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Antiplatelet treatment has a pivotal role in modern management of coronary artery disease, and use of clopidogrel has facilitated the emergence of intravascular stenting as common cardiological practice. However, clopidogrel responsiveness is heterogeneous within the population, with a sizeable proportion seemingly unresponsive to its antiplatelet effects and at higher risk of cardiovascular events as a result.1 2

Clopidogrel is a pro-drug that is metabolised by cytochrome P450 (CYP) enzymes (including the 3A4 and 2C19 isoforms) to an active thiol metabolite that antagonises the platelet adenosine diphosphate (ADP) receptor P2Y12. Carriers of loss-of-function polymorphisms in the genes coding for CYP2C19 have lower levels of the active metabolite, reduced clopidogrel-induced platelet inhibition and are at increased risk of cardiovascular events and stent thrombosis, compared with non-carriers.3 Drugs that inhibit hepatic CYP450 enzymes might be expected to reduce clopidogrel activation in a similar way with similar adverse clinical results. Calcium-channel blockers (CCBs) are frequently used in patients with cardiovascular disease; both non-dihydropyridine and dihydropyridine CCBs are metabolised by, and inhibit, the 3A4 isoform of CYP450 and have potential for interaction with other drugs in this way.4

In this issue of Heart, Gremmel and colleagues describe a prospective observational study of the influence of CCBs on clopidogrel-mediated ADP-inducible platelet inhibition assessed by light transmission aggregometry and the VerifyNow P2Y12 assay in 162 patients who underwent percutaneous intervention (peripheral, coronary or carotid) and stent implantation (see page 186).5 All patients received aspirin and clopidogrel (with loading doses for those not already taking it). Measured at 24 h, patients taking CCBs (mainly dihydropyridines) had higher on-treatment platelet reactivity than those not taking CCBs. High residual platelet reactivity (defined as assays in the top quartile) was more common in those taking CCBs than in those who were not.

We are aware of only one previous study to have directly dealt with this topic. In a prospective study of 200 patients with coronary artery disease undergoing percutaneous coronary intervention, clopidogrel responsiveness was tested using the vasodilator-stimulated phosphoprotein assay and aggregometry.6 Among participants receiving CCB treatment, the platelet reactivity index and ADP-induced platelet aggregation were both higher, and decreased platelet inhibition was significantly more common, than among the remainder. At 2 years, the cumulative occurrence of a composite clinical outcome (cardiovascular death, non-fatal myocardial infarction, stent thrombosis, percutaneous revascularisation or coronary artery bypass grafting) was more common in those receiving CCBs. Ex vivo incubation with various CCBs did not alter platelet function of patients taking clopidogrel, suggesting that CCBs do not exert a direct inhibitory effect.

The clinical significance of the findings of both studies is unclear. Both were observational and, therefore, subject to the limitations associated with such study design. Tests of platelet function may have been influenced by significant differences in baseline characteristics (CCB-treated patients in both studies were more likely to be hypertensive and to have diabetes). Although multivariate analysis was used to adjust for such differences, it remains possible that residual statistical confounding may have affected the results. In the earlier study, those receiving CCBs were likely to have had worse cardiovascular disease and to be at greater risk of future events and this may, at least in part, explain the worse clinical outcomes; furthermore, the observed excess of cardiovascular events was driven by greater numbers of revascularisation procedures that would not necessarily be expected to be affected by platelet activity.

The broader clinical significance of ex vivo tests of platelet function remains to be determined and is the subject of debate. Although non-responsiveness to clopidogrel measured using ex vivo techniques is associated with adverse clinical cardiovascular outcomes,2 7 the role of platelets in thrombosis is complex and in vitro tests on isolated platelets measure only parts of this process. The heterogeneity of in vitro techniques for assessing platelet function, the inherent limitations and lack of standardisation of these techniques and wide interindividual variation in platelet reactivity have led some to question the physiological value of such tests in the identification of clinical (in vivo) clopidogrel “resistance”, or indeed whether any such a phenomenon really occurs.8 9

This is highlighted by conflicting experience with statins and proton pump inhibitors (PPIs). Certain statins are metabolised by CYP3A4, and atorvastatin has been shown to reduce metabolism of clopidogrel to its active metabolite10 and, in some studies, to attenuate ex vivo clopidogrel-induced inhibition of platelet aggregation.11 Despite this, however, large cohort studies have failed to observe any increased risk of adverse clinical outcomes in patients taking both drugs.12 PPIs exhibit varying degrees of competitive inhibition of CYP2C19 and ex vivo studies have demonstrated that they reduce the platelet inhibitory effects of clopidogrel.13 Unlike statins, some observational studies have shown that PPIs (particularly omeprazole) are associated with increased risk of cardiovascular events in patients also taking clopidogrel,14 leading to recent advice from the Medicines and Healthcare products Regulatory Agency that concomitant use should be avoided unless considered essential. This has not been replicated in other observational studies,15 however, nor in the recently presented (albeit preliminary) results of the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) study, a randomised placebo-controlled trial of omeprazole in patients receiving clopidogrel and aspirin in which omeprazole use was not associated with an increase in cardiovascular events.16

In conclusion, the observation of reduced ex vivo clopidogrel-induced platelet inhibition in patients taking both CCBs and clopidogrel is of interest and
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consistent with a mechanistically plausible interaction between these commonly used drugs. However, past experience with other drugs potentially interacting via the same CYP450 mechanism, as well as substantial uncertainty about the clinical significance of ex vivo assessments of platelet function, suggests that we should be cautious in our interpretation of the findings. Further prospective studies, ideally randomised, are required to further explore whether this is a clinically meaningful interaction in vivo. In the meantime, there is insufficient evidence to support a change in practice.

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Competing interests NC has received honoraria from Pfizer, manufacturer of the calcium-channel blocker, amlodipine.

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