Harnessing the Power of Pharmacometabolomics

The Metabolic Footprint of Statins

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It has been 30 years since the approval of lovastatin, the first commercially available statin by the US Food and Drug Administration. Since that time, the uptake in statin use has been remarkable, with over 1 in 4 United States adults now taking statins for hyperlipidemia and cardiovascular disease, and nearly half of adults estimated to be statin eligible based on the 2013 ACC/AHA cholesterol treatment guidelines.[1,2] Clearly, the cardioprotective effects of statins are linearly related to LDL-C (low-density lipoprotein cholesterol) lowering.[3] However, despite the widespread use of statins, the extent to which event reduction is directly related to LDL lowering, versus effects on other lipid subclass or even pleiotropic effects remains unclear.

See Article by Kofink et al

The emerging use of metabolomic platforms to interrogate metabolites broadly representative of human metabolism has the potential to unravel on- and off-target effects and lend new insights into drug responses, referred to as pharmacometabolomics.[4] In this issue, Kofink et al[5] illustrate the power of pharmacometabolomics, by examining the metabolic effects of pravastatin within the context of a randomized clinical trial, PREVEND IT (Prevention of Renal and Vascular End-Stage Disease Intervention Trial). The authors performed comprehensive metabolic profiling of 231 lipoprotein and metabolite measures among 195 participants randomized to pravastatin, and 199 participants taking placebo over 3 months. In addition to LDL lowering, this study demonstrated widespread effects of pravastatin on both lipoprotein subclasses and actual lipid composition within subclass. Specifically, pravastatin reduced apolipoprotein B-rich lipoproteins and remnant cholesterol, both thought to play causal roles in cardiovascular disease.[6,7]

The authors are to be commended for this large-scale effort, which elucidates the metabolic footprint of pravastatin in the context of the gold standard randomized controlled trial for evaluation of interventions. Interestingly, we can now compare the gold standard to another recent pharmacometabolomics study, which demonstrated extensive differences in lipid subclasses beyond LDL within an observational cohort of statin users and nonusers. This was complemented by a Mendelian randomization analysis, which examined the effect of a genetic variant mimicking statin use, and showed similar associations.[8] When taken together with the current study from PREVEND IT, the 2 pharmacometabolomic studies demonstrate remarkable consistency within results (Figure for select lipid metabolites). Although more modest effect sizes in PREVEND IT may be attributed to lower potency statin used, the agreement across observational, genetic, and randomized controlled trial data illustrate the power of complementary study designs that can lend insights into complex drug effects.

Can pharmacometabolomics be harnessed to provide insights into beneficial drug mechanisms, as well as potential adverse effects? The currently study supports the latter as well: one interesting finding in both PREVEND IT and the observational study was the lack of change in amino acids with statin use.[5,8] Metabolite profiling has previously demonstrated a potential key role of branched chain and aromatic amino acids in the development of diabetes mellitus.[9] In light of increased rates of incident diabetes mellitus with statin use in randomized controlled trials,[3] the current study is notable, and suggests that the mechanism of increased diabetes mellitus risk may not involve alterations in amino acid metabolism. Another recent example further illustrates the potential of Omics technologies to improve drug safety: Williams et al[10] examined a case–control sample of patients randomized to torcetrapib (a cholesterol ester transfer protein inhibitor) versus placebo in the ILLUMINATE trial. Proteomic analysis in this study revealed an increase in a 9-protein risk score previously associated with greater cardiovascular risk within the first 3 months of therapy before onset of clinically overt adverse events, as well as alterations in proteins of inflammation and immunity. One wonders whether Omic technologies may in the future enable us to study early beneficial responses or adverse risk profiles after initiation of drug therapy, which in turn could inform management decisions to maximize benefit and minimize harm.

In sum, PREVEND IT investigators have leveraged pharmacometabolomics to better understand the widespread effect of statins on human metabolism in the context of a randomized controlled clinical trial. Results are consistent with prior observational and Mendelian randomization studies, and support the idea that pharmacometabolomics can be applied across a variety of study designs. Last, Omic technologies may refine current understanding of on- and off-target drug

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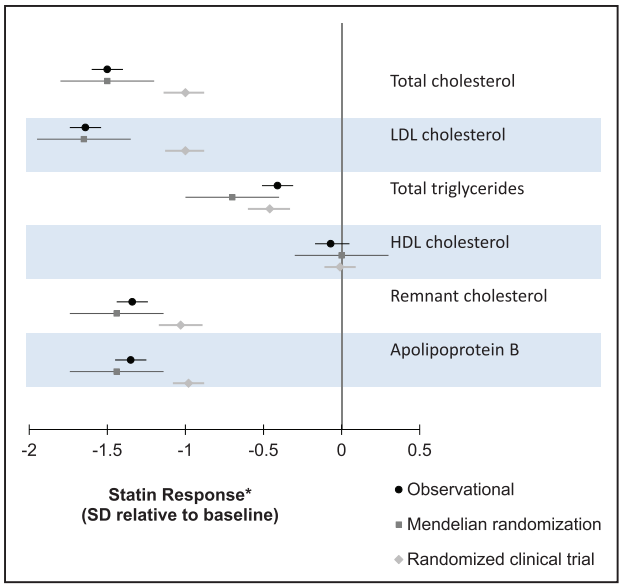

Figure. Effect sizes of statin on select lipid subclasses across 3 different study designs. *Observational and Mendelian randomization effect estimates are approximate, and adapted from Wurtz et al[8]. They represent changes associated with starting statin vs persistent nonusers scaled to SD (observational study), and associations with rs12916 in *HMGCR* (Mendelian randomization study) scaled to the corresponding lowering effect on LDL (low-density lipoprotein).[7] Randomized clinical trial effect estimates are adapted from Kofink et al,[5] and represent changes in SD units associated with pravastatin treatment compared with placebo over 3 mo. HDL indicates high-density lipoprotein.

effects with an eye toward drug safety, and an overall goal of advancing precision medicine.

Disclosures

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