# Professor John Chapman

## BIOGRAPHY

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**John Chapman** is Research Professor at the Pierre and Marie Curie University, and Director Emeritus of the National Institute for Health and Medical Research (INSERM) at the Pitié-Salpêtrière University Hospital in Paris, France. Professor Chapman is a Past-President of the European Atherosclerosis Society (EAS), Past-President of the French Atherosclerosis Society, an Honorary Fellow of the ESC, a European Society of Cardiology (ESC)/EAS Task Force member on Guidelines for the Management of Dyslipidaemia and on PCSK9 inhibitor use in very high cardiovascular risk patients. He has jointly spearheaded EAS Consensus Panels on lipoprotein(a); high-triglyceride/low high-density lipoprotein (HDL) dyslipidaemias; heterozygous, homozygous and paediatric familial hypercholesterolaemia; statin-associated muscle symptoms; causality of LDL in atherosclerotic cardiovascular disease; and plant sterols and stanols in cardiovascular disease prevention. Professor Chapman's research activities have focused on metabolism of apoB-containing lipoproteins and their pharmacological modulation to decrease cardiovascular risk, the role of cholesteryl ester transfer protein in lipoprotein metabolism, pathophysiology of lipoprotein(a), and the metabolism, function and dysfunction of HDL. The recipient of several awards including the International Society of Atherosclerosis (ISA) Distinguished Career Award and the 2015 ISA Antonio Gotto Jr Award in Atherosclerosis Research, he is Co-chair of the PCSK9 Education and Research Forum. Professor Chapman is also Associate Editor of Pharmacology and Therapeutics, and an Editorial Board member of Arteriosclerosis, Thrombosis, and Vascular Biology; Journal of Lipid Research; and Atherosclerosis. He has authored numerous articles in international peer-reviewed journals, and is co-author of a book entitled 'HDL: Structure, Metabolism, Function and Therapeutics'.

ABSTRACT

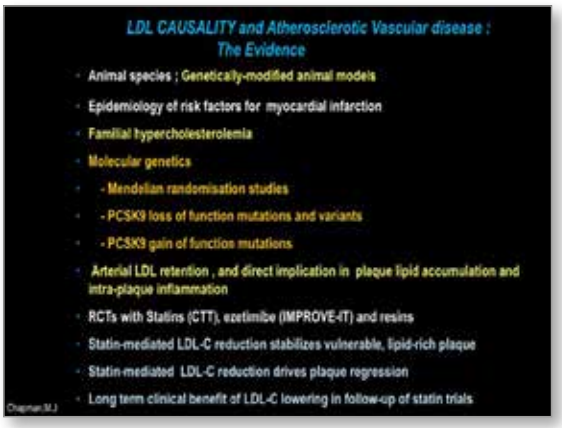
**Understanding new PCSK9 outcome data: From LDL-C hypothesis to LDL-C causality**

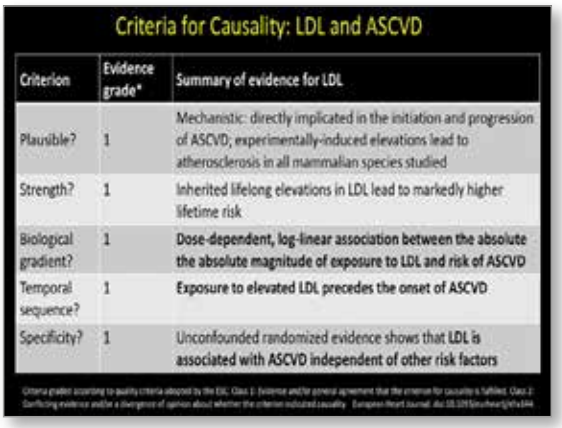
Atherosclerotic cardiovascular disease (ASCVD) and its clinical manifestations, such as myocardial infarction (MI) and ischaemic stroke, constitute the leading cause of morbidity and mortality throughout the world. Multiple exposures have been reported to be associated with an increased risk of cardiovascular events . The most extensively studied of these exposures by far is low density lipoprotein (LDL). Multiple lines of evidence have established that cholesterol-rich low-density lipoprotein and other apolipoprotein B (apoB)-containing lipoproteins, including very low-density lipoproteins (VLDL) and their remnants, intermediate density lipoproteins (IDL), and lipoprotein(a) [Lp(a)], are directly implicated in the development of ASCVD . Despite this extensive body of evidence, however, some commentators still express scepticism concerning the causal nature of the relationship between LDL and the development of ASCVD . Indeed, the "LDL hypothesis" , which focuses on the premise that high levels of LDL-cholesterol are intimately associated with elevated risk of ASCVD, is considered unproven by many such commentators. With the availability of new, highly efficacious LDL lowering agents such as the PCSK9 inhibitors, and the development of additional novel lipid lowering agents with prolonged duration of action, there has been an urgent need for a consensus to evaluate whether LDL causes ASCVD in order to inform treatment guidelines and to help shape regulatory agency guidance for the approval of new medicines.

