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The variability in response to thienopyridines (clopidogrel, Plavix® and prasugrel, Efient®): the clinical significance of a pharmacogenetic study

Clopidogrel (Plavix®), combined with aspirin, is the thienopyridine of choice in the prevention of ACS (acute coronary syndrome) and within the scope of coronary interventions. Thienopyridine is a second-line agent (in contrast to ticlopidine, which at present demonstrates more side-effects).
Numerous publications highlight the lack of a biological response (platelet inhibition is limited or absent) and/or a lack of a clinical response (recurrence of ACS and stent thrombosis) with conventional doses (300 mg loading dose then 75 mg/day maintenance dose). The measured values for poor responders are, on average, 30%. Prasugrel (Efient®) (the most recently developed agent) has the same mechanism of action as clopidogrel, but its degree of platelet inhibition is greater.

Pharmacodynamics and pharmacokinetics of thienopyridines

Clopidogrel is a prodrug that is transformed in the liver to the-Platelet renewal accelerated active metabolite (thiol derivative of clopidogrel) by the enzyme CYP2C19. This metabolite irreversibly inhibits the binding of the pro-platelet agent ADP to its platelet receptor P2Y12.

Variability in response to thienopyridines ascribable to non-genetic factors (figure 1):

- **BMI,**
- **Clinical setting:** the acute character of angioplasty, the complexity and spread of coronary lesions,
- **The type of stent,**
- **The existence of a comorbidity** (notably diabetes, LVEF ‹ 40%),
- **drugs likely to inhibit or potentiate the hepatic metabolism of clopidogrel** (notably statins, calcium antagonists and proton pump inhibitors antacids),
- **The number of "young" circulating platelets** (known as reticulated platelets) and platelet turn-over: these platelets demonstrate an increased response to ADP and can therefore vary the response intensity to clopidogrel.

The variability in response to thienopyridines ascribable to genetic factors (figure 1):

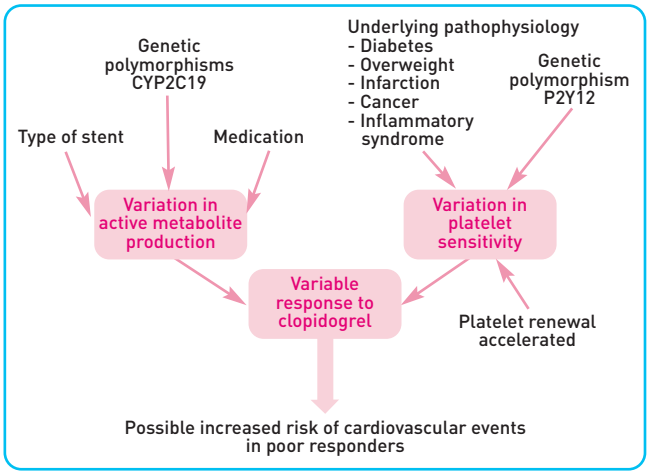

Figure 1: genetic and environmental factors involved in the variability of clopidogrel response

- **CYP2C19 polymorphisms** (15% of the variability of allele 2): allele *1 corresponds to the reference allele, *1*1 patients known as "rapid metabolisers". Several mutated alleles have been described: allele *2 and allele *3, which are responsible for a decrease in enzyme function and thus a decrease in active clopidogrel production in carrier patients. Heterozygous *1*2 and *1*3 subjects are intermediate metabolisers, *2*2, *2*3 and *3*3 subjects are described as slow metabolisers. These mutated profiles are characterised by a decrease in platelet aggregation inhibition in comparison to *1*1 subjects and therefore evoke an increased risk of repeat ACS and stent thrombosis.

  Contrarily, another polymorphism has been described as being associated with an increase in platelet inhibition through an increase in the synthesis of the active metabolite: it is allele *17, which is responsible for a hyper-response to clopidogrel and therefore could potentially result in an increased risk of haemorrhages (ultra-rapid metabolisers). The distribution of these alleles varies depending on the ethnic group (Table 1).

Type	Nomenclature	Allelic Frequency	Frequency of carriers with at least one copy of the mutated allele
Loss of function			
	*2	15%	28%
	*3	< 1%	-
	*4	1%	2%
	*5	< 1%	-
	*6	< 1%	-
Gain of function			
	*17	23%	41%

Table 1: CYP2C19 allelic distribution in the Caucasian population.

