

Response to antiplatelet treatment: from genes to outcome



Dual antiplatelet therapy (aspirin plus clopidogrel) is the standard of care for patients with acute coronary syndrome who are managed medically or by percutaneous coronary intervention (PCI).^{1,2} Clopidogrel has substantial benefit in patients undergoing PCI and stent implantation.^{1,2} However, major adverse cardiovascular events, including stent thrombosis, can occur despite antiplatelet therapy, and a recent meta-analysis showed that persistent platelet reactivity on clopidogrel treatment confers a five-fold increased risk of major adverse cardiovascular events.³

Multiple chronic or transient mechanisms involved in high on-clopidogrel platelet reactivity have been identified: inadequate drug compliance, drug-drug interactions, age, diabetes, body-mass index, left-ventricle ejection function, and inflammation.⁴ Platelet response to clopidogrel is highly heritable and not entirely explained by CYP2C19, an isoform of the cytochrome P450 involved in clopidogrel's metabolism, which suggests that further genetic variants in different genes play a pivotal role in determining individual susceptibility to antiplatelet drug response.^{4,5} In 2007, the CYP2C19*2 polymorphism was found to be associated with residual platelet reactivity in patients with acute coronary syndrome who were undergoing PCI on antiplatelet treatment.⁶ Successively, in different clinical settings and at different follow-up, CYP2C19*2 and other allelic variants in this gene were shown to be independent determinants of major adverse cardiovascular events in patients on clopidogrel.^{4,7,8} In May, 2009, the US Food and Drug Administration recommended the change to clopidogrel's prescribing label to reflect these findings.⁹

New P2Y₁₂-receptor antagonists are now available. Prasugrel is a third-generation thienopyridine associated with greater active metabolite generation, superior inhibition of ADP-induced platelet aggregation, and less response variability than with clopidogrel.¹⁰ In the TRITON-TIMI 38 trial of patients with acute coronary syndrome who were undergoing PCI, the prevalence of cardiovascular death, non-fatal myocardial infarction, or stroke was lower with prasugrel than with clopidogrel.¹¹ However, rates of bleeding were higher in the prasugrel group.

The novel antiplatelet agent ticagrelor was also evaluated against clopidogrel in patients with acute

coronary syndrome in the PLATO trial.¹² Ticagrelor was associated with significant reduction in cardiovascular death, myocardial infarction, and stroke, without any difference in the overall incidence of major bleeding, but with an increase in major bleeding related to non-coronary-artery bypass graft.

The issue of the optimum dose of clopidogrel and/or the personalisation of alternative antiplatelet therapeutic strategies aimed at reducing ischaemic events and minimisation of bleedings is open. We think that the relevance of obtaining an "adequate residual platelet reactivity" on antiplatelet treatment is now well founded and the crucial goal is now to identify the clinical, environmental, procedural, and genetic determinants of the increased risk of major adverse cardiovascular events and of bleedings in these high-risk patients.

In *The Lancet* today, Jessica Mega¹³ and Lars Wallentin,¹⁴ and their respective colleagues, have addressed the important issue of finding further genetic variants beside those in CYP2C19 and beside the other clinical and procedural risk factors associated with major adverse cardiovascular events in patients with acute coronary syndrome who are on antiplatelet therapy. Both papers confirmed the independent role of the CYP2C19 loss-of-function alleles as a determinant of major adverse cardiovascular events in these patients on clopidogrel, even if with a lower impact in PLATO than in TRITON-TIMI-38 or in the recent meta-analyses,^{7,8} whereas they did not show any effects of CYP2C19 genetic variants in patients on prasugrel¹³ or ticagrelor.¹⁴

