Blockbuster interactions: are they bad for the patient?

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This editorial refers to ‘Accelerated platelet inhibition by switching from atorvastatin to a non-CYP3A4-metabolized statin in patients with high platelet reactivity (ACCEL-STATIN) study†, by Y. Park et al., on page 2151

Variability in individual responsiveness to clopidogrel has been widely acknowledged and investigated in these last few years. Clopidogrel inhibits platelet activation and aggregation by directly inhibiting the platelet P2Y12 adenosine diphosphate (ADP) receptor. It has become established that a significant proportion of patients display high platelet reactivity on clopidogrel treatment and thus are exposed to a greater risk of death, myocardial infarction, and stent thrombosis.1

One source of the variability is the hepatic metabolism of clopidogrel, which is a prodrug that requires metabolic activation to generate its active thiol metabolite.2 Specifically, clopidogrel activation requires two oxidative steps involving a variety of hepatic enzymes from the cytochrome P450 (CYP) system, the major catalyst of oxidative biotransformation reactions involved in drug metabolism.3 CYP2C19 is involved in both steps and contributes to an estimated 45% of the 2-oxo-clopidogrel and 21% of active metabolite generation.4 CYP3A4/5, another CYP isoenzyme, is also a significant contributor to clopidogrel bioactivation. Loss-of-function CYP2C19 genetic variants have been associated with reduced concentrations of active drug metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events.5 On the other hand, there is no common genetic polymorphism associated with alteration in CYP3A4 activity.

Among the non-genetic sources of variability, drug–drug interaction (DDI) is one of major concern; DDI may inhibit or induce the function of CYP isoenzymes and consequently affect the response to CYP-metabolized drugs including clopidogrel.3 Hence, CYP3A4 inhibitors and inducers are considered as important candidates to interfere with clopidogrel response (Figure 1). The antifungal agents ketoconazole anditraconazole are potent inhibitors of CYP3A4. In a study conducted in healthy subjects, ketoconazole co-administration resulted in a significant reduction in clopidogrel active metabolite formation and significantly reduced platelet inhibition.6 On the other hand, co-administration with a CYP3A4 inducer, such as rifampicin, led to an increased production of the clopidogrel active metabolite and a greater P2Y12 receptor blockade in two studies.7 Calcium channel blockers (CCBs) can also inhibit CYP3A4, and some studies have suggested a decrease in clopidogrel responsiveness after co-administration with CCBs.8

The lipophilic statins such as atorvastatin, simvastatin, and lovastatin are metabolized by CYP3A4, whereas rosuvastatin and pravastatin are not. There is no real debate on the role of CYP3A4 in clopidogrel bioactivation, but whether there is an interaction between clopidogrel and CYP3A4-metabolized statins has been more controversial. In 2003, Lau et al. first reported that atorvastatin but not pravastatin competitively inhibits clopidogrel bioactivation.9 Many studies have, however, failed to confirm a significant pharmacological interaction, but with different drug doses, timing of sampling, and measurement techniques. In post-hoc analyses of the CREDO and CHARISMA studies, there was no significant sign of an increased cardiovascular risk in patients treated with clopidogrel CYP3A4-metabolized statins as compared with those receiving non-CYP3A4-metabolized statins.10,11

Park et al. have now provided an important new piece of information.12 Whereas most of the previous studies were observational or retrospective assessments in registries, Park et al. performed a prospective randomized study where Korean patients post-percutaneous coronary intervention (PCI) with high on-treatment platelet reactivity (HPR) during clopidogrel and atorvastatin long-term co-administration were switched to a non-CYP3A4-metabolized statin, either rosuvastatin 10 mg daily or pravastatin 20 mg daily, by randomization. All other medications, especially clopidogrel (75 mg/day) and aspirin (100 mg/day), remained the same during the study period. Fifteen days later, platelet reactivity (HPR) during clopidogrel and atorvastatin long-term co-administration were switched to a non-CYP3A4-metabolized statin, either rosuvastatin 10 mg daily or pravastatin 20 mg daily, by randomization. All other medications, especially clopidogrel (75 mg/day) and aspirin (100 mg/day), remained the same during the study period. Fifteen days later, platelet function assays were performed again. First, in the 122 screened

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patients, 56 (46%) presented with a HPR as defined by 20 μM ADP-induced maximal platelet activation >50%. Secondly, switching to a non-CYP3A4-metabolized statin resulted in a significant decrease in platelet reactivity and consequently in the prevalence of HPR in these patients. Thirdly, the switching effect on platelet reactivity was similar in the rosuvastatin and pravastatin groups, suggesting a CYP3A4-related mechanism whatever the statin used.

