What is the Role of Genetics in Antiplatelet Therapy?

Learnings from the European Society of Cardiology Congress, Stockholm 2010

Introduction

To exert their pharmacologic effect, many drugs require metabolic conversion—usually through the liver's cytochrome P450 system—to an active metabolite. The rate at which this conversion takes place can vary substantially between individuals, based on a number of factors, including genetic variations in their metabolic pathways. These variations, in turn, lead to variability in terms of the drug's effects, with poor or non-metabolizers not deriving the intended effects from standard therapeutic doses.

Other drugs administered concomitantly can also impact the rate of conversion if they have effects on the metabolic pathway. These effects can cause other drugs to be converted more rapidly or more slowly, either of which can also have a clinically important impact on efficacy and/or side effects.

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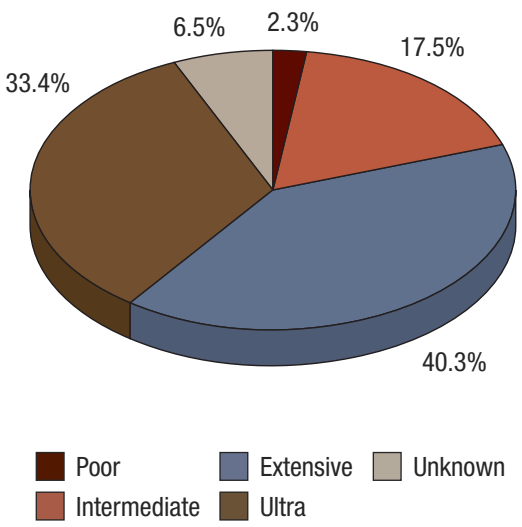
With respect to antiplatelet therapy, one of the most commonly used agents, clopidogrel, relies on one of the P450 enzymes (CYP2C19) to convert the parent drug into its active metabolite. This active metabolite is responsible for platelet inhibition. Several recent reports have suggested that dual antiplatelet therapy with clopidogrel plus aspirin following acute coronary syndromes (ACS) or coronary stenting may be less effective in individuals with genetic polymorphisms of CYP2C19.[1-3]

While this is an important observation, it is also essential to realize that CYP2C19 polymorphisms account for only approximately 12% of the variability in platelet response to clopidogrel.[2] Many other parameters, including type of ACS, use of percutaneous intervention (stenting), underlying risk factors, renal function, inflammation and timing can also affect antiplatelet efficacy.

Antiplatelet therapy is one of the cornerstones of effective cardiovascular (CV) risk-reduction strategies. As such, it is imperative to understand all the variables that can affect the utility of these agents in various situations. This understanding will become even more important to clinical decision-making as the

FIGURE 1. **Distribution of Metabolizer Phenotypes in the CURE Genetic Study[5,6]**



antiplatelet landscape becomes more populated with newly available agents.

A number of papers presented at the recent European Society of Cardiology (ESC) annual congress, and concurrently published, help to clarify this issue and provide guidance to clinicians treating patients in the acute and long-term follow-up settings. These papers are summarized in this report.

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Effects of Genetic Variants on Clopidogrel Treatment in the CURE and ACTIVE Trials

CURE. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial[4] was one of the most important antiplatelet studies published in the past decade. The trial involved 12,562 patients with recent (past 24 hours) unstable angina, who all received aspirin and were randomized to receive clopidogrel (300 mg loading dose, followed by 75 mg once daily) or placebo (6,303 patients) for three to 12 months. The trial had two primary outcomes: a composite of death from CV causes, nonfatal myocardial infarction (MI), and stroke; and another composite including all of the above plus refractory ischemia. For the first primary endpoint, there was a significant 20% relative risk reduction (absolute risk reduction 2.1%) with clopidogrel + aspirin compared with placebo + aspirin. Similar results were observed for the second primary composite endpoint. There was a significantly higher risk of major bleeding with clopidogrel + aspirin (3.7%) compared to placebo + aspirin (2.7%), but no significant difference in terms of life-threatening bleeding. These findings, together with those of other studies conducted during the same period, led to the recommendation for dual antiplatelet therapy following all ACS with or without percutaneous interventions.

