Interaction between statins and clopidogrel: is there anything clinically relevant?

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Summary

Since their introduction several years ago, the 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors—the statins—have been widely used for hyperlipidemia and for the primary/secondary prevention of cardiovascular diseases. They have been shown to be safe as well as efficacious in a number of different clinical trials; however, studies have suggested that they can interact with other co-administered therapies. More recently, the thienopyridines have been successfully integrated with the conventional medical treatment of coronary disease as they showed effectiveness in reducing platelet activity both in stable and unstable settings. They also improve the outcome of patients treated with percutaneous coronary intervention. The potential interaction of statins and thienopyridines is a matter of concern. Despite some preclinical data suggesting an interaction between statins metabolized by the liver cytochrome P3A4—such as atorvastatin, lovastatin and simvastatin—and clopidogrel, there is no compelling clinical evidence to stop their co-administration.

Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors or statins are widely used to treat a number of medical conditions ranging from hypercholesterolaemia to cardiovascular disease.¹ Their clinical importance is underlined both by their relative safety compared to other cholesterol lowering agents and their beneficial effects on morbidity and mortality particularly in the arena of cardiovascular diseases.¹ Recently there has been concern and controversy in literature about potential interactions between statins and the anti-platelet thienopyridine, clopidogrel. Thienopyridines which act by inhibiting the adenosine diphosphate (ADP) receptor on platelets play a pivotal role whereas platelet inhibition is beneficial particularly in patients with acute coronary syndrome (ACS) and/or treated with percutaneous coronary intervention (PCI) where they significantly reduce the incidence of adverse events.²,³ Both classes of agents are often utilized simultaneously, and any potential interaction is therefore a matter of concern. There is much conjecture about the clinical significance of this interaction and this article will examine the present literature on this subject.

Main pharmacokinetic and pharmacodynamic features of statins

Statins exert their anti-cholesterol effect by competitively inhibiting HMGCoA reductase, which is pivotal in catalyzing the rate-limiting step of cholesterol biosynthesis, by preventing substrate access to active sites of the enzyme.⁴
Overall, there are very few drug-to-drug interactions. Given a relatively specific inhibition of HMGCoA reductase, any interaction of statins with other medications at a pharmacodynamic level is unlikely. Along with structural differences (Figure 1), important pharmacokinetic differences exist among statins (Table 1).\(^5\) Statins undergo extensive first-pass metabolism in the liver with all but pravastatin being metabolized by the cytochrome 450 (CYP) group of enzymes. Different isoenzymes are responsible for the metabolism of each statin in a different extent: e.g. CYP3A4 metabolizes lovastatin, simvastatin and atorvastatin while CYP2C9 is the major isoenzyme responsible for the metabolism of fluvastatin. CYP3A4 inducers such as St Johns wort, rifampicin and troglitazone can reduce plasma statin concentrations, whilst conversely statin levels can be increased by CYP3A4 inhibitors such as calcium antagonists, cimetidine and grapefruit juice.

There is also some evidence to support a pharmacokinetic interaction between fluvastatin and warfarin leading to a potentiation of the latter’s effects by inhibition of CYP29 by fluvastatin. Both fluvastatin and the potent s-isomer of warfarin are metabolized by CYP2C9, but fluvastatin can also inhibit the enzyme’s metabolic activity, thereby increasing warfarin levels.\(^6\) The statin cerivastatin was withdrawn from the market after it was reported that co-administration with the

![Figure 1. Biochemical structure of statins.](image)

