genotype groups for any type of major bleeding.

Similar data regarding the important impact of polymorphisms on clopidogrel variability were drawn from the TRITON-TIMI 38 study (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition). TRITON-TIMI 38 associated prasugrel with a significant reduction in thrombotic

complications in ACS patients with scheduled percutaneous intervention (PCI) relative to clopidogrel (Wiviott et al. *N Engl J Med* 2007;357:2001-15). In new polymorphism data published in the same issue of *The Lancet* as in the PLATO genetic substudy, both the CYP2C19 and the ABCB1 3435 TT polymorphisms predicted increased risk of thrombotic events in those on clopidogrel but not on prasugrel (Mega et al. 2010; epub ahead of print August 29). According to the genotyping study of the TRITON-TIMI 38 study, which was similar to the genotyping substudy of the PLATO trial, nearly one third of the study participants had TT polymorphisms.

However, there are several important differences between PLATO and TRITON-TIMI 38; in particular, the fact that all ACS patients, regardless of ST-segment elevation or prior treatment with clopidogrel, were eligible for PLATO, whereas entry into TRITON-TIMI 38 was limited only to those scheduled for a PCI. Additionally, in the PLATO trial, patients were randomized to ticagrelor or clopidogrel as soon as possible after admission while in the TRITON-TIMI 38 study, the drug was administered any time between randomization and one hour after leaving the catheterization

Table 1. PLATO Substudy: Outcomes in Relation to the CYP2C19 Genotype

	Ticagrelor 90 mg b.i.d.			Clopidogrel 75 mg q.d.			Hazard ratio (95% CI)	P value	P value (interaction)*
	Number of patients	Patients with events	Kaplan-Meier event rate	Number of patients	Patients with events	Kaplan-Meier event rate			
<b>CV death, myocardial infarction and stroke</b>									
Any loss-of-function allele	1384	115 (8.3%)	8.6%	1388	149 (10.7%)	11.2%	0.77 (0.60–0.99)	0.0380	0.46
No loss-of-function allele	3554	296 (8.3%)	8.8%	3516	332 (9.4%)	10.0%	0.86 (0.74–1.01)	0.0608	–
<b>CV death and myocardial infarction</b>									
Any loss-of-function allele	1384	102 (7.4%)	7.7%	1388	138 (9.9%)	10.4%	0.73 (0.57–0.95)	0.0184	0.30
No loss-of-function allele	3554	273 (7.7%)	8.0%	3516	306 (8.7%)	9.2%	0.86 (0.73–1.01)	0.0734	–
<b>Definite stent thrombosis†</b>									
Any loss-of-function allele	943	15 (1.6%)	1.6%	934	21 (2.2%)	2.3%	0.71 (0.36–1.37)	0.30	‡
No loss-of-function allele	2341	22 (0.9%)	1.0%	2300	35 (1.5%)	1.5%	0.62 (0.36–1.05)	0.0772	–
<b>Major bleeding (loss-of-function allele)</b>									
Any loss-of-function allele	1380	149 (10.8%)	11.8%	1380	143 (10.4%)	11.3%	1.04 (0.82–1.30)	0.77	0.60
No loss-of-function allele	3547	331 (9.3%)	10.3%	3506	340 (9.7%)	10.6%	0.96 (0.83–1.12)	0.61	–
<b>Major bleeding (gain-of-function allele)</b>									
No loss-of-function or gain-of-function allele	1846	176 (9.5%)	10.5%	1856	161 (8.7%)	9.5%	1.12 (0.90–1.38)	0.31	0.19
Any loss-of-function but no gain-of-function allele	1011	108 (10.7%)	11.6%	1053	108 (10.3%)	11.1%	1.03 (0.79–1.34)	0.84	–
Any gain-of-function allele	2070	196 (9.5%)	11.5%	1977	214 (10.8%)	11.9%	1.03 (0.79–1.34)	0.13	–
<b>Major bleeding related to non-CABG</b>									
Any loss-of-function allele	1380	56 (4.1%)	4.6%	1380	41 (3.0%)	3.2%	1.39 (0.93–2.08)	0.11	0.31
No loss-of-function allele	3547	121 (3.4%)	3.9%	3506	110 (3.1%)	3.6%	1.08 (0.84–1.40)	0.55	–
<b>Major bleeding related to CABG</b>									
Any loss-of-function allele	1380	96 (7.0%)	7.6%	1380	107 (7.8%)	8.6%	0.87 (0.66–1.14)	0.31	0.93
No loss-of-function allele	3547	218 (6.1%)	6.8%	3506	246 (7.0%)	7.7%	0.88 (0.73–1.05)	0.16	–
<b>Net clinical benefit</b>									
Any loss-of-function allele	1384	204 (14.7%)	15.2%	1388	231 (16.6%)	17.1%	0.88 (0.72–1.06)	0.17	0.88
No loss-of-function allele	3554	476 (13.4%)	14.0%	3516	533 (15.2%)	15.8%	0.86 (0.76–0.97)	0.0172	–

CABG=coronary artery bypass graft.