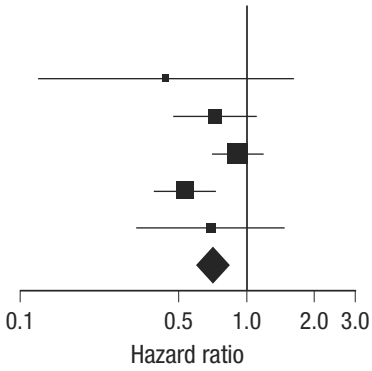
At the 2010 ESC congress, researchers presented the results of a genetic study of the CURE cohort[5] (subsequently published in the *New England Journal of Medicine*[6]). Of the 12,562 subjects in the trial, genotype information was available for 5,059 patients. These patients were classified into categories of metabolizer phenotypes (Figure 1), depending on the number of abnormalities at the three CYP2C19 allele variants known to be associated with diminished clopidogrel metabolism. The categories were: poor metabolizers (2.3% of the population), intermediate metabolizers (17.5%) and extensive metabolizers (40.3%). There is also a genetic variant known to increase clopidogrel metabolism. Those with this variant were classified as ultra metabolizers (33.4% of the population). Finally, those with an allele variant of both types (for increased and decreased metabolism) were classified as unknown metabolizers (6.5%). Patients with at least one variant known to slow metabolism were classified as "loss of function allele carriers" and those with the variant for increased metabolism were classified as "gain of function carriers." Of note, in the CURE study, only a small minority of patients underwent percuta-

FIGURE 2. **Hazard Ratios for First CURE Primary Endpoint by Metabolizer Phenotypes[5,6]**

First primary endpoint (composite of CV death, MI, stroke)

Metabolizer phenotype	Placebo + aspirin event rate	Clopidogrel + aspirin event rate	Hazard ratio (95% CI)
Poor	10.9% (6/55)	6.6% (4/61)	0.44 (0.12-1.61)
Intermediate	12.2% (54/442)	8.5% (37/437)	0.72 (0.48-1.10)
Extensive	12.3% (121/987)	10.8% (112/1,033)	0.92 (0.71-1.19)
Ultra	13.6 (112/826)	7.8% (66/847)	0.53 (0.39-0.72)
Unknown	10.2% (18/176)	7.2% (11/152)	0.69 (0.33-1.47)
Total	**12.5% (311/2,486)**	**9.1% (230/2,530)**	**0.71 (0.60-0.84)**

Heterogeneity p value = 0.12



neous intervention (approximately 15% of the patients in the genetic study).

For both primary outcomes of CURE, the investigators of the genetic study did not detect any significant differences between the various metabolizer phenotypes (Figure 2 shows hazard ratios for the first primary outcome). There also were not any significant differences in terms of bleeding rates.

The investigators also performed the CURE first primary-outcome analysis among patients who were "loss of function carriers" and those who were not. There were no significant differences noted between these groups; clopidogrel + aspirin was associated with significantly lower event rates than placebo + aspirin in each group.