**Table 1** Pharmacokinetic profile of clinically available statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>(T_{\text{max}}) (h)</th>
<th>(C_{\text{max}}) (ng/ml)</th>
<th>Bioavailability (%)</th>
<th>Lipophilicity</th>
<th>Protein binding (%)</th>
<th>Metabolism</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>2–3</td>
<td>27–66</td>
<td>12</td>
<td>yes</td>
<td>80–90</td>
<td>CYP3A4</td>
<td>15–30</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>0.5–1</td>
<td>448</td>
<td>19–29</td>
<td>Yes</td>
<td>&gt;99</td>
<td>CYP2C9</td>
<td>0.5–2.3</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>2–4</td>
<td>10–20</td>
<td>5</td>
<td>Yes</td>
<td>&gt;95</td>
<td>CYP3A4</td>
<td>1.3–2.8</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0.9–1.6</td>
<td>45–55</td>
<td>5</td>
<td>No</td>
<td>43–55</td>
<td>Sulphation</td>
<td>1.3–2.8</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>3</td>
<td>37</td>
<td>18</td>
<td>No</td>
<td>88</td>
<td>CYP2C9</td>
<td>20.8</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1.3–2.4</td>
<td>10–34</td>
<td>5</td>
<td>Yes</td>
<td>94–98</td>
<td>CYP3A4</td>
<td>2–3</td>
</tr>
</tbody>
</table>
that consists of clopidogrel, ticlopidine and more. Thienopyridines are an anti-platelet class of drug used in secondary prevention of significant coronary artery disease and total vascular disease. These beneficial effects were seen in drug interaction within the class e.g. co-administration of St John’s wort and simvastatin, which is predominantly metabolized by CYP3A4, lowers its plasma levels; pravastatin levels however are unaffected as it is not metabolized via this isoenzyme. Other pharmacokinetic interactions, independent of CYP have also been postulated including increased statin bioavailability and toxicity during co-administration with the P-glycoprotein transporter inhibitor digoxin.

Clinical relevance of statins

Statins are powerful low-density lipoprotein (LDL)-lowering drugs. More than 50 000 people have been randomized to placebo or statin in several trials, and the latter significantly reduced the risk of every clinical manifestation of the atherosclerotic process. More specifically, long-term results from clinical trials have demonstrated a decrease in the incidence of significant coronary artery disease and total mortality; reductions in myocardial infarctions, revascularization procedures, stroke and peripheral vascular disease. These beneficial effects were not gender-related and mostly evident in middle-aged and older patients both in primary or secondary prevention. Moreover, owing to their easy administration, statins showed a very high rate of patient’s compliance.

A comprehensive assessment of statins’ safety in routine practice apart from clinical trials has not been fully reported; therefore it is conceivable that side effects might be more frequent in ‘real world’, i.e. whereas patients are not monitored as closely as they are in clinical trials. Nevertheless, in comparison to other cholesterol-lowering medications, statins have a better safety profile. Well described side adverse effects include myopathy, hepatic and renal dysfunction. The beneficial effect of statins in atherosclerosis is thought to extend beyond their lipid-lowering capacity through mechanisms such as plaque stabilization and reducing vascular inflammation, thrombogenicity and endothelial dysfunction.

Thienopyridines

Thienopyridines are an anti-platelet class of drug that consists of clopidogrel, ticlopidine and more recently prasugrel. Ticlopidine was the first member of this class to be used, but owing to concerns relating to neutropenia and thrombotic thrombocytopenic purpura it has largely been superseded by clopidogrel that is currently the most widely used member of this group because of its better risk/benefit profile. Prasugrel showed a more intense platelet inhibition capacity compared with clopidogrel at the expense of a significantly higher risk of bleeding, therefore, its possible clinical application needs further investigation. Few structural peculiarities probably account for such different risk/benefit profiles (Figure 2).