\*P value of interaction indicates significance of effects of genotype groups on the results of comparisons between treatment groups.

†Stent thrombosis population includes patients who received at least one stent at any time during the study, which was about 64% of patients participating in the genetic substudy.

‡Interaction P value not calculated because of low number of events.

Adapted from Wallentin et al. *Lancet* 2010; epub ahead of print.

laboratory. There were also important differences in outcome. While prasugrel was associated with a 19% ( $P<0.001$ ) relative reduction in major thrombotic events, it was also associated with a 32% ( $P=0.03$ ) increase in major bleeding, and it did not yield a significant mortality benefit. In contrast, the 16% relative reduction ( $P<0.001$ ) in the composite end point of major thrombotic events on ticagrelor relative to clopidogrel was accompanied by a 22% relative reduction ( $P<0.001$ ) in death from any cause and no significant overall increase in major bleeding.

### Impact on Diabetic Patients

The search for more reliable antiplatelet agents has expanded to the intravenous P2Y<sub>12</sub> inhibitors cangrelor and elinogrel. Although an initial trial with cangrelor was terminated when it failed to show non-inferiority to clopidogrel, this agent is still being evaluated for short-term antiplatelet bridging in patients who are not candidates for oral agents. Phase II results of elinogrel presented at the ESC suggested that this agent may be more potent than clopidogrel and a phase III study is being considered. Again, the interest in this agent is particularly driven by the consistency of effect.

“While clopidogrel is a well-established and effective therapy, it does not work for all patients, so it is important that we explore alternatives to improve efficacy,” reported the senior investigator of the phase II elinogrel trial, Dr. Sunil Rao, Duke Clinical Research Institute, Durham, North Carolina.

One of the key goals of any new agent will be to reduce thrombotic events without increasing risk of bleeding events. Reversible P2Y<sub>12</sub> receptor inhibitors such as elinogrel and ticagrelor are expected to provide a greater distance between antiplatelet effect and bleeding because, unlike previous P2Y<sub>12</sub> inhibitors, including both clopidogrel and prasugrel, they come off the receptor, restoring platelet function, when stopped. This is an important feature for patients who require unanticipated surgical procedures. However, these drugs may also have an inherently larger therapeutic window even independent of their reversibility. In PLATO, major bleeding in the subgroup not related to coronary artery bypass grafting (CABG) was increased by 19%, but there was no overall difference in major bleeding, including no difference in fatal or life-threatening bleeding. New substudy data from the 25% of PLATO participants with diabetes mellitus have demonstrated that although the presence of diabetes increased the risk of both thrombotic events and major bleeding, the reduction in events on ticagrelor relative to clopidogrel was similar to that observed in the total PLATO population without any exacerbation of the bleeding risk.

“The overall findings are consistent with the PLATO trial results and show that the primary efficacy composite end point of CV death, MI and stroke was lower on ticagrelor relative to clopidogrel irrespective of the presence of diabetes, the relative

glycemic control, the presence of insulin treatment or the type of diabetes,” reported co-investigator of the PLATO substudy, Dr. Stefan James, Uppsala Clinical Research Center.

Table 2. Association of Diabetes-related Variables with End Points

Characteristic <sup>a</sup>	χ <sup>2</sup>	HR (95% CI)	P value
<b>Efficacy end points</b>			
<b>CV death, MI, or stroke</b>			
Diabetes	108.78	1.66 (1.51–1.82)	<0.0001
Baseline glucose (truncated) <sup>b</sup>	67.22	1.12 (1.09–1.15)	<0.0001
Baseline HbA <sub>1c</sub> (truncated) <sup>b</sup>	90.72	1.30 (1.23–1.37)	<0.0001
<b>All-cause death</b>			
Diabetes	78.87	1.84 (1.61–2.10)	<0.0001
Baseline glucose (truncated) <sup>b</sup>	83.47	1.21 (1.16–1.25)	<0.0001
Baseline HbA <sub>1c</sub> (truncated) <sup>b</sup>	75.14	1.40 (1.30–1.51)	<0.0001
<b>MI</b>			
Diabetes	44.09	1.53 (1.35–1.73)	<0.0001
Baseline glucose (truncated) <sup>b</sup>	9.92	1.06 (1.02–1.10)	0.0016
Baseline HbA <sub>1c</sub> (truncated) <sup>b</sup>	34.85	1.24 (1.15–1.33)	<0.0001
<b>Definite stent thrombosis<sup>c</sup></b>			
Diabetes	1.91	1.26 (0.91–1.77)	0.1673
Baseline glucose (truncated) <sup>b</sup>	12.68	1.19 (1.08–1.31)	0.0004
Baseline HbA <sub>1c</sub> (truncated) <sup>b</sup>	5.20	1.24 (1.03–1.50)	0.0226
<b>Safety end points</b>			
<b>Major bleeding</b>			
Diabetes	48.13	1.41 (1.28–1.55)	<0.0001
Baseline glucose	14.91	1.03 (1.01–1.04)	0.0001
Baseline HbA <sub>1c</sub>	20.39	1.07 (1.04–1.11)	<0.0001
<b>Non-CABG major bleeding</b>			
Diabetes	14.50	1.38 (1.17–1.62)	0.0001
Baseline glucose	9.78	1.04 (1.01–1.06)	0.0018
Baseline HbA <sub>1c</sub>	0.03	1.00 (0.95–1.06)	0.8676
<b>CABG-related major bleeding</b>			
Diabetes	34.16	1.42 (1.26–1.60)	<0.0001
Baseline glucose	5.49	1.02 (1.00–1.04)	0.0191
Baseline HbA <sub>1c</sub>	28.65	1.10 (1.06–1.14)	<0.0001