The most interesting novel data from these two papers^{12,13} are those about the role of the 3435C→T polymorphism in ABCB1, a gene coding the P-glycoprotein involved in drug absorption, on the efficacy of the three different antiplatelet treatments. Previous data, from patients presenting with an acute myocardial infarction in a nationwide French registry and receiving clopidogrel, showed that patients with two ABCB1 variant alleles (3435 TT genotype) had a higher rate of cardiovascular events at 1 year than did those with the 3435 CC genotype.¹⁵ However, in that study, the ABCB1 polymorphism was not an independent predictor of outcome in the subgroup of patients undergoing percutaneous coronary intervention.¹⁴ For the ABCB1 polymorphism, even

Published Online
August 29, 2010
DOI:10.1016/S0140-
6736(10)61313-X

See Online/Articles
DOI:10.1016/S0140-
6736(10)61273-1 and
DOI:10.1016/S0140-
6736(10)61274-3

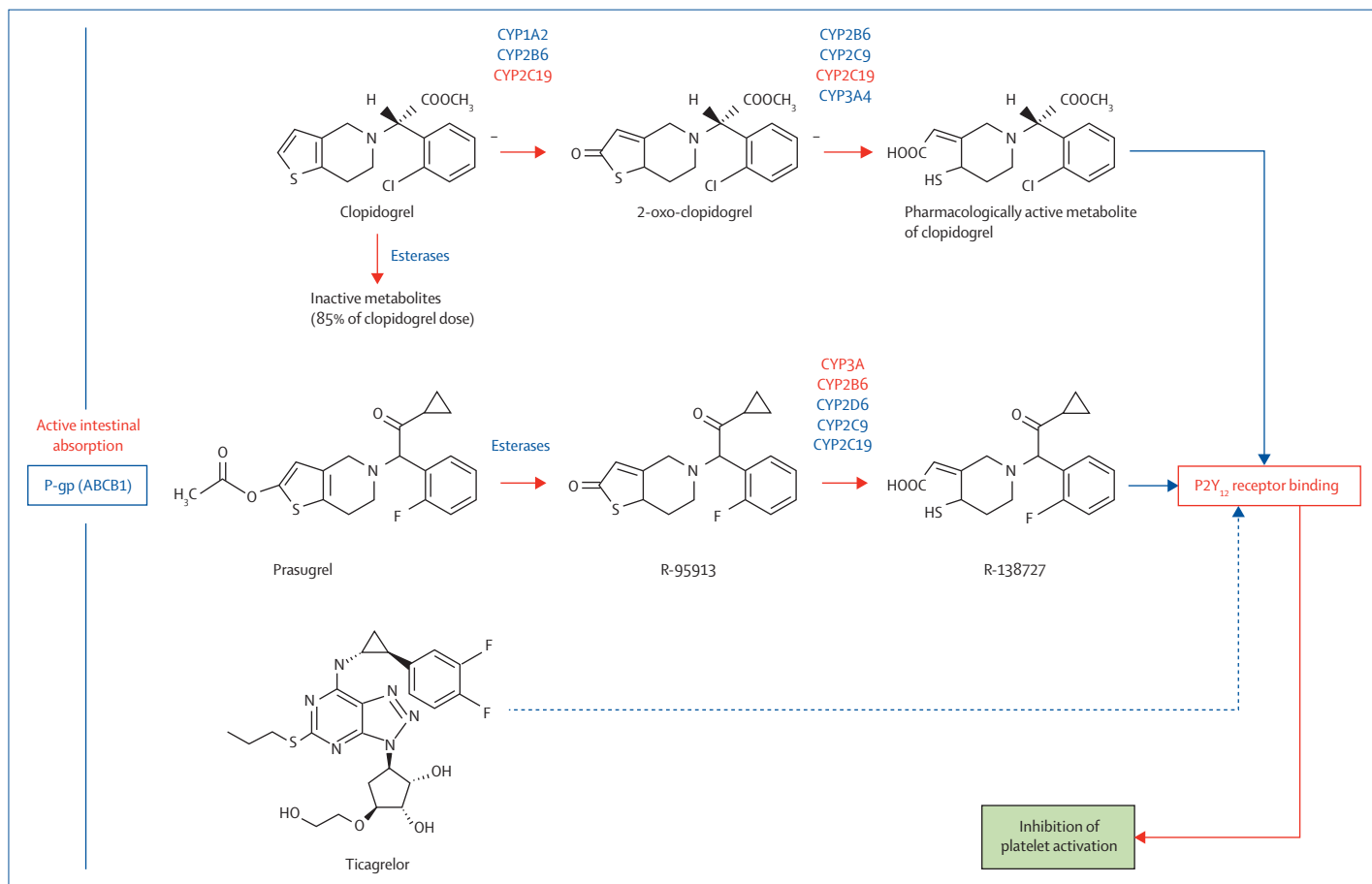


Figure: Mechanism of action and metabolic pathways for clopidogrel, prasugrel, and ticagrelor

All three drugs are absorbed intestinally. In this step, P-glycoprotein, encoded ABCB1, could intervene. Clopidogrel is mostly hydrolysed by esterases to inactive carboxylic acid derivative that accounts for 85% of clopidogrel-related circulating compounds. Several cytochrome P450 (CYP450) enzyme isoforms are responsible for oxidation of thiophene ring of clopidogrel to 2-oxo-clopidogrel, which is further oxidised by other CYP450 isoforms to result in opening of the thiophene ring and formation of carboxyl and thiol groups. Thiol group irreversibly binds to ADP P2Y₁₂ receptor expressed on platelet surface and causes irreversible blockade of ADP binding. Prasugrel is rapidly hydrolysed by carboxyesterases to a thiolactone (R-95913), which is subsequently metabolised to the prasugrel-active metabolite, R-138727. Conversion of R-95913 to R-138727 is catalysed by several CYP450 enzymes, with greatest contributions from