Main pharmacokinetic and pharmacodynamic features of clopidogrel

Clopidogrel irreversibly inhibits the P2Y12 ADP receptor on platelets resulting in blockage of ADP-mediated platelet activation and aggregation. Clopidogrel is an inactive pro-drug that is metabolized in the liver to yield active (15%) and inactive metabolites. As the active form (a thiol metabolite) is poorly defined, unstable and difficult to measure, pharmacological-based studies basically measured either the plasma concentration of the inactive form (a carboxylic acid metabolite), the parent compound or the degree of inhibition of ADP-induced platelet aggregation. Recently, an assay to directly measure the active thiol metabolite has been developed. Clopidogrel is highly protein bound (as is its active metabolite), eliminated both in the faeces (46%) and urine (50%) and has an approximate half-life of 8 h with a time to peak of 1 h. Studies have shown that between 4% and 34% of patients have inadequate anti-platelet response to clopidogrel on the basis of ex vivo platelet function tests and that these individuals are at higher risk of adverse clinical events in both acute and chronic coronary heart disease. Clopidogrel absorption is not known to be significantly affected by foods or age and its plasma levels correlate with oral dosing. Genetic factors, however, such as a variance in the human multidrug-resistance 1 (MDR1) gene, which encodes the intestinal transporter P-glycoprotein, are thought to contribute to variability in clopidogrel absorption. This notion is supported by a recent study that evaluated the pharmacokinetics of clopidogrel in 10 healthy volunteers after a high loading dose (600 mg). The investigators used a novel highly specific liquid chromatography tandem mass spectrometry system to quantify the plasma concentrations of unmodified clopidogrel, its active thiol metabolite and its inactive carboxyl metabolite to assess possible
pharmacokinetic determinants of response variability. The study found significant differences between patients in pharmacokinetic parameters. However, there was a linear relationship between maximal platelet inhibition and peak plasma concentrations \( C_{\text{max}} \) of unmodified clopidogrel and its two metabolites. Moreover, a linear relationship was also observed between \( C_{\text{max}} \) of clopidogrel and its metabolites suggesting that absorption, rather than bioactivation played an important part in response variability.\(^{23} \) In a separate study von Beckerath and colleagues\(^{28} \) demonstrated that increasing the loading dose of clopidogrel from 300 mg to 600 mg results in an increased \( C_{\text{max}} \) of both clopidogrel and its active metabolite along with a more extensive platelet inhibition, while a further increase in the loading dose up to 900 mg does not produce any further significant increase in \( C_{\text{max}} \) or of platelet inhibition.\(^{28} \) This would suggest that absorption limits any further increase in plasma concentrations of clopidogrel and platelet inhibition at loading doses of clopidogrel beyond 600 mg.

### Clinical relevance of clopidogrel

Clopidogrel is currently used for a number of indications in the setting of both chronic and acute cardiovascular disease, and PCI. In patients with stable angina, clopidogrel administration alone is advisable whereas there is contraindication to or aspirin intolerance.\(^{29} \) In the acute myocardial infarction setting, for patients who have undergone diagnostic cardiac catheterization and for whom PCI is planned, clopidogrel should be started and continued for at least 1 month after bare metal stent implantation and for several months after drug-eluting stent implantation, up to 12 months in patients who are not at high risk for bleeding.\(^{30} \) In patients with unstable angina, clopidogrel should be started promptly and administered at least 1 month, up to 9 months (with a level of evidence B).\(^{31} \) Overall, for those patients treated with PCI the co-administration of aspirin (permanently) and clopidogrel is mandatory. Clopidogrel is administered after implantation of bare metal coronary stents and drug-eluting stents for at least 1 month and 1 year, respectively.\(^{32} \)

### Pharmacokinetic interactions between clopidogrel and statins

As both clopidogrel and statins are metabolized by the CYP enzymes in the liver, with the former being activated in its oxidized form and the latter largely inactivated, concern about the possibility of a significant pharmacokinetic interaction arose.\(^{33} \) Given the widespread co-administration of these drugs in a number of clinical settings, several studies sought to assess possible ominous effects of such interaction eventually providing evidence of a significant pharmacokinetic interaction. Clarke and Waskell\(^{34} \) sought to identify which isoenzymes were responsible for clopidogrel metabolism in humans by means of genetically engineered human
Of these, 17 received atorvastatin (20–40 mg daily), 31 received pravastatin (10–20 mg daily), and 22 received simvastatin (10–20 mg daily) and 22 no statins. Platelet activity was assessed measuring surface P-selectin expression using flow cytometry after ex vivo platelet stimulation with ADP. The study reported a significant inhibitory effect of atorvastatin on clopidogrel anti-platelet activity 5 h after administration of the clopidogrel-loading dose. This inhibitory effect was also seen after 48 h, but the extent of the effect was reduced. Muller and colleagues39 studied the effect of a high loading dose of clopidogrel (600 mg) in combination with statins on platelet aggregation ex vivo. Seventy-seven patients with coronary disease received a 20 mg dose of either atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, cerivastatin (0.3 mg) or placebo, along with 600 mg of clopidogrel and aspirin. No significant effect on anti-platelet activity of clopidogrel was detected at either 2 or 4 h following clopidogrel administration. A limitation of this study, however, was the early time-points used for blood sampling, at which neither drug would have reached steady state levels. Of note, compared with the previous reports, in this study a significantly higher loading dose of clopidogrel was administered.

