

# Anti-platelet drugs, pharmacogenomics and stent thrombosis: What's new?

## A current perspective on the prevention of stent thrombosis

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### INTRODUCTION

Stent thrombosis is a catastrophic complication of percutaneous coronary intervention (PCI) and is associated with a mortality of between 25 to 40%. Various trials report the frequency of stent thrombosis as (0.8-2%),<sup>(1,2)</sup> Most evaluations however come from registries that are likely to underestimate the real prevalence.<sup>(3)</sup> The perception that stent thrombosis is very low in all patients has resulted in a lack of adherence to professional guidelines.<sup>(4)</sup> New data to identify patients at increased risk for stent thrombosis are emerging. The COURAGE and FAME trials should have tempered over-exuberant PCI, and hopefully now the interventionalists will also be proactive in seeking out the patient at higher risk for stent thrombosis. Numerous risk factors for stent thrombosis have been established (Table 1).<sup>(5,6)</sup>

**TABLE 1:** Established risk factors for stent thrombosis

Treatment discontinuation	Stent malpositioning
Active smoking	Poor stent apposition
Diabetes	Recent MI
Bifurcations	Cancer
Small arteries	Renal failure
Low TIMI flow	Heart failure
Increased stent length	Chronic inflammatory diseases
Stent type	Polymer type

### ABSTRACT

**Stent thrombosis is a catastrophic complication of percutaneous coronary intervention (PCI) and is associated with a mortality of 25 to 40%. The perception that stent thrombosis is very low in all patients has resulted in a lack of adherence to professional guidelines. New data to identify patients at increased risk for stent thrombosis are emerging. Clopidogrel is a prodrug and the activation of clopidogrel is dependent on CYP2C19. Numerous alleles of CYP2C19 exist. The allele CYP2C19\*2 has been associated with a marked decrease in platelet responsiveness to clopidogrel. Heterozygote carriers of the CYP2C19\*2 have a 2.7 fold increased risk and homozygotes a 4.8 fold increased risk of stent thrombosis. Prospective randomised clinical trials will be necessary to determine the efficacy of CYP2C19 genotype-directed therapy in evidence-based clinical decision making. Point-of-care platelet-function tests are becoming available and some centres are now performing such tests on their PCI patients. The most recent AHA/ACC/SCAI guidelines recommend testing for clopidogrel responsiveness in patients at high risk of sub acute stent thrombosis and recommend increasing the dose of clopidogrel in non-responders. SAHeart 2010; 7:150-153**

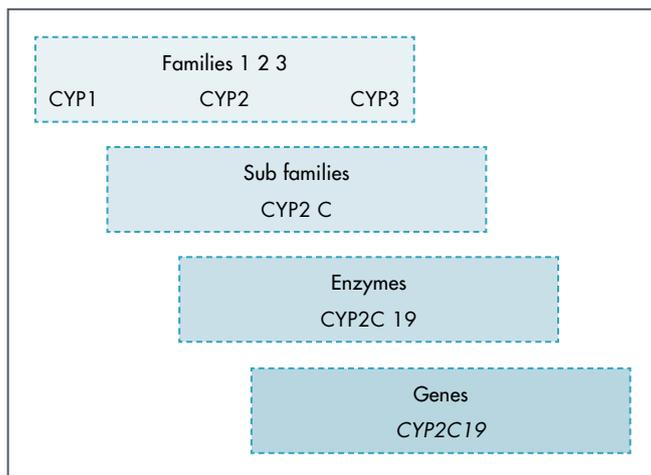
Treatment discontinuation remains the single most important and potentially preventable risk factor for stent thrombosis.<sup>(7)</sup>

### NEW RISK FACTORS FOR STENT THROMBOSIS

In order to appreciate the effects of variant alleles of the cytochrome P-450 system, the pharmacokinetics and pharmacogenetics of clopidogrel are reviewed.

#### Clopidogrel pharmacokinetics and the P-450 enzyme system

Most drugs are dependent on the cytochrome P-450 enzymes for their metabolism and elimination and many require bioactivation to form the active compound. Figure 1 summarises the nomenclature of the cytochrome P-450 system.