<sup>a</sup>Glucose and HbA<sub>1c</sub> values are treated as linear for the range of values for the safety end points. <sup>b</sup>For efficacy outcomes, glucose values <5 and <10 are treated as 5 and 10, respectively. For efficacy outcomes, HbA<sub>1c</sub> values >8 are treated as 8. <sup>c</sup>Of the 11,289 patients who received a stent, 2520 had diabetes mellitus.

Adapted from James et al. *Eur Heart J* 2010; epub ahead of print.

In patients with diabetes, all adverse outcomes were increased substantially in the 4662 patients with diabetes relative to the 13,951 patients without diabetes irrespective of treatment. This included a 66% relative increase ( $P<0.0001$ ) in the composite end point, an 84% ( $P<0.0001$ ) increase in mortality and a 41% increase ( $P<0.0001$ ) in major bleeding (Table 2).

### Non-invasive Management

The fact that ticagrelor provides protection against major thrombotic events without increasing total major bleeding is important because these have been typically linked in the past. Although the benefit:risk ratio may still favour a more potent agent, the data with the reversible P2Y<sub>12</sub> inhibitor ticagrelor suggest for the first time that this trade-off is not inherent. In ACS patients who receive antiplatelet agents on an urgent basis, there has been particular concern about using optimally potent antiplatelet regimens if the risk is increased bleeding in relatively low-risk patients. Reassuring data from another PLATO substudy, also presented by Dr. James, suggested that relative benefits were similar for ticagrelor vs. clopidogrel even in patients who did not have a planned invasive procedure.

“For patients with non-ST-elevation ACS and planned non-invasive management, the clinical benefits of ticagrelor vs. clopidogrel were consistent with overall findings in the PLATO trial,” confirmed Dr. James, who reported on a set of data that included 5216 patients (28%) scheduled for non-invasive management. Adding that there was no significant difference in the rates of major bleeding in those with a planned non-invasive management, he reported that even in this group, there was a statistically significant difference in all-cause mortality favouring ticagrelor (6.1% vs. 8.2%;  $P=0.01$ ).

### Dyspnea

Regarding safety, the most significant difference between ticagrelor and clopidogrel in PLATO was the incidence of dyspnea (13.8% vs. 7.8%;  $P<0.001$ ). The cause of this side effect is unclear, but a new substudy led by PLATO substudy co-investigator Dr. Storey confirmed that dyspnea considered medication-related was more common on ticagrelor than clopidogrel (15% vs. 6.9%;  $P<0.0001$ ). However, most cases were mild to moderate in both groups (99.6% vs. 99.7%). Patients who developed dyspnea had

a higher discontinuation rate for any reason compared to those without dyspnea (26.2% vs. 23.2%, respectively). Most importantly, dyspnea was not found to alter the major results or conclusions.

“Dyspnea during ticagrelor treatment does not appear to be associated with any differences in efficacy or bleeding-related clinical outcomes compared with clopidogrel,” Dr. Storey told delegates.

Overall, it is the variability in the clopidogrel response that is driving efforts to provide better strategies for protection against thrombotic events, not only in ACS patients but also in those who require long-term antiplatelet treatment, such as those with intracoronary stents. Ticagrelor and prasugrel both have a more rapid onset of action as well as a greater peak antiplatelet effect than clopidogrel in commonly prescribed doses, but it is the relative consistency of effect that may be most important in patient care.

“When added to ASA, clopidogrel is effective, but the newer agents ticagrelor and prasugrel are more potent and provide a more consistent effect across patients,” observed Dr. Christopher Cannon, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts. He predicted that “we will be moving to the newer therapies” not only for greater overall efficacy but also for less variability of effect that leaves some patients on clopidogrel at high risk.

### Summary

The ability of the newer antiplatelet agents ticagrelor and prasugrel to provide greater protection against major thrombotic events in patients with ACS vs. clopidogrel cannot only be attributed to a more rapid effect and greater antiplatelet potency, but also to a substantial proportion of patients who have a diminished response to clopidogrel due to genetic polymorphisms that reduce the availability of its active metabolite. While genetic testing can be performed to screen patients unlikely to respond to clopidogrel, the newer agents, which are not dependent on these metabolic pathways, appear to be a more practical solution. □

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