Mitsios et al.40 administered clopidogrel (375 mg loading dose and then 75 mg daily) and either 10 mg atorvastatin or 40 mg of pravastatin to hypercholesterolaemic patients who underwent coronary stent implantation. After 5 weeks of combined therapy there was no significant difference in CD40L and ADP-induced platelet aggregation, or P-selectin and CD40L surface expression suggesting no significant effect on platelet function. The dose of atorvastatin used in this study, however, was much lower than that used in other studies and in clinical practice, and the study was not adequately powered to detect a difference between pravastatin and atorvastatin.

Mach and colleagues41 demonstrated using ex vivo testing of platelets that not all statins inhibited the metabolism of clopidogrel. Twenty-one healthy volunteers were treated with clopidogrel 75 mg orally daily for 10 weeks. After the first week of clopidogrel alone, volunteers then received oral doses of 5 different statins (rosuvastatin 10 mg daily, simvastatin 20 mg daily, fluvastatin 80 mg daily, pravastatin 40 mg daily and atorvastatin 20 mg daily) each for 1 week, separated by a wash-out period of 1 week of clopidogrel alone. The investigators demonstrated that after 1 week of dual therapy, ex vivo ADP-mediated aggregation of platelets was attenuated only in patients treated with simvastatin or fluvastatin.

Surprisingly, the co-administration of atorvastatin and clopidogrel did not affect platelet aggregation. This may be due to differences in assays used to measure platelet activity.
assess platelet activity and to the selection of only ‘clopidogrel responders’, which had not been done in the previous studies and could have become a confounding variable.

Ayalasomayajula and investigators\textsuperscript{42} assessed the effect of clopidogrel administration on the steady state kinetics of fluvastatin. Fluvastatin undergoes extensive first pass metabolism via CYP2C9 in the liver, which facilitates its excretion in the bile. \textit{In vitro} studies\textsuperscript{41} have shown that clopidogrel was able to inhibit CYP2C9 activity. Therefore, the authors hypothesized that such an interaction may reduce the excretion of fluvastatin and increase its potential toxicity. Furthermore, they postulated that increased levels of fluvastatin itself could then cross-inhibit clopidogrel metabolism leading to attenuation of its effect by reducing the formation of its active metabolite. They enrolled 30 patients treated with daily doses of 80 mg of fluvastatin. After 10 days patients were loaded with 300 mg of clopidogrel and maintained on a 75 mg daily dose. Fluvastatin concentrations have been assessed and \textit{ex vivo} platelet activity testing performed. The key observation was that a higher plasma concentration of fluvastatin was achieved in patients who received clopidogrel compared with those on fluvastatin alone. There was no clopidogrel alone control group in this study, however, the authors reported that the degree of inhibition of anti-platelet activity by fluvastatin was not significantly different to other studies in which patients were treated with clopidogrel only. Possible explanation of the disparity between pharmacokinetic findings \textit{in vitro} and \textit{in vivo} might be that the clopidogrel dose required for a therapeutic effect \textit{in vivo} was not sufficient to inhibit fluvastatin metabolism. Nevertheless, this study must be interpreted with caution because of lack of appropriate controls.

The interaction study\textsuperscript{44} compared the effects on platelet function of treatment with clopidogrel and atorvastatin, clopidogrel and other statins or clopidogrel alone following coronary stent implantation. After 4 and 24 h of clopidogrel therapy there was no significant differences between groups in all parameters except a reduction in platelet expression of G-protein coupled protease-activated thrombin receptor-1 (PAR-1) in patients treated with any statin. The authors concluded that atorvastatin did not affect clopidogrel anti-platelet activity compared to other statins and postulated that the reduction in PAR-1 observed in patients taking any statin could reflect a novel anti-platelet effect exerted by statins. A major criticism is that this study included patients taking both lipophilic and hydrophilic statins and was not sufficiently powered to detect a difference between atorvastatin and non-lipophilic statins.

Overall, the above studies aimed at evaluating the effects of CYP3A4 statins on the anti-platelet activity of clopidogrel. The presence of a number of methodological limitations made unlikely any definitive conclusion. Furthermore, due to technical difficulties in measuring the active metabolite of clopidogrel at the time these studies were conducted, pharmacokinetic inferences were based on the inhibition of platelet activity as surrogate marker of clopidogrel levels. New developments now allow direct sampling and measurement of plasma concentration of clopidogrel metabolites, thus, a carefully designed study would now be able to add more reliable insights.

**Clinical significance of statin–clopidogrel interaction**

Several studies have sought to address whether any potential pharmacokinetic interaction between clopidogrel and statins results in clinically relevant consequences (Table 2).

In a \textit{post hoc} analysis of the clopidogrel for the reduction of events during observation (CREDO) trial, investigators assessed 1001 patients taking CYP3A4 statins and 158 patients taking non-CYP3A4 statins and found no significant difference at 1 year in the composite endpoint of death, myocardial infarction and stroke\textsuperscript{45}.

Analysis of data from two prospective multicenter registries, the GRACE\textsuperscript{46} and MITRA PLUS\textsuperscript{47} also showed no clinically adverse outcome in patient’s co-administered with CYP3A4 statins and clopidogrel. The study by the GRACE investigators assessed 15 693 patients who had presented with a non-ST elevation myocardial infarction or unstable angina. A Kaplan–Meier analysis performed at 6 months demonstrated a survival benefit in those patients treated with aspirin, clopidogrel and statin in comparison to aspirin and statin alone. Limitations of this study include not differentiating between the different statins used, its retrospective design and lack of drug compliance or dose data. The study conducted by the MITRA PLUS study group analysed data from 2086 patients presenting with an ACS. There was no significant difference between the groups in the combined end-point of long-term mortality and stroke. As lipophilic statins were administered in both study groups, any meaningful conclusion about the issue of a potential clinically relevant interaction between lipophilic statins and clopidogrel remained difficult.
Furthermore, the doses of statins and drug compliance data were not presented.

Mukherjee and investigators\(^48\) conducted a prospective single centre cohort study of 1651 patients presenting ACS. In this study, there was no significant difference in mortality or major adverse cardiac events in patients receiving a CYP3A4 statin and clopidogrel in comparison to those taking a non-CYP3A4 statin and clopidogrel.

Brophy and colleagues\(^49\) retrospectively assessed 2927 patients who were prescribed clopidogrel within 5 days before undergoing PCI. Of these, 727 patients received atorvastatin and only 55.2% of the control group received a statin which included both CYP3A and non-CYP3A statins. This study found that patients taking atorvastatin and clopidogrel had an almost 2-fold increased risk of major adverse events at 30 days compared with those on clopidogrel alone. In addition, a delay in filling the clopidogrel prescription and taking other medications which are CYP3A4 substrates also significantly increased the likelihood of an adverse event. This study suggested for the first time a clinically relevant interaction between CYP3A4 statins and clopidogrel. However, a number of limitations has to be acknowledged including the retrospective design and the lack of data on drug compliance, doses and the exclusion of older patients.

The largest clinical study to examine a potential clinical interaction between statins and clopidogrel was a post hoc analysis of the copidogrel for high atherothrombotic risk and ischaemic stabilization, management and avoidance (CHARISMA) study. The CHARISMA study randomized 15 604 patients with either clinical evidence of or risk factors for cardiovascular disease to either aspirin or aspirin and clopidogrel. Median follow up was 28 months. A relevant post hoc analysis of the CHARISMA study was performed by Saw and colleagues\(^50\) who

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Comparison</th>
<th>Primary end point</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREDO substudy(^45)</td>
<td>1159</td>
<td>\textit{Post hoc} analysis categorizing baseline statin use to those predominantly metabolized by CYP3A4 or not</td>
<td>1 year composite endpoint of death, myocardial infarction and stroke</td>
<td>No detrimental effect</td>
</tr>
<tr>
<td>GRACE(^46)</td>
<td>15 693</td>
<td>Four groups: group I received aspirin alone, group II aspirin and clopidogrel, group III aspirin and statin and group IV aspirin, clopidogrel and statin</td>
<td>6 month mortality adjusted for baseline characteristics, in-hospital medications and procedures, re-hosp and revascularization</td>
<td>No detrimental effect</td>
</tr>
<tr>
<td>MITRA plus(^47)</td>
<td>2086</td>
<td>Two groups: group I received atorvastatin and clopidogrel, group II other statins (both lipophilic and non-lipophilic) and clopidogrel</td>
<td>Long-term mortality</td>
<td>No detrimental effect</td>
</tr>
<tr>
<td>Mukherjee et al.(^48)</td>
<td>1651</td>
<td>Two groups: group I received CYP3A4 statin plus clopidogrel, group II received non-CYP3A4 statin plus clopidogrel</td>
<td>In-hospital and 6 month mortality</td>
<td>No detrimental effect</td>
</tr>
<tr>
<td>Brophy et al.(^49)</td>
<td>2927</td>
<td>Two groups: group I received clopidogrel and atorvastatin, group II clopidogrel alone</td>
<td>30-day rates of adverse cardiovascular events (composite of death, myocardial infarction, unstable angina, stroke or transient ischaemic attack and repeat revascularization procedures)</td>
<td>Worse outcome associated with statins</td>
</tr>
<tr>
<td>CHARISMA substudy(^50)</td>
<td>10 078</td>
<td>\textit{Post hoc} analysis categorizing baseline statin use to those predominantly metabolized by CYP3A4 or not</td>
<td>Composite of myocardial infarction, stroke or cardiovascular death at median follow-up of 28 months</td>
<td>No detrimental effect</td>
</tr>
</tbody>
</table>
focused on patients taking statins at baseline. Of the total of 10,078 patients, 8,246 were on a lipophilic statin and 1,748 on non-lipophilic statins. There was no difference in the primary end-point between the groups suggesting no significant interactions between statin type and clopidogrel intake. Whilst this study provides strong evidence against a clinically relevant interaction there a number of limitations which need to be considered when interpreting this study. It was performed retrospectively, statin allocation was left to the physician’s discretion and no data on dose or compliance were presented. Moreover, no mention was made about other medications influencing CYP system such as calcium channel blockers.

Overall, the above studies suggested that co-administration of clopidogrel and statins has no net detrimental effect, despite methodological short-comings. However, a possible interaction in patients on high doses of CYP3A4 statins could not be reasonably ruled out.

**Limitation of platelet function monitoring**

Several different systems have been used to assess platelet function. Each of them has advantages as well as drawbacks (Table 3). Moreover, the correlation between ex vivo platelet test results and in vivo tests and clinical outcomes is still a matter of debate. Accordingly, a general consensus about the most reliable in vivo test is still lacking.

**Conclusions**

There is some evidence supporting a possible pharmacokinetic interaction between statins and the anti-platelet drug clopidogrel. In particular, it has

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Overview of the currently available analytical tools to assess platelet function and the studies in which they have been used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>Bleeding time</td>
<td>Physiological</td>
</tr>
<tr>
<td>PFA-100</td>
<td>Whole blood assay</td>
</tr>
<tr>
<td>Aggregometry</td>
<td></td>
</tr>
<tr>
<td>Lau et al.35, Muller et al.39, Mach et al.41, Ayalasomayajula et al.42</td>
<td></td>
</tr>
<tr>
<td>Verifinow</td>
<td>Small volume, whole blood sample</td>
</tr>
<tr>
<td>Impact analyser</td>
<td></td>
</tr>
<tr>
<td>Small volume, whole blood sample</td>
<td></td>
</tr>
<tr>
<td>P-selectin, GP IIb/IIIa, leucocytic-platelet aggregates</td>
<td></td>
</tr>
<tr>
<td>Serebruany et al.37, Neubauer et al.38, Serebruany et al.44</td>
<td></td>
</tr>
<tr>
<td>Sample preparation, requires flow cytometer</td>
<td></td>
</tr>
<tr>
<td>Vasodilator-stimulated phosphoprotein</td>
<td></td>
</tr>
<tr>
<td>Serum thromboxane B2</td>
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</tr>
<tr>
<td>Urinary 11-dehydro thromboxane B2</td>
<td>COX 1 dependent</td>
</tr>
<tr>
<td>Platelet-derived microparticles</td>
<td>COX 1 dependent</td>
</tr>
<tr>
<td>Plasma soluble CD40 ligand</td>
<td>Small volume, whole blood sample</td>
</tr>
<tr>
<td>Mitsios et al.40</td>
<td>Very good specificity</td>
</tr>
<tr>
<td></td>
<td>Sample preparation likely to cause artifacts</td>
</tr>
</tbody>
</table>

been suggested that this interaction is more likely with lipophilic statins which share the same CYP450 metabolizing isoenzyme.

However, discordance between ex vivo data which points in favour of an interaction and the majority of clinical studies which failed to detect a clinically relevant effect has to be acknowledged. This raises a few issues. First it questions the interpretation and translatability of ex vivo platelet activity testing. Whilst a number of methodologies have been clinically validated, these were not used in all the relevant studies. Some experts have even argued that a comprehensive assessment of platelet activity requires assessment of three events: activation, adhesion and aggregation. Whilst such an approach may be more physiologically appealing there is sufficient evidence to correlate ex vivo assessment of the degree of inhibition of ADP-induced platelet aggregation with clinical outcomes. Second, other in vitro tests used to determine pharmacokinetic interactions may not reflect other in vivo mechanisms that could ‘compensate’ for the inhibition of the metabolic activity of one isoenzyme. This may be particularly relevant for instance in patients with low CYP3A4 activity. Third, clinical studies that had addressed this topic have a number of methodological issues including retrospective designs, lack of dose or compliance reporting and irrelevant control groups. Furthermore, a number of studies reported a composite end-point, which included myocardial infarction and bleeding which fails to address the principle purported mechanism of statin–clopidogrel interaction which is to impede clopidogrel’s anti-platelet action. One would therefore expect an increase in myocardial infarction and decrease in bleeding and if presented as a combined outcome could conceivably offset an important interaction.

The issue of responsiveness to thienopyridines has been also investigated in order to define whether it is a ‘class effect’ or a ‘drug-specific’ effect. Of note, while a poor response to either clopidogrel or ticlopidine was common, resistance to both has been shown to be rare suggesting that the underlined mechanisms are different. As for Prasugrel, the third generation of thienopyridines in our knowledge there is no data showing, which is the rate of non-responsiveness compared with other drugs of the same class as it has been compared in a cohort of patients unselected with respect to clopidogrel responsiveness.

In conclusion, whilst there is presently no compelling clinical evidence to stop co-administration of CYP3A4 statins and clopidogrel, it is plausible that an important pharmacokinetic interaction exists, and further more robustly designed studies are needed to address this issue.

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Conflict of interest: None declared.

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40. Mitsios JV, Papanathanasiou AI, Rodis FI, Eliafi M, Goudevenos JA, Tselepis AD. Atorvastatin does not affect the antiplatelet potency of clopidogrel when it is