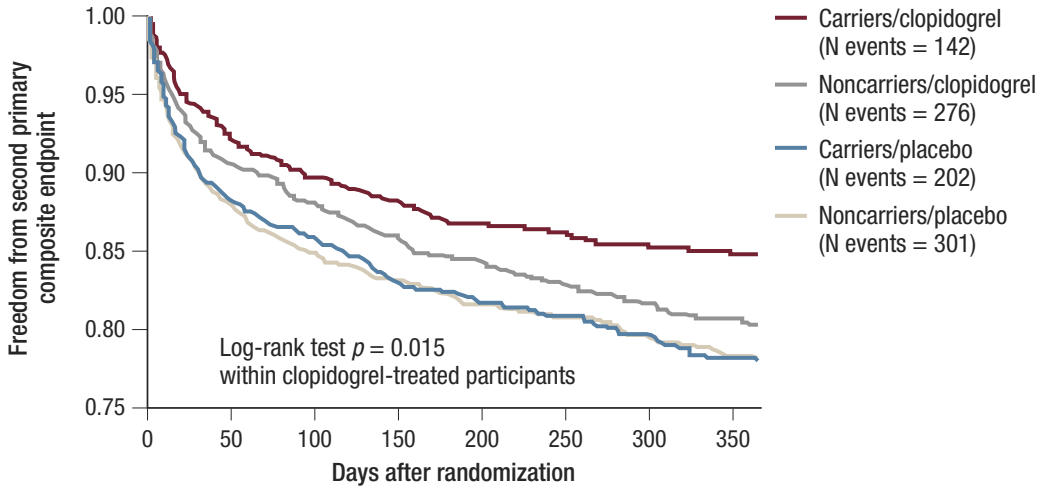
However, another analysis showed a larger benefit in the group with the gain-of-function allele than among those who did not carry this variant (p = 0.06 for interaction in the first primary endpoint and p = 0.02 for the second primary endpoint). In those with the gain-of-function allele, the event rates for the first primary endpoint were 7.7% for clopidogrel + aspirin and 13.0% for placebo + aspirin (HR 0.55, 95% CI 0.42-0.73), while those without the gain-of-function allele had event rates of 10.0% and 12.2% for clopidogrel + aspirin and placebo + aspirin, respectively (HR 0.85, 95% CI 0.68-1.05). For the second primary endpoint, the pattern was similar, and reached statistical significance (Figure 3).

The effect of clopidogrel on bleeding did not vary by loss-of-function or gain-of-function status.

It seems pertinent to ask why there was no loss of effect seen in the group with loss-of-function genetic variants in this analysis. It is likely that this is due to the management strategy employed in this study; most of these ACS patients did not undergo percutaneous interventions with stenting. Vascular interventions such as stents result in endothelial damage and associated increased platelet activation, suggesting a possible need for increased antiplatelet potency. As such, the small difference in potency attributable to the loss-of-function variants might be expected to have more of an impact in such a situation. In the CURE cohort, however, since the proportion of patients who underwent percutaneous in-

For both primary outcomes of CURE, the investigators of the genetic study did not detect any significant differences between the various metabolizer phenotypes. There also were not any significant differences in terms of bleeding rates.

FIGURE 3. **Freedom From Second Primary Endpoint in CURE According to Gain-of-function Carrier Status[5,6]**



No. at risk								
Carriers/clopidogrel	1,001	919	882	780	664	592	467	390
Noncarriers/clopidogrel	1,536	1,386	1,319	1,174	1,035	897	736	612
Carriers/placebo	1,004	883	851	740	629	551	453	374
Noncarriers/placebo	1,489	1,310	1,251	1,122	970	842	701	572

terventions was low, there was no significant impact of loss-of-function status on clopidogrel's efficacy.

ACTIVE-A. The ACTIVE-A study investigated the relative efficacy and safety of aspirin + clopidogrel vs. aspirin + placebo among 7,554 patients with atrial fibrillation (AF) who were not suitable for warfarin therapy.[7] The primary outcome was the composite of stroke, MI, non-central nervous system systemic embolism, or death from vascular causes.

Vascular interventions such as stents result in endothelial damage and associated increased platelet activation, suggesting a possible need for increased antiplatelet potency.

After a median of 3.6 years of follow-up, the annual event rates for the primary outcome were 6.8% for aspirin + clopidogrel and 7.6% for aspirin + placebo (absolute risk reduction 0.8%, relative risk 0.89; 95% CI 0.81-0.98). The difference was mainly attributed to a significant reduction in stroke risk (absolute risk reduction 0.9%, relative risk 0.72; 95% CI 0.62-0.83). Major bleeding occurred in 2.0% of aspirin + clopidogrel patients per year and 1.3% of aspirin + placebo patients (absolute additional risk 0.7%, relative risk 1.57; 95% CI 1.29-1.92).

