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APPLICATION OF BEMPEDOIC ACID AS A POSSIBLE APPROACH TO REDUCE STATINS-CAUSED ENDOTHELIAL DYSFUNCTION.

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Statins are front-line lipid-lowering therapies that are known to impart cardiovascular benefits in part through pleiotropic effects on endothelial function including upregulation of endothelial nitric oxide synthase (eNOS) and inhibition of RhoA. However, evidence gathered in the past decade suggests statins have paradoxical endothelial toxicity under certain circumstances including high-dose statin therapy, chronic treatment with lipophilic statins, and statin abrupt withdrawal. The improvement of endothelial function by statins at low-to-moderate doses is thought to occur through inhibition of RhoA as well as activation of eNOS via PI3K/Akt and downregulation of NADPH oxidase.

In contrast, endothelial cell and mitochondrial uptake of high dose lipophilic statins (specifically atorvastatin and simvastatin) decreases coenzyme Q10 leading to an increase in reactive oxygen species that uncouples eNOS and changes its function from a nitric oxide synthase to a producer of superoxide. Abrupt withdrawal from statins results in rebound RhoA hyperactivation accompanied by a superoxide burst that decreases flow-mediated dilation to below baseline levels.

The CLEAR Harmony trial showed that a novel cholesterol-preventing drug, bempedoic acid, which is a liver-specific prodrug that is not activated in endothelial cells, does not cause either muscle or endothelial toxicity, acting as a negative control that confirms this mechanistic hypothesis. This biphasic dose-response highlights several important pharmacological concepts including the J-shaped dose response relationship, decrease in therapeutic index at higher dosages, importance of lipophilicity in drug off-target toxicity, and drug withdrawal.

There are many knowledge gaps that require future investigation: no prospective trials have compared endothelial function among high dose statin monotherapy to moderate statins with either ezetimibe or bempedoic acid ; no validated biomarkers have been identified that would screen which patients are predisposed to statin-induced endothelial dysfunction; and no clinical trials have investigated CoQ10 supplementation to prevent high dose statin toxicity or compared abrupt vs tapered statin withdrawal. Familiarity with this biphasic pharmacology is critical for clinicians treating statin intolerant patients and for pharmacologists teaching principles of drug actions that can have both positive and negative effects based on clinical context.