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Amlodipine – Not a Significant Contributor to Clopidogrel Non-Response?

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The current study by Li *et al*¹ examines the pharmacodynamic interaction of amlodipine and clopidogrel. Dual antiplatelet therapy with aspirin and clopidogrel is standard of care for patients with coronary stenting and acute coronary syndromes, although newer, more potent P2Y₁₂ inhibitors such as prasugrel and ticagrelor have recently become available. Clopidogrel is a prodrug that is metabolised in a two-step process by cytochrome P450 (CYP) and esterases to its principal metabolites (figure 1).² Large interpatient variability has been observed in pharmacodynamic studies of clopidogrel response and pharmacokinetic studies measuring active clopidogrel thiol metabolites. Among the CYP450 isoforms, CYP2C19, CYP3A4, CYP2C9 and CYP2B6 have been identified as being involved in the second step of 2-oxo clopidogrel metabolism and active thiol formation. A variety of esterases are thought to mediate inactivation of parent clopidogrel and metabolites, thus influencing the availability of active thiol metabolite and eventually the pharmacodynamic response to clopidogrel. The term ‘clopidogrel non-response’ has been used to describe persistent high ADP induced platelet reactivity during treatment with clopidogrel and has been defined by various ex vivo assays.

The importance of individual CYP450 enzymes in clopidogrel metabolism to its active form has been illustrated by the finding that carriers of CYP2C19*2 polymorphisms who are treated with clopidogrel after coronary stenting are at increased risk of adverse thrombotic events.³ This enzyme is vulnerable to drug-drug interactions, as are other CYP450 isoforms involved in clopidogrel metabolism. Many drugs that are commonly prescribed to patients with coronary artery disease happen to interact with these enzymes. Statins, some of which are metabolised by CYP3A4, and proton pump inhibitors, which are often metabolised by CYP2C19 have received particular attention as concerns have surfaced regarding possible clinically significant interactions associated with these drugs.⁴

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In the case of atorvastatin and simvastatin, evidence suggests a limited degree of pharmacokinetic interaction due to the presence of alternative pathways, incomplete competition for CYP3A4 metabolism and the relatively weak ability of these drugs to inhibit CYP3A or CYP2C19.⁴⁻⁶

In the case of proton-pump inhibitors (PPI), pharmacokinetic studies have shown a significant reduction of active thiol metabolite formation by concomitant therapy with omeprazole.⁷ While observational clinical studies have shown conflicting results regarding the association of PPIs with increased rates of thrombotic events, the only double-blind randomised clinical trial of clopidogrel and omeprazole Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) was halted early. Findings from the COGENT trial suggested no increase in clinical thrombotic events but conclusions are limited due to lack of long term follow-up, low power in terms of cardiovascular event rates and specific dosing formulation used.⁸

Calcium channel blockers and in particular amlodipine are among the pivotal drugs used in primary and secondary prevention of cardiovascular disease and among the most commonly co-prescribed drugs in patients with coronary artery disease. Amlodipine is metabolised by CYP3A5, CYP3A4, and CYP2B6, and these enzymes have been shown to be inactivated by amlodipine in vitro, albeit with enzymatic inhibitory coefficients (K_i) that are notably higher than those observed in plasma during clinical use.^{9,10} As estimates of clinical inhibition based on in vitro data are challenging since it is difficult to estimate the concentration of drugs at the 'effect site', which in this context is the active site of CYP450 enzymes located in the hepatic endoplasmic reticulum, clinical outcome data are important.

Several studies using observational data have demonstrated increased on-treatment platelet reactivity and higher rates of clopidogrel non-response in subjects treated with concomitant amlodipine.¹¹⁻¹⁴ Estimates suggested an OR of 2.3 (95% CI 1.4 to 3.9, $p=0.001$) for clopidogrel non-response in patients treated with amlodipine.¹² Although these observations were made in large cohorts of subjects, limited conclusions can be drawn due to the inherent bias of therapy assignment which generally includes older age and higher prevalence of other comorbidities.