Genetic information was available for 1,156 of the 7,445 patients in the ACTIVE-A study. The results of this analysis were also reported at the ESC 2010 congress and published in the same *New England Journal of Medicine* article as the CURE genetic results.[5,6]

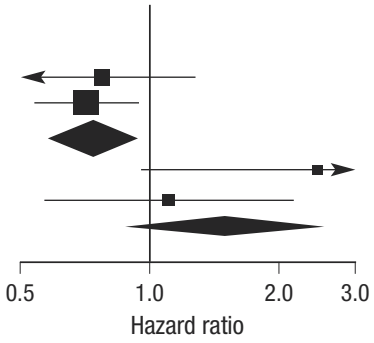
For the genetic analysis, the same definitions were used to classify the patients into subgroups. The proportion of patients in the ACTIVE-A genetic analysis who were classified as poor metabolizers was 1.9%; 16.3% were intermediate metabolizers, 38.3% were extensive metabolizers, 37.2% were ultra metabolizers and 6.3% unknown metabolizers.

FIGURE 4. **Hazard Ratios for ACTIVE-A Primary Endpoint and Bleeding by Loss- or Gain-of-function Status[5,6]**

4A. Loss-of-function Carrier Status

Outcome	Carrier status	Aspirin + Pbo event rate	Aspirin + Clop. event rate	Hazard ratio (95% CI)
First primary composite	Carriers	25.0% (35/140)	20.9% (29/139)	0.78 (0.48-1.28)
	Noncarriers	26.9% (118/438)	19.9% (84/422)	0.72 (0.54-0.95)
	Total	**26.5% (153/578)**	**20.1% (113/561)**	**0.74 (0.58-0.94)**
Major bleed	Carriers	4.3% (6/140)	10.1% (14/139)	2.48 (0.95-6.47)
	Noncarriers	3.9% (17/438)	4.3% (18/422)	1.10 (0.56-2.13)
	Total	**4.0% (23/578)**	**5.7% (32/561)**	**1.49 (0.88-2.55)**

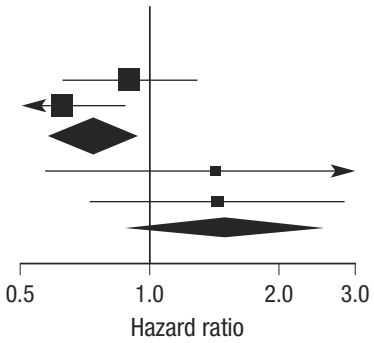
No heterogeneity for the primary ($p = 0.73$) or safety ($p = 0.16$) endpoints.



4B. Gain-of-function Carrier Status

Outcome	Carrier status	Aspirin + Pbo event rate	Aspirin + Clop. event rate	Hazard ratio (95% CI)
First primary composite	Carriers	25.8% (61/236)	21.8% (57/261)	0.90 (0.62-1.29)
	Noncarriers	27.2% (93/342)	18.4% (56/305)	0.63 (0.45-0.88)
	Total	**26.6% (154/578)**	**20.0% (113/566)**	**0.74 (0.58-0.94)**
Major bleed	Carriers	3.4% (8/236)	4.6% (12/261)	1.41 (0.57-3.46)
	Noncarriers	4.4% (15/342)	6.6% (20/305)	1.44 (0.73-2.82)
	Total	**4.0% (23/578)**	**5.7% (32/566)**	**1.49 (0.88-2.55)**

No heterogeneity for the primary ($p = 0.17$) or safety ($p = 0.96$) endpoints.



There were no differences in the ACTIVE-A primary outcome or bleeding rates by loss-of-function or gain-of-function subgroup analysis. Likewise, the loss-of-function and gain-of-function analyses did not reveal any significant differences in efficacy or bleeding (Figure 4).

As in the CURE study, the reason there was minimal effect of the genetic CYP2C19 variants on clopidogrel's efficacy in ACTIVE-A is likely due to the patient group studied. These were medically managed patients with AF; we can postulate that the absence of vascular interventions led to less platelet activation and the minor variance attributable to the loss-of-function alleles was not sufficient to affect the overall efficacy of clopidogrel in this population.