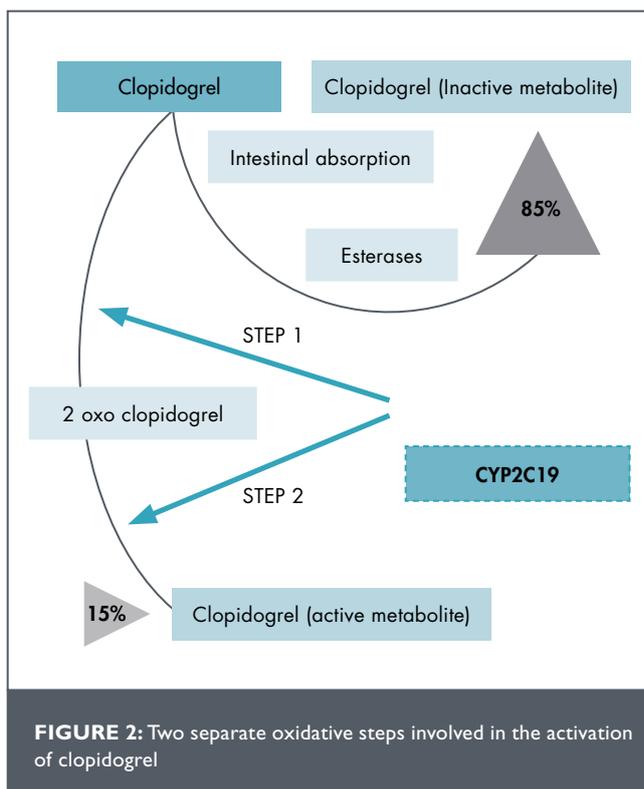


**FIGURE 1:** Nomenclature of the cytochrome P-450 Enzyme System (CYP). CYP-450 enzymes are designated with the abbreviation (CYP), followed by an Arabic numeral indicating the family, a capital letter indicating the subfamily and another numeral for the individual enzyme. The convention is to italicise the name when referring to the gene. For example, *CYP2C19* is the gene that encodes the enzyme CYP2C19.

A simplified diagram of some CYP-450 enzymes relevant to cardiologists is reviewed in Table 2.

Three of the many enzymes evolved in drug metabolism are highlighted. CYP2C19 is important in the elimination of proton pump inhibitors (PPIs) and statins but activates the prodrug clopidogrel. CYP3A4/5 metabolises many drugs. CYP3A4/5 is inhibited by grapefruit juice which would result in slower elimination of affected drugs. CYP2C9 is important in warfarin metabolism and elimination.

Clopidogrel is a prodrug. After absorption 85% is converted into an inactive form by esterases. Only 15% is then available for conversion to its active metabolite. This conversion process is complex and involves numerous enzymes. CYP2C19 in particular is required at two separate oxidative steps (Figure 2).



**FIGURE 2:** Two separate oxidative steps involved in the activation of clopidogrel

Eighty-five percent of absorbed clopidogrel is converted into an inactive form by esterases. Only 15% is then available for conversion to its active metabolite. Clopidogrel activation is dependent on CYP2C19 as it is involved in both of the hepatic oxidative steps.

**Basic pharmacogenetics of clopidogrel**

Numerous alleles of *CYP2C19* exist. The allele *CYP2CP\*2* has been associated with a loss of function which results in a marked decrease in platelet responsiveness to clopidogrel.<sup>(8)</sup> The presence of genetically poorly functioning *CYP2C19\*2* has been shown to effect clopidogrel activation, especially when it is present in the homozygous state (*CYP2C19\*2/\*2*).<sup>(9)</sup>

The FAST-MI study demonstrated an association between stent thrombosis and *CYP2C19\*/\**. The TRITON TIMI 38 study demonstrated an association between stent thrombosis *CYP2C19\** and *CYP2C19\*/\**.<sup>(10,11)</sup>

A recent collaborative meta-analysis involving 9 studies presented at the American Heart Association in November 2009 by Mega, revealed that heterozygote carriers of the *CYP2C19\*2*, had a 2.7-fold increased risk and homozygotes a 4.8-fold increased risk of stent thrombosis. In this meta-analysis, 26% of the population were heterozygous carriers of the variant allele and 2% were homozygous carriers.

TABLE 2: CYP-450 enzymes relevant to cardiologists	
CYP2C19	<p><b>Activates:</b> Clopidogrel</p> <p><b>Metabolises:</b> PPIs, statins</p>
CYP3A4/5	<p><b>Metabolises many drugs:</b></p> <p>Lipid soluble statins, calcium channel blockers, Amiodarone, PPIs, sildenafil, macrolides</p>
CYP2C9	<p><b>Metabolises:</b> Warfarin</p>

Prasugrel (a third generation thienopyridine) does not have the same reliance on CYP2C19 as clopidogrel. In a predefined subgroup analysis of the TRITON-TIMI 38, clinical outcomes of patients on prasugrel were not affected by CYP2C19 polymorphisms. In particular, there was less stent thrombosis. Prasugrel recently received FDA approval based on results of the TRITON-TIMI 38 study.<sup>(12)</sup> These benefits were, in part, offset by a higher risk of bleeding in prasugrel-treated patients. However an increased bleeding risk did not occur if certain groups were excluded. This subgroup analysis included patients with a history of stroke, age >75 years and those with a body weight of less than 60 kg.

Ticagrelor is a reversible oral P2Y12 receptor antagonist in a new chemical class of anti-platelet agents termed cyclopentyl-triazolopyrimidines that does not require metabolic conversion to an active form. The PLATO trial demonstrated that ticagrelor achieved a statistically significant reduction in the primary efficacy endpoint (cardiovascular death, myocardial infarction or stroke) compared to clopidogrel.<sup>(13)</sup>

Prasugrel and ticagrelor are not yet available in South Africa. This poses the question if we should be testing for CYP2C19\* in patients on clopidogrel then. Prospective randomised clinical trials will be necessary to determine the efficacy of CYP2C19 genotype-directed therapy in evidence-based clinical decision-making. Rapid genetic testing for the CYP2C19\*2 variant is not available but is being developed.