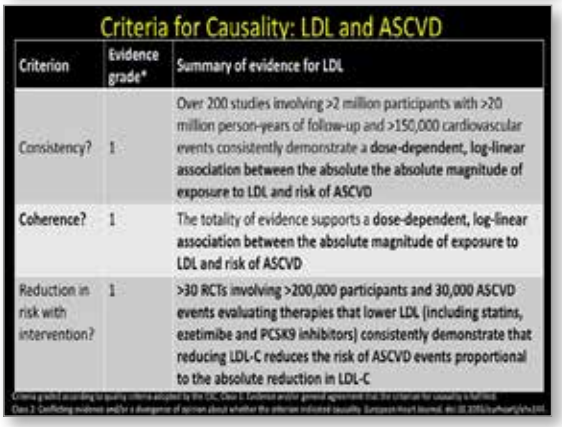
The recent EAS Consensus Statement (1) appraises evidence from genetic, epidemiologic and clinical intervention studies. In clinical studies, plasma LDL burden is usually estimated by determination of plasma LDL cholesterol level (LDL C). Rare genetic mutations that cause reduced LDL receptor function lead to markedly higher LDL-C and a dose-dependent increase in the risk of ASCVD, whereas rare variants leading to lower LDL-C are associated with a correspondingly lower risk of ASCVD.

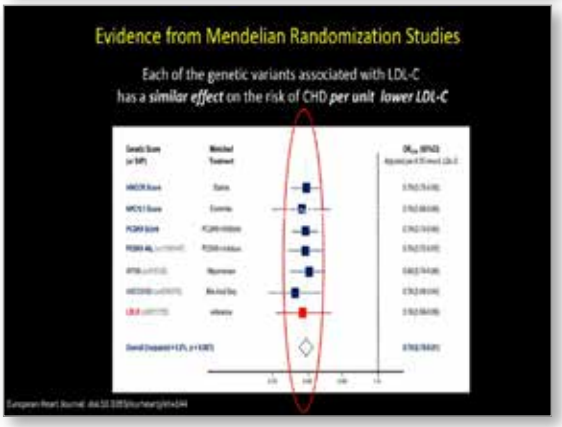
Most publications that question the causal effect of LDL on the development of ASCVD tend to cite evidence from individual studies or a small group of highly selected studies, often without a quantitative synthesis of the presented evidence . Therefore, to avoid this type of selection bias, we based our conclusions on the totality of evidence from separate meta-analyses of genetic studies, prospective epidemiologic studies, Mendelian randomization studies, and randomized clinical lipid lowering trials primarily involving statins, and most recently, evolocumab, an efficacious monoclonal antibody inhibitor of PCSK9. This evidence base includes over 200 studies involving over 2 million participants with over 20 million person-years of follow-up and more than 150,000 cardiovascular events. demonstrate a remarkably consistent dose-dependent log-linear association between the absolute magnitude of arterial exposure to LDL-C and the risk of ASCVD; this effect appears to increase with increasing duration of exposure to LDL-C. Together, this wide spectrum of clinical and genetic studies provides remarkably consistent and unequivocal evidence that LDL causes ASCVD.

Reference (1): Ference et al, Europ Heart J, 2017 online

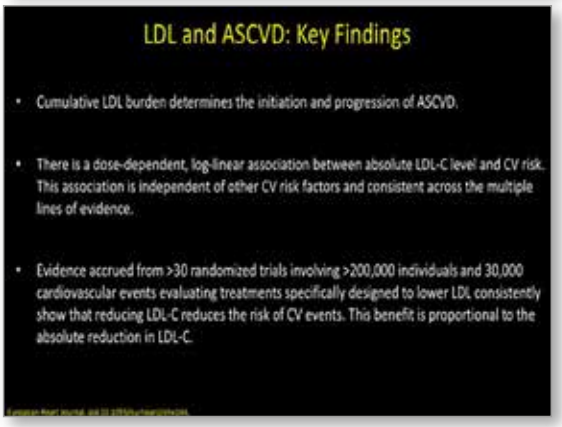




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