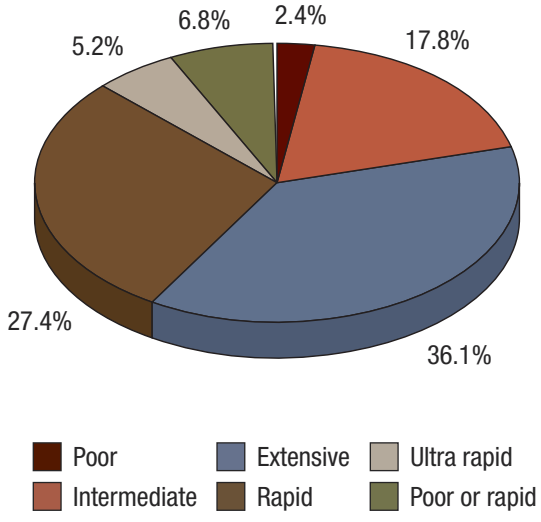
Effect of Genetic Variants on Outcomes in the PLATO trial

The Platelet Inhibition and Patient Outcomes (PLATO) trial[8] investigated a group of patients that was substantially different from those of the above-mentioned studies. The PLATO investigators enrolled 18,624 patients hospitalized for ACS, with or without ST-segment elevation. They were randomized to aspirin + clopidogrel (300- to 600-mg loading dose, then 75 mg daily) or aspirin + ticagrelor (180-mg loading dose, then 90 mg twice daily). Of note, 72.0% of the cohort (13,408 patients) had a planned invasive strategy as part of their post-ACS management.

There were no differences in the ACTIVE-A primary outcome or bleeding rates by loss-of-function or gain-of function subgroup analysis.

For the primary composite endpoint (death from vascular causes, MI or stroke), the investigators re-

FIGURE 5. **Distribution of Metabolizer Phenotypes in the PLATO Genetic Study[9,10]**



ported an 11.7% event rate for clopidogrel and a 9.8% event rate for ticagrelor (absolute reduction 1.9%, HR 0.84; 95% CI 0.77-0.92). There were no significant differences in the overall rates of major bleeding, but there was an excess risk of major non-CABG bleeding with ticagrelor compared to clopidogrel (absolute added risk 0.7%, HR 1.19; 95% CI 1.02 to 1.38).

The results of [the PLATO] study support the hypothesis that there is greater benefit to be gained from more potent antiplatelet therapy in the acute period following percutaneous intervention.

At the 2010 ESC congress, the results of the PLATO genetic study were presented[9] (and concurrently published in the *Lancet*[10]). Genetic data were available for 10,285 of the 18,624 patients. The classification system used to describe the metabolizer phenotypes was different from that used in the CURE and ACTIVE-A analyses: the PLATO investigators identified six distinct genetic groups by clopidogrel-metabolizer status: poor, intermediate, extensive, rapid, ultra rapid, and poor or rapid. The breakdown of the population into these groups is shown in Figure 5. The investigators also stratified into those patients with or without loss-of-function variants.

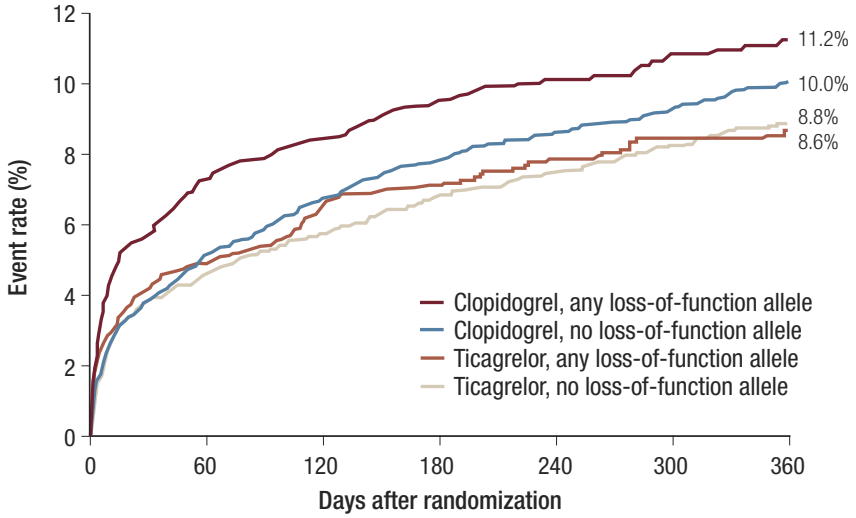
For the primary PLATO endpoint, the investigators of the genetic study found that efficacy rates were significantly better with ticagrelor than with clopidogrel among those with loss-of-function variants, but this difference was just outside of statistical significance among those without such variants (Figure 6). In the loss-of-function group, the event rates were 8.6% for ticagrelor and 11.2% for clopidogrel (absolute reduction 2.6%, HR 0.77; 95% CI 0.60-0.99), while the event rates in those without loss-of-function variants were 8.8% for ticagrelor and 10.0% for clopidogrel (absolute difference 1.2%, HR 0.86; 95% CI 0.74 to 1.01).

