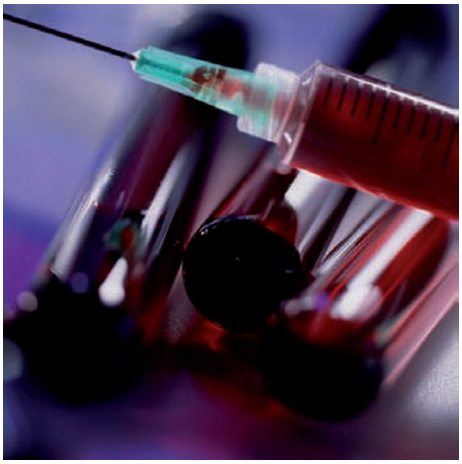
CARDIOVASCULAR DRUGS

A determinant of clopidogrel efficacy



The antiplatelet drug clopidogrel (Plavix; Sanofi-Aventis/Bristol-Myers Squibb) — which is a purinergic P2Y12 receptor antagonist — is widely used for the management of clot-related cardiovascular events. However, there is high inter-individual variability in the antiplatelet response to the drug. Now, writing in *Nature Medicine*, Bouman and colleagues identify paraoxonase 1 (PON1) as a key enzyme involved in the variable clinical efficacy of clopidogrel.

As most of the variability in the platelet response to clopidogrel is thought to be due to variations in plasma concentrations of the active thiol metabolite of the drug, the authors postulated that genetic variants of drug-metabolizing enzymes would affect the efficacy of clopidogrel. Using a microsomal expression system composed of metabolizing enzymes, they showed that the rate-limiting step in the bioactivation of clopidogrel is the hydrolysis of 2-oxo-clopidogrel (which is formed by the oxidation of clopidogrel) to the active thiol metabolite, and demonstrated that the esterase PON1 is the key enzyme in this reaction.

Out of the two common coding polymorphisms of the *PON1* gene, Q192R and L55M, the Q192R polymorphism was expected to affect substrate affinity. Subsequently, the authors tested the clinical relevance of the *PON1* Q192R genotype in a case–cohort study of individuals with coronary artery disease who underwent stent implantation and received clopidogrel therapy for 6–12 months. The authors compared 41 incident cases of patients with non-fatal stent thrombosis, and 71 randomly selected subjects without stent thrombosis, out of a total of 7,719 eligible subjects.

Individuals who were *PON1* QQ192 homozygous had a considerably higher risk of stent thrombosis, lower PON1 activity in the plasma, lower plasma concentrations of the active metabolite and lower platelet inhibition compared with individuals who were RR192 homozygous. Indeed, the *PON1* Q192R genotype was the only significant factor that was independently associated with the occurrence of stent thrombosis in statistical analysis. A replication study in a prospective cohort of 1,982 individuals with acute coronary syndromes confirmed the findings of the case–cohort study.

This paper indicates that the *PON1* Q192R gene variant is a major determinant of the platelet response to clopidogrel. Although large randomized replication studies are needed to confirm these results, these findings suggest that *PON1* genotyping or measuring PON1 activity in the plasma could provide prognostic information on the clinical efficacy of clopidogrel.

Charlotte Harrison

ORIGINAL RESEARCH PAPER Bourman, H. J. *et al.* Paraoxonase-1 is a major determinant of clopidogrel efficacy. *Nature Med.* **17**, 110–116 (2011)