**Drug interactions**

PPIs are metabolised by CYP2C19 and may therefore compete for CYP2C19 when used in conjunction with clopidogrel.

There have been numerous observational studies which suggest that the clopidogrel and PPI interaction can lead to adverse cardiovascular outcomes<sup>(14)</sup> (Figure 3). Omeprazole, in particular, has been incriminated while pantoprazole has reputedly less interaction with PPIs.<sup>(15)</sup> In the subgroup analyses of the CREDO and TRITON trials<sup>(16,17)</sup> no interaction was found. Preliminary analysis of data from the COGENT trial, a trial dedicated to specifically examining clopidogrel with a PPI vs placebo, failed to suggest a negative interaction. There is therefore conflicting evidence, but as some concern still exists prescribers should avoid the use of PPIs if possible. On November 17, 2009, the FDA updated the clopidogrel label with new warnings on omeprazole and other drugs that inhibit the CYP2C19 enzyme that could interact with clopidogrel.

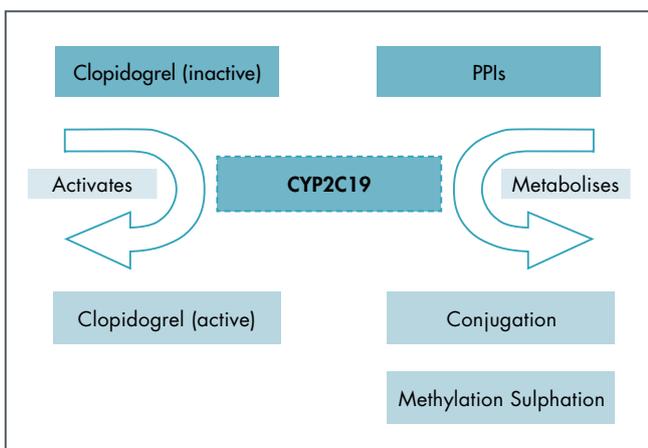
**High on-treatment platelet reactivity**

There are consistent data that patients who have persistently increased platelet reactivity despite clopidogrel therapy have an increased risk of ischaemic events. Recent findings have shown that a considerable number of patients who are resistant to clopidogrel may also be resistant to aspirin, which further increase their risk of stent thrombosis.<sup>(18)</sup>

Should we be measuring platelet function in patients who are taking clopidogrel after stent implantation? Should the dose of clopidogrel be increased in patients resistant to standard doses? It is interesting that the recently presented CURRENT OASIS-7 study (presented at the European Society of Cardiology 2009) revealed that a loading dose of 600mg together with a higher maintenance dose of clopidogrel (150mg for one week after PCI) was associated with less stent thrombosis. There was no increased risk of bleeding when the TIMI major bleeding criteria were used. There was however a small increased risk of red cell transfusion.

Point-of-care platelet-function tests are becoming available and some centres are now performing such tests on their PCI patients. Unfortunately, there is no evidence that modifying the treatment of a hypo-responsive patient improves outcomes. Numerous trials are being conducted in this regard:

- GRAVITAS (Gauging Responsiveness with a Verify Now Assay-Impact on Thrombosis and Safety) trial, randomising patients deemed non-responsive to clopidogrel on point-of-care testing to receive higher dosing of clopidogrel.<sup>(19)</sup>



**FIGURE 3:** PPIs are metabolised by CYP2C19. CYP2C19 also activates clopidogrel. The theoretical potential for an adverse interaction exists when the drugs are used together.

- TRIGGER PCI is assessing the efficacy of prasugrel versus clopidogrel for the reduction of adverse cardiovascular outcomes in drug-eluting stent (DES) patients with high platelet reactivity on clopidogrel, using the Verify Now test.
- ARCTIC double randomisation of a monitoring adjusted anti-platelet treatment versus a common anti-platelet treatment for DES-implantation and interruption versus continuation of double anti-platelet therapy.

## CONCLUSION

The most recent AHA/ACC/SCAI guidelines recommend testing for clopidogrel responsiveness in patients at high risk of sub-acute stent thrombosis and recommend increasing the dose of clopidogrel in non-responders. The United Kingdom's National Institute for Health and Clinical Excellence (NICE) has issued its provisional guidance on the use of prasugrel. The guidelines include patients undergoing primary PCI for ST-segment elevation MI, subsequent to stent thrombosis having occurred on clopidogrel treatment and in patients with diabetes mellitus.<sup>(20)</sup>

In France prasugrel is not available but compassionate usage has been increasing (Montalescot - personal communication).

Prasugrel and ticagrelor are not yet available in South Africa, so what should we do?

- A conservative approach would be to initially accept the results of the CURRENT OASIS-7 study and double the loading dose of clopidogrel to 600mg and increase the maintenance dose of clopidogrel to 150mg for one week, while waiting for the results of the randomised trials.
- A more proactive approach would be to measure platelet function and increase the dose of clopidogrel in non-responders and if there is no improvement in response, consider obtaining compassionate use of prasugrel.

It should be emphasised however, that when stent thrombosis has occurred on clopidogrel treatment, serious consideration should be given to changing treatment to prasugrel.

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