- **T744C polymorphisms of P2RY12** (target receptor for thienopyridines): the haplotype H1 (T744) is the reference haplotype, with normal P2RY12 functioning. The haplotype H2 (C744) however, demonstrates a gain in platelet function and thus leads to a decrease in clopidogrel response. According to the publications, the impact of this polymorphism remains uncertain.

Action to be taken and dose adjustments for clopidogrel in function to both genetic and non-genetic criteria

The identification of genetic and clinical criteria (clinicogenomic approach) allows patients with a high-risk of stent thrombosis in cases of angioplasty to be identified (for certain patients, the identified risk is 8 times greater) (ONAS-SIST register: individual predictive approach).

The therapeutic possibilities are as follows **(figure 2)**:

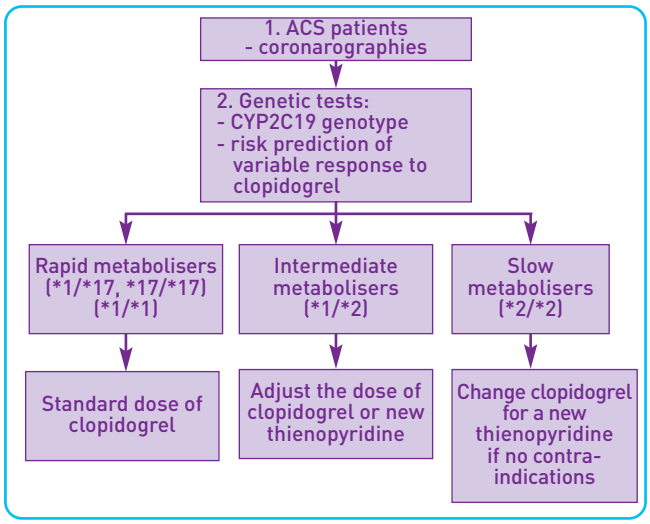

Figure 2: action to be taken depending on the CYP2C19 variant

- **adjusting the dose with an increase in the dose:** change to 600 or even 900 mg for the clopidogrel loading dose, followed by 150 mg for the maintenance dose. This increase in dose is statistically efficient in intermediate-metaboliser patients but ineffective in slow metabolisers (full resistance).
- change of molecule and switch to thienopyridine

prasugrel (Efient®): prasugrel presents the same mecha nism of action as clopidogrel, however, its degree of platelet inhibition is more significant. Its efficacy is therefore greater in cases of a non-response to clopidogrel. The same can be said for slow-metaboliser homozygous or compound heterozygous genotypes. However, prasugrel must be used with care due to the greater risk of haemorrhagic risk than with clopidogrel, notably for subjects aged over 75 and weighing less than 60 kg. As such, in cases of allele *17, the haemorrhagic risk increases with the administration of presugrel **(figure 3)**.

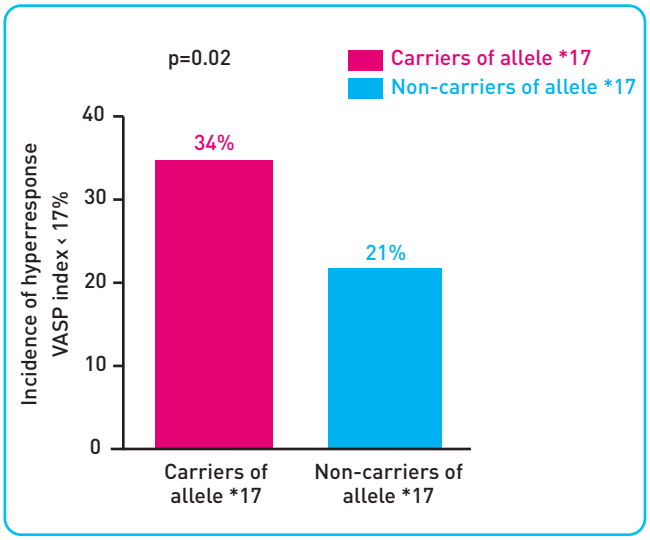

Figure 3: response to prasugrel depending on the CYP2C19*17 variant (hyper-response defined by a VASP test < 17%)

Please note

Numerous articles demonstrate the link between the biological resistance to thienopyridines and the onset of clinical events. The identification of CYP2C19 polymorphisms enables the doses of clopidogrel to be adapted in order to optimise the degree of platelet inhibition. In cases of therapeutic failure, the investigation can guide the use of anti-platelet treatments, notably to predict the haemorrhagic risk should prasugrel be used.

Bibliography

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