The authors have to be congratulated on conducting the first randomised, open label trial examining the pharmacodynamic effects of amlodipine compared with non-calcium channel blocker standard therapy in patients with ischaemic heart disease who are treated with clopidogrel. The strengths of the current study include the real world study design allowing the use of appropriate and defined alternate treatments for blood pressure and angina control, as well as exclusion of drugs that are known to significantly affect CYP450 enzyme activity. The authors did not find a significant difference in 30 day on-treatment platelet reactivity between groups and no significant increase in clopidogrel non-response using a definition used in the GRAVITAS trial. Although results were not significantly different, the mean platelet reactivity measured by VerifyNow P2Y12 was numerically higher in subjects treated with amlodipine as compared with controls (227 ± 84 vs 214 ± 90 VNP2Y12 platelet reactivity unit (PRU), mean $\pm$ SD). This difference (12.7 PRU, 95% CI -22 to +47, $p=0.47$) is smaller than the mean difference reported by Harmsze *et al* among 623 patients treated

with clopidogrel (26.9 PRU, 95% CI 11.9 to 36.2, $p < 0.0001$).¹² The large 95% CI of the mean difference in the current study by Li *et al* implies that a potentially larger difference might be observed in a larger population. In addition, large studies are generally required to rule out small increases in cardiovascular risk associated with mild reductions in pharmacodynamic response to clopidogrel. Such small increases in risk may still be important, since, even small pharmacodynamic interactions can lead to a significant number of adverse events, if the drugs in question are prescribed commonly and in a large number of patients, which certainly is the case with clopidogrel and amlodipine. That said, the differences in platelet reactivity observed in the study by Li *et al* appear to be smaller than those in pharmacodynamic studies of omeprazole and clopidogrel for which larger clinical studies have found inconclusive evidence for higher rates of clinical adverse events.

CYP2C19*2 genotype was found to account for 3.7% of variability in VerifyNow P2Y12 platelet reactivity in 1069 subjects in the study by Bouman *et al*.¹⁵ Thus, even in the case of the clinically ascertained additional risk conferred by the CYP2C19*2 genotype, a relatively small difference in pharmacodynamic effect size can be observed. Findings from several studies have suggested that the risk of pharmacodynamic interaction may be modified and potentiated by co-occurrence of multiple factors affecting multiple metabolic pathways. Findings by Park *et al* suggested that an interaction between amlodipine and clopidogrel was only observed in subjects who were CYP3A5 non-expressers and thus lacked an alternate CYP3A metabolising pathway after inhibition of CYP3A4 by amlodipine.¹³ Bouman further illustrated the concept that small individual inhibitions to clopidogrel bioactivation could result in a larger conglomerate effect when multiple variables were taken into context.¹⁵ In the study by Harmsze *et al*, the presence of proton pump inhibitor use, calcium channel blocker use, and CYP2C19*2 carrier status had additive effects with highest platelet reactivity seen in subjects with concomitant presence of all three variables.¹⁴ In this study, concomitant use of calcium channel blocker and proton pump inhibitors was associated with a HR of 2.2 (95% CI 1.1 to 4.4, $p = 0.034$) for the occurrence of the primary composite ischaemic endpoint as compared with non-users for both drugs.¹⁴ In contrast a retrospective analysis of a large population based cohort of Danish patients treated with clopidogrel after coronary stenting showed no significant increase in risk of adverse ischaemic events in patients taking amlodipine (HR 1.06, 95% CI 0.89 to 1.25).¹⁶ Similarly, subgroup analysis of the Clopidogrel for the Reduction of Events During Observation trial showed no evidence of decreased clopidogrel efficacy with use of calcium channel blockers.¹⁷ However, clinical event rates in large cohorts of patients of Asian or African origin, who exhibit lower prevalence of CYP3A5*3 and higher prevalence of 2C19*2 genotypes, have not been examined.

In general, the interpretation of observational findings remains difficult due to the non-randomised nature of studies and likely differences in comorbidities, such as arterial hypertension.

In summary, the results of the study by Li *et al*, suggest that the pharmacokinetic interaction of amlodipine and clopidogrel, if indeed present, is associated with no or relatively small pharmacodynamic interaction and no significant reduction of clopidogrel response in Chinese patients with coronary artery disease. As such the data imply that the current

practice of concomitant therapy with clopidogrel and amlodipine should not need be revised based on the available evidence. Further prospective validation in a larger cohort of patients may be necessary to confirm these findings.

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Figure 1.
Metabolism of clopidogrel by cytochrome P450 isoenzymes and esterases.