CYP3A and CYP2B6, lesser contributions from CYP2C9 and CYP2C19, and even less from CYP2D6. Active metabolite of prasugrel irreversibly binds to ADP P2Y₁₂ receptor. Unlike the other two thienopyridines, ticagrelor does not need to be converted by liver into active metabolite, and is a reversible ADP-receptor antagonist. P-gp=P-glycoprotein. ABCB1=ATP-binding cassette sub-family B member 1. Dotted arrow=no liver conversion and reversible binding to P2Y₁₂ receptor.

though both studies investigated relatively large populations, Mega and colleagues and Wallentin and colleagues obtained contrasting results. Mega and colleagues found that patients on clopidogrel who had the ABCB1 3435 TT genotype were at increased risk of recurrent ischaemic events, probably due to less platelet inhibition according to their observations in healthy individuals. On the other hand, Wallentin and colleagues observed a numerically higher rate of primary efficacy events for the high-expression group (patients with the ABCB1 3435 CC genotype) who were on clopidogrel.

Interpreting the results from the two studies, we should consider that several important differences occur or are not deeply valuable—eg, clinical setting

(in the PLATO cohort, only two-thirds of patients were managed invasively), severity of disease, available clinical information, geographic origin, and percentage of platelets naive to antiplatelet treatment. On the other hand, few and contrasting data are available on the possible effect of the 3435C→T ABCB1 polymorphism on clopidogrel's absorption or metabolism.¹⁶⁻¹⁸

The fact that prasugrel's and ticagrelor's efficacy was not influenced by CYP2C19 and ABCB1 polymorphisms does not mean that other polymorphisms in different genes (eg, CYP3A4 or CYP3A5) could not affect their pharmacodynamics and pharmacokinetics. In fact, on the basis of available knowledge, CYP2C19 and ABCB1 have a marginal or no role on prasugrel's and ticagrelor's metabolism and absorption.