With respect to bleeding, interaction between treatment and genotype groups was not significant for any type of major bleeding in the PLATO genetic study.

The investigators also noted that the differences between ticagrelor and clopidogrel were seen entirely within the first 30 days following the index event. After this time, loss-of-function variants were not associated with different outcomes compared with the non carriers in terms of ischemic events or bleeding.

The results of this study support the hypothesis that there is greater benefit to be gained from more potent antiplatelet therapy in the acute period following percutaneous intervention. A large proportion of patients in PLATO underwent planned invasive management, which sets this trial population apart from the largely medically managed patients in CURE and ACTIVE-A. Once the acute period has passed, however, there does not appear to be any residual additional efficacy associated with the more potent agent, ticagrelor, compared to clopidogrel.

FIGURE 6. **Cumulative Incidence of Primary Outcome Events in the PLATO Genetic Study, by Presence or Absence of Loss-of-function Variants[9,10]**



Number at risk							
Clopidogrel							
Any loss-of-function allele	1388	1275	1259	1226	1027	801	658
No loss-of-function allele	3516	3321	3256	3186	2691	2123	1757
Ticagrelor							
Any loss-of-function allele	1384	1305	1274	1250	1053	834	683
No loss-of-function allele	3554	3352	3301	3222	2718	2127	1761

Further Discussion: CURRENT-OASIS 7 and GRAVITAS

Subsequent to the 2010 ESC Congress, the main results of the CURRENT-OASIS 7 trial were published in the *New England Journal of Medicine*,[11] while a PCI sub-study of this trial was published in the *Lancet*.[12] In the main study, 25,086 individuals with ACS and intended early PCI were randomly assigned to double-dose vs. standard-dose clopidogrel, and high-dose vs. low-dose aspirin. The PCI sub-study included only those who underwent PCI (n = 17,263).

In the main study, the use of double-dose clopidogrel did not result in a reduction of ischemic events, whereas in the PCI substudy, a significant benefit was observed with double-dose clopidogrel. This is consistent with the hypothesis that PCI produces activated platelets that require increased potency of platelet inhibition.

In the future, it may be possible to tailor antiplatelet therapy to individual responsiveness. The ongoing Gauging Responsiveness with A VerifyNow Assay–Impact on Thrombosis And Safety (GRAVITAS) trial[13] will screen PCI patients to identify those who have a reduced response to clopidogrel (based on platelet activity). These patients will be randomized to standard or double-dose clopidogrel and followed for six months.

> In the future, it may be possible to tailor antiplatelet therapy to individual responsiveness.

This broader approach—stratifying patients by antiplatelet resistance by any mechanism—may be

more practical than relying on genetic testing to identify those who may be less likely to respond (*i.e.*, a phenotypic approach as opposed to a genotypic approach).

Conclusions

In the context of antiplatelet management outside of the acute PCI period, genetic polymorphisms do not appear to dictate a need to deviate from current practice. The genetic substudies of CURE and ACTIVE-A indicate that clopidogrel's efficacy is not markedly affected by the presence of genetic loss-of-function variants. Although newer P2Y12 receptor antagonists, prasugrel and ticagrelor, have demonstrated long-term benefit in reduction of ischemic events over clopidogrel, genetic variation does not appear to be the mechanism of this effect beyond the acute post-PCI period.

One should note, however, that these more potent antiplatelet agents also carry a higher risk of bleeding than clopidogrel. As such long-term therapeutic strategies should take into account the net clinical benefit of the antiplatelet agent employed.

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