RAPID, DIRECT EFFECTS OF STATIN TREATMENT ON ARTERIAL REDOX STATE AND NITRIC OXIDE BIOAVAILABILITY IN HUMAN ATHEROSCLEROSIS VIA TETRAHYDROBIOPTERIN-MEDIATED ENOS COUPLING

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Authors: Charalambos A. Antoniades, Alexios S. Antonopoulos, Tim Van-Asche, Colin Cunnington, Dimitris Tousoulis, Costantinos Bakogiannis, Michael Demosthenous, Chandi Ratnatunga, Christodoulos Stefanadis, Keith M. Channon, University of Oxford, Oxford, United Kingdom

Background: The direct effects of statins on vascular redox state in humans are unclear. We examined the effects of atorvastatin on the mechanisms regulating endothelial nitric oxide synthase (eNOS) coupling, in patients with CAD.

Methods: We recruited 492 patients undergoing CABG. During surgery segments of internal mammary arteries (IMA) were obtained. Arterial O2- was determined by lucigenin chemiluminescence (+/-LNAME), while acetylcholine-induced vasorelaxations were assessed ex-vivo. In a 2nd study, IMA segments from 10 patients were incubated ex vivo with atorvastatin, for 6h (+/- mevalonate (Mev)). Vascular tetrahydrobiopterin (BH4 was measured by HPLC, while GTP-cyclohydrolase I (GTPCH-I) gene expression was determined by qRT-PCR.

Results: Statin treatment was associated with improved vascular NO bioavailability (A) and reduced O2- generation (B) in IMA. Ex vivo exposure of IMAs to atorvastatin, reduced arterial O2- (C) by improving eNOS coupling (D), as a result of increased vascular BH4 bioavailability (E) and up-regulation of GTPCH-I gene expression (F). Importantly these effects were reversed by mevalonate.

Conclusions: This study demonstrates direct effects of statins on human vascular wall, independent of LDL lowering. Atorvastatin improves NO-mediated endothelial function and reduces vascular O2-, through BH4 mediated eNOS coupling. These findings provide new insights into the mechanisms mediating the beneficial vascular effects of statins in human atherosclerosis.