

## 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

### LDL CAUSALITY and Atherosclerotic Vascular disease : The Evidence

- Animal species ; Genetically-modified animal models
- Epidemiology of risk factors for myocardial infarction
- Familial hypercholesterolemia
- Molecular genetics
  - Mendelian randomisation studies
  - PCSK9 loss of function mutations and variants
  - PCSK9 gain of function mutations
- Arterial LDL retention , and direct implication in plaque lipid accumulation and intra-plaque inflammation
- RCTs with Statins (CTT), ezetimibe (IMPROVE-IT) and resins
- Statin-mediated LDL-C reduction stabilizes vulnerable, lipid-rich plaque
- Statin-mediated LDL-C reduction drives plaque regression
- Long term clinical benefit of LDL-C lowering in follow-up of statin trials

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### Criteria for Causality: LDL and ASCVD

Criterion	Evidence grade*	Summary of evidence for LDL
Plausible?	1	Mechanistic: directly implicated in the initiation and progression of ASCVD; experimentally-induced elevations lead to atherosclerosis in all mammalian species studied
Strength?	1	Inherited lifelong elevations in LDL lead to markedly higher lifetime risk
Biological gradient?	1	Dose-dependent, log-linear association between the absolute the absolute magnitude of exposure to LDL and risk of ASCVD
Temporal sequence?	1	Exposure to elevated LDL precedes the onset of ASCVD
Specificity?	1	Unconfounded randomized evidence shows that LDL is associated with ASCVD independent of other risk factors

\*Criteria graded according to quality criteria adopted by the ESC. Class 1: Evidence and/or general agreement that the criterion for causality is fulfilled. Class 2: Conflicting evidence and/or a divergence of opinion about whether the criterion indicated causality. European Heart Journal, doi:10.1093/eurheartj/ehv334

### Criteria for Causality: LDL and ASCVD

Criterion	Evidence grade*	Summary of evidence for LDL
Consistency?	1	Over 200 studies involving >2 million participants with >20 million person-years of follow-up and >150,000 cardiovascular events consistently demonstrate a dose-dependent, log-linear association between the absolute the absolute magnitude of exposure to LDL and risk of ASCVD
Coherence?	1	The totality of evidence supports a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD
Reduction in risk with intervention?	1	>30 RCTs involving >200,000 participants and 30,000 ASCVD events evaluating therapies that lower LDL (including statins, ezetimibe and PCSK9 inhibitors) consistently demonstrate that reducing LDL-C reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C

\*Criteria graded according to quality criteria adopted by the ESC. Class 1: Evidence and/or general agreement that the criterion for causality is fulfilled. Class 2: Conflicting evidence and/or a divergence of opinion about whether the criterion indicated causality. European Heart Journal, doi:10.1093/eurheartj/ehv334

### Evidence from Mendelian Randomization Studies

Each of the genetic variants associated with LDL-C has a similar effect on the risk of CHD per unit lower LDL-C

European Heart Journal, doi:10.1093/eurheartj/ehv334

### Evidence from Randomized Controlled Trials

Absolute yearly event rate on LDL-lowering treatment was strongly and linearly associated with the absolute achieved LDL-C level

European Heart Journal, doi:10.1093/eurheartj/ehv314

### LDL and ASCVD: Key Findings

- Cumulative LDL burden determines the initiation and progression of ASCVD.
- There is a dose-dependent, log-linear association between absolute LDL-C level and CV risk. This association is independent of other CV risk factors and consistent across the multiple lines of evidence.
- Evidence accrued from >30 randomized trials involving >200,000 individuals and 30,000 cardiovascular events evaluating treatments specifically designed to lower LDL consistently show that reducing LDL-C reduces the risk of CV events. This benefit is proportional to the absolute reduction in LDL-C.

European Heart Journal, doi:10.1093/eurheartj/ehv334

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