The study suffers, however, from limitations that weaken the conclusions of the authors. Although randomized, this study does not have a control group defined by randomization. The sham group is a parallel group, possibly a historical group of patients, about whom we have little information and that may differ from the patients randomized to one or the other non-CYP3A4-metabolized statins. In the same vein, a crossover study design using CYP3A4-dependent or-independent statins would have been more appropriate. The absence of blinding is also questionable for a single-centre study with a small population and a biological primary endpoint evaluated on-site. Finally, vasodilator-stimulated phosphoprotein (VASP) was not measured and would have been a more robust endpoint to measure of clopidogrel platelet reactivity. With these limitations in mind, the authors report a significant but tiny reduction of maximal platelet aggregation after a switch to a non-CYP3A4-metabolized statin. The clinical relevance of this finding could not be assessed in this study.

The authors provide three messages that significantly add to the scientific debate.

First, this study emphasizes that DDIs are more likely to affect some specific patient subgroups rather than all patients. Expression of CYP3A4 varies 40-fold in humans, and metabolism of CYP3A4 substrates varies 10-fold in vivo. It is likely that the minority of patients with the lowest CYP3A4 capacity (or low metabolizers) at baseline will be much more susceptible to experiencing a significant CYP3A4-mediated drug interaction as compared with the majority of CYP3A4 high metabolizers. This is particularly true when considering weak inhibitors such as lipophilic statins. As opposed to potent CYP3A4 inhibitors such as antifungal drugs, the amplitude of CYP3A4 inhibition by lipophilic statins is anticipated to be much lower. By selecting patients based on their high platelet reactivity on clopidogrel and atorvastatin, it is likely that Park et al. have enriched their study population with CYP3A4 low metabolizers even if this possibility was not investigated. We cannot rule out also that these results may have been influenced by the ethnicity of the enrolled patients as CYP3A4 activity might differ according to ethnicity.

Secondly, this study indicates the current limitations of retrospective and observational studies to draw firm conclusions on the relevance of DDIs. In most cohort studies, patient compliance is rarely assessed in the long term, thus underestimating the potential for DDIs. Post-hoc analyses of randomized clinical trials cannot

Figure 1 Proposed mechanism for clopidogrel and atorvastatin interaction. The blue lines represent the usual steps for clopidogrel absorption, bioactivation, active metabolite generation, and inhibition of the ADP platelet receptor (P2Y12). The red arrows represent the putative effect observed in the case of atorvastatin co-administration.
completely adjust for differences in confounders as no randomization or stratification was done for the interacting drug. Many of the published ‘negative’ studies have not been appropriately powered to address clopidogrel–drug interaction. Alternatively, prospective interventional studies would be more appropriate to elucidate the potential of DDIs, but it is unlikely they would ever be launched.

Thirdly, as for other DDIs, this study rules out a class effect. These results rather support a clopidogrel–CYP3A4-metabolized statins interaction that can be simply overcome by switching to a non-CYP3A4-metabolized statin such as rosuvastatin or pravastatin. Similar results have been observed with proton pump inhibitors (PPIs). Based on platelet data, there is a huge amount of evidence to support the existence of a significant pharmacological interaction between clopidogrel and omeprazole, esomeprazole, and lansoprazole, but no or limited interaction has been shown with pantoprazole, again suggesting the absence of a class effect of PPIs on clopidogrel response.

In conclusion, these results support a significant but limited effect of interaction between clopidogrel and atorvastatin on platelet reactivity. The clinical relevance of this finding is not known, although previous retrospective analyses of clinical trials suggest little effect on clinical outcomes. However, all patients might not experience the same consequences of a DDI, and being able to identify those patients at risk is another challenge. Because multiple risk factors contribute to antiplatelet resistance and to the occurrence of cardiovascular events, it is intuitively possible that several DDIs (e.g. omeprazole plus atorvastatin) will lead to an additional deleterious effect, but this has not been really studied. Drug interaction is a major concern to physicians and patients, while health authorities are more and more vigilant and less prone to accept a global benefit demonstrated in a large population against a potential harmful risk identified in a limited number of patients. On the statin–clopidogrel interaction issue, we would clearly need much stronger information to change any-thing in the current recommendations and practice.

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