Nitric oxide-donating statins: a new concept to boost the lipid-independent effects

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This editorial refers to ‘Nitric oxide enhances the anti-inflammatory and anti-atherogenic activity of atorvastatin in a mouse model of accelerated atherosclerosis’ by S. Momi et al., pp. 428–438, this issue.

Statins decrease endogenous hepatic cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase and augment systemic clearance of cholesterol-rich lipoproteins by the up-regulation of hepatic LDL receptors. Furthermore, this class of drug exerts a variety of so-called pleiotropic beneficial effects on the cardiovascular system. Atherosclerosis is initiated by impaired endothelial function characterized by a reduction in endothelial nitric oxide (NO) bioavailability. LDL-cholesterol (LDL-C) is an important negative regulator of endothelial NO synthase activity. In addition to their lipid-lowering effects, one central biological action of statins is their ability to ameliorate the impaired bioavailability of NO.

Mechanistically, this occurs through increased expression (by inhibition of geranylgeranylation of small G-proteins) or enhanced activation (phosphorylation, activation of phosphatidylinositol 3-kinase and Akt) of endothelial NO synthase (eNOS). Consequently, statins improve vasodilation, exert antioxidative effects, and inhibit platelet aggregation, monocyte adhesion, and smooth muscle proliferation—all processes with disturbed regulation in atherosclerosis. The group has elaborated previously on modification of cardiovascular drugs to introduce NO-donating molecules. From animal models, they reported additive beneficial effects using NO-donating aspirin instead of regular aspirin. Momi et al. now present an elegant study in which addition of an NO-donating moiety to atorvastatin reduced atherosclerosis and inflammation more strongly than statin therapy alone in a mouse model of severe endothelial dysfunction, in vivo peroxidation, vascular inflammation, and lipid-induced, reactive oxygen species (ROS)-accelerated atherosclerosis. Atherosclerotic plaque development, production of ROS, circulating inflammatory cytokines, and endothelial dysfunction were reduced to a larger extent by using NO-donating atorvastatin (NCX6560) when compared with atorvastatin alone. The authors are to be commended for their consistent research work on strategies to optimize anti-atherosclerotic and anti-inflammatory activity of cardiovascular drugs.

Statins can be considered one of the most powerful drugs in primary and secondary prevention of cardiovascular disease, and their favourable molecular effects are corroborated by extensive prospective clinical evidence. In addition to their lipid-lowering properties, the role of statins as NO-enhancing agents is well established. Given the multitude of favourable physiological effects of NO (an overview is shown in Figure 1), the potential therapeutic impact of an even further optimized, i.e. more NO-releasing (statin), therapy in cardiovascular secondary prevention is huge. To mention just one effect, NO not only averts progression of negative vascular remodeling, but it is also an important contributor to vascular growth as a potent natural adaptive mechanism to overcome detrimental effects of atherosclerosis.

Have we finally identified the panacea of atherosclerosis? In vascular physiology, NO signalling occurs in a balanced state, and there are no all-or-nothing effects. Importantly, not all NO is equal, i.e. beneficial: unfavourable delivery or excessive concentrations provide an easily reacting radical. NO forms peroxynitrite when reacting with superoxide anions, leading to enhanced instead of reduced levels of oxidative stress. So-called uncoupling of eNOS can lead to a similar situation. Here, eNOS produces superoxide anions and hence increases oxidative stress. Recent evidence suggests that statins...
induce rapid, direct effects on arterial redox state and NO bioavailability in human atherosclerosis via tetrahydrobiopterin-mediated eNOS coupling. As mentioned above, in high-risk patients with a high burden of oxidized lipoproteins and vascular inflammation, the system may be overwhelmed. In the experimental models used by Momi et al., the NO-donating atorvastatin used apparently has the right pharmacokinetic features to overcome this limitation. Both the fluorometric assay used to semi-quantitatively determine ROS in vascular tissue and the systemic lipid peroxidation levels showed no signs of increased peroxidation.

The therapeutic concept of boosting NO levels in the vasculature is not new, and several approaches have been undertaken previously. Of note, other NO-donating drugs were hitherto unsuccessful (nitrate, sydnonimines, nicorandil). While inhibition of superoxide production by organic nitrates (isosorbide mononitrate) has been demonstrated, none of the substances consistently displayed anti-atherosclerotic effects in vivo or succeeded to clinical application for the treatment of atherosclerosis.

Which novel findings can potentially be taken from bench to bedside? Intriguingly, in the present study, the superiority of the NO-donating compound in decreasing atherosclerotic lesion size, oxidative stress, and both vascular and systemic inflammation was in the same magnitude as the reduction in LDL-C concentrations achieved by NCX6550 when compared with atorvastatin alone. Although cholesterol-independent effects of statins and NO are well demonstrated, this finding fuels the discussion regarding the quantitative contribution of the cholesterol-lowering property for the observed vascular effects. Due to their mechanisms of action, both compounds (statins by HMG-CoA-inhibition, NO possibly by lowered cholesterol absorption and decreased hepatic coenzyme A activity) will always lower LDL-C concentrations, rendering the identification of genuine cholesterol-independent anti-oxidative effects difficult.

Amidst the hope raised by favourable vascular effects in animal models, we must not forget the severity of endothelial dysfunction and oxidative stress present in the genetically modified murine model. Excessively high levels of oxidative stress and cholesterol...
concentrations are justified in an experimental setting where the aim is proof-of-principle rather than fine-tuning of drug effects. Clinical trials must still provide evidence that comparable effects are detectable in patients with traditional risk factors suffering from atherosclerotic disease and not only in those suffering from genetic aberrations such as familial hypercholesterolemia. Preliminary clinical data on pharmacokinetics and safety of NO-donating atorvastatin are promising. In keeping with other data on NO in the treatment of atherosclerotic vascular disease, the approach of modifying a drug already firmly established in secondary prevention of cardiovascular disease deserves our attention and calls for further preclinical as well as clinical investigation.

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