The temptation to find the easier way by choosing the “superior” drug on the basis of large trials in which participants with different risk profiles venture to be considered equal is not desirable. The issue is not to choose the lesser of the evils, but the better of the goods—by identifying the therapeutic strategy that, in consideration of individual characteristics, warrants the higher benefit/risk ratio. Evaluation of the best management should also take into account the clinical determinants of platelet reactivity—from age and sex to body-mass index, diabetes, and inflammation—which might modulate platelet function, while also considering the timing from the acute event, as shown by the CURRENT-OASIS 7 study.¹⁹

For this purpose, starting from these experiences, the scientific community should draw the indications to standardise experimental designs. Prospective studies evaluating different antiplatelet treatments tailored to individual characteristics of patients—genetic profile, residual platelet reactivity, drug–drug interactions, and traditional and procedural risk factors—are urgently needed to identify therapeutic strategies that will provide the best benefit for the single patient in this high-risk clinical setting.

*Betti Giusti, Rosanna Abbate

Department of Medical and Surgical Critical Care, University of Florence–Atherothrombotic Diseases Centre, Careggi Hospital, 50134 Florence, Italy
betti.giusti@unifi.it

BG declares that she has no conflicts of interest. RA has received consultancy fees from Eli Lilly.

- 1 Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons; endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007; **116**: e148–304.
- 2 Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009; **120**: 2271–306.
- 3 Sofi F, Marcucci R, Gori AM, Giusti B, Abbate R, Gensini GF. Clopidogrel non-responsiveness and risk of cardiovascular morbidity: an updated meta-analysis. *Thromb Haemost* 2010; **103**: 841–48.
- 4 Giusti B, Gori AM, Marcucci R, Abbate R. Relation of CYP2C19 loss-of-function polymorphism to the occurrence of stent thrombosis. *Expert Opin Drug Metab Toxicol* 2010; **6**: 393–407.
- 5 Shuldiner AR, O’Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009; **302**: 849–57.
- 6 Giusti B, Gori AM, Marcucci R, et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenet Genomics* 2007; **17**: 1057–64.
- 7 Sofi F, Giusti B, Marcucci R, Gori AM, Abbate R, Gensini GF. Cytochrome P450 2C19(*)2 polymorphism and cardiovascular risk in patients taking clopidogrel: a meta-analysis. *Pharmacogenomics J* 2010; published online March 30. DOI:10.1038/tpj.2010.21.
- 8 Hulot JS, Collet JP, Silvain J, et al. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol* 2010; **56**: 134–43.
- 9 US Food and Drug Administration. Plavix (clopidogrel bisulfate) 75 mg tablets. May, 2009. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm165166.htm> (accessed Aug 23, 2010).
- 10 Gurbel PA, Tantry US. Prasugrel, a third generation thienopyridine and potent platelet inhibitor. *Curr Opin Investig Drugs* 2008; **9**: 324–36.
- 11 Wiviott SD, Braunwald E, McCabe CH, et al, for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357**: 2001–15.
- 12 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361**: 1045–57.
- 13 Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 2010; published online Aug 29. DOI:10.1016/S0140-6736(10)61273-1.
- 14 Wallentin L, James S, Storey RF, et al, for the PLATO investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* 2010; published online Aug 29. DOI:10.1016/S0140-6736(10)61274-3.
- 15 Simon T, Verstruyft C, Mary-Krause M, et al, for the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; **360**: 363–75.
- 16 Taubert D, von Beckerath N, Grimb G, et al. Impact of P-glycoprotein on clopidogrel absorption. *Clin Pharmacol Ther* 2006; **80**: 486–501.
- 17 Owen A, Goldring C, Morgan P, Chadwick D, Park BK, Pirmohamed M. Relationship between the C3435T and G2677T(A) polymorphisms in the ABCB1 gene and P-glycoprotein expression in human liver. *Br J Clin Pharmacol* 2005; **59**: 365–70.
- 18 Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc Natl Acad Sci USA* 2000; **97**: 3473–38.
- 19 Mehta SR, Bassand JP, Chrolavicius S, et al, on behalf of the CURRENT OASIS 7 Steering Committee. Design and rationale of CURRENT-OASIS 7: a randomized, 2 x 2 factorial trial evaluating optimal dosing strategies for clopidogrel and aspirin in patients with ST and non-ST-elevation acute coronary syndromes managed with an early invasive strategy. *Am Heart J* 2008; **156**: 1080–1088.e1.