Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

Brian A. Ference[1]*, **Henry N. Ginsberg**[2], **Ian Graham**[3], **Kausik K. Ray**[4], **Chris J. Packard**[5], **Eric Bruckert**[6], **Robert A. Hegele**[7], **Ronald M. Krauss**[8], **Frederick J. Raal**[9], **Heribert Schunkert**[10,11], **Gerald F. Watts**[12], **Jan Borén**[13], **Sergio Fazio**[14], **Jay D. Horton**[15,16], **Luis Masana**[17], **Stephen J. Nicholls**[18], **Børge G. Nordestgaard**[19,20,21], **Bart van de Sluis**[22], **Marja-Riitta Taskinen**[23], **Lale Tokgözoğlu**[24], **Ulf Landmesser**[25,26], **Ulrich Laufs**[27], **Olov Wiklund**[28,29], **Jane K. Stock**[30], **M. John Chapman**[31]†, and **Alberico L. Catapano**[32]†

[1]Division of Translational Research and Clinical Epidemiology, Division of Cardiovascular Medicine, Wayne State University School of Medicine, Detroit, MI 48202, USA; [2]Irving Institute for Clinical and Translational Research, Columbia University, New York, NY, USA; [3]Trinity College Dublin, Ireland; [4]Department of Primary Care and Public Health, Imperial Centre for Cardiovascular Disease Prevention, Imperial College, London, UK; [5]College of Medical, Veterinary, and Life Sciences, University of Glasgow, Glasgow, UK; [6]INSERM UMRS1166, Department of Endocrinology-Metabolism, ICAN - Institute of CardioMetabolism and Nutrition, AP-HP, Hôpital de la Pitié, Paris, France; [7]Department of Medicine, Robarts Research Institute, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada; [8]Department of Atherosclerosis Research, Children's Hospital Oakland Research Institute, Oakland, CA 94609, USA; [9]Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; [10]Deutsches Herzzentrum München, Technische Universität München, Munich 80636, Germany; [11]Deutsches Zentrum für Herz und Kreislauferkrankungen (DZHK), Partner Site Munich Heart Alliance, Munich 81377, Germany; [12]Lipid Disorders Clinic, Centre for Cardiovascular Medicine, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia; [13]Department of Molecular and Clinical Medicine, Wallenberg Laboratory, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden; [14]Department of Medicine, Center for Preventive Cardiology of the Knