The Clopidogrel-Statin Interaction
– Reopening Pandora’s Box –

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It is well established that clopidogrel therapy is associated with a widely variable pharmacodynamic response whereby approximately 1 in 3 patients will have high platelet reactivity (HPR), which has been strongly linked to the occurrence of post-PCI ischemic events. In addition to the presence of CYP2C19 loss-of-function allele (LoF) carriage, a diminished antiplatelet response to clopidogrel has been associated with co-administration of proton-pump inhibitors, lipophilic statins, and calcium-channel blockers that share either CYP2C19 or CYP3A4 isoenzymes with clopidogrel for their metabolism.¹⁻³

The first evidence supporting the pivotal role of hepatic CYP3A4 activity in influencing the antiplatelet effect of clopidogrel came from the work of Lau et al.⁴⁻⁵ Over a decade ago, those authors demonstrated that atorvastatin co-administration attenuated the antiplatelet effect of clopidogrel and the pharmacologic modulation of CYP 3A4 activity directly influenced the pharmacodynamic effect of clopidogrel. That groundbreaking study opened the “Pandora’s box” of the clopidogrel response variability phenomenon related to drug-drug interactions. The phenomenon of clopidogrel response variability and resistance paved the way for the concept of personalized antiplatelet therapy. Now, platelet function (PF) testing to ensure optimal platelet

Figure. Proposed mechanism for clopidogrel-atorvastatin interaction in patients with high levels of on-clopidogrel platelet reactivity. HPR, high platelet reactivity.
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A decade later, Pelliccia et al are reopening the Pandora’s box of clopidogrel-statin interactions to further explore the mysteries of its contents. In this well conducted study, the investigators enrolled 155 patients with coronary artery disease receiving 75 mg clopidogrel plus 100 mg aspirin for at least 30 days following angioplasty. The patients were randomly treated with lipophilic atorvastatin (20 mg daily) or hydrophilic pitavastatin (4 mg daily) for 30 days. After a 1-week washout period, patients crossed over to the other statin and continued for another 30 days. PF was assessed by VerifyNow P2Y12 assay before randomization (pretreatment) and at 2h after the last clopidogrel dose and 10h after the last statin dose during both study periods (post-treatment). The authors found that patients had significantly higher P2Y12 reactivity units (PRU) after 30 days of atorvastatin treatment. The increase in PRU associated with atorvastatin therapy was confined to patients with HPR >208 PRU before randomization to atorvastatin. However, in patients with <208 PRU before randomization neither atorvastatin nor pitavastatin therapy affected PF.

However, findings discordant from those observed by Pelliccia et al can be found in the recent literature. In 1 study, treatment with high-dose atorvastatin (80 mg) plus 150 mg clopidogrel vs. 150 mg clopidogrel alone administered immediately after elective PCI was associated with lower PRU values and HPR prevalence. In another study, treatment with rosuvastatin vs. atorvastatin therapy for 6 months in addition to dual antiplatelet therapy (DAPT) was associated with greater PRU. Park et al demonstrated that patients who were on chronic atorvastatin and clopidogrel therapy and undergoing angioplasty had a significantly improved antiplatelet response and a lower prevalence of HPR after treatment with either rosvuvastatin or pravastatin for 15 days in addition to DAPT. Discrepancies in the antiplatelet effect of clopidogrel may be related to differences in the timing of each study, the latter hypotheses are the major limitations of this study. In summary, Pelliccia et al have potentially unraveled some of the mystery inside the Pandora’s box of clopidogrel-statin interactions. Future studies that include analyses of genotype, pharmacokinetics and measurements of CYP activity will enhance our understanding of the statin-clopidogrel interaction.

Disclosures

Dr Gurbel has acted as a consultant for Daiichi Sankyo, Eli-Lilly, Bayer, AstraZeneca, Accumetrics, Nanosphere, Sanofi-Aventis, Merck, Medtronic, CSL and Haemonetics; has previously received grants from or has pending grants with the NIH, Daiichi Sankyo, Eli-Lilly, CSL, AstraZeneca, Haemonetics, Medtronic, Harvard Clinical Research Institute and Duke Clinical Research Institute; and has provided lectures/speaker bureau services to Eli-Lilly, Daiichi Sankyo, Nanosphere, Sanofi-Aventis, Merck and Iverson Genetics. Dr Gurbel holds stock or stock options in Merck, Medtronic, and Pfizer; and patents in the area of personalized antiplatelet therapy and interventional cardiology. Dr Jeong has received honoraria for lectures from Sanofi-Aventis, Daiichi Sankyo/Lilly, AstraZeneca, Nanosphere, Haemonetics, and Accumetrics; and research grants or support from Hanmi Pharmaceuticals, Boehringer-Ingelheim, Otsuka, Accumetrics, and Haemonetics. Dr Tantry reports no conflicts.

References

CYP3A4 genetic status may be associated with increased vulnerability to the inhibitory effect of calcium-channel blockers on clopidogrel. Circ J 2013; 77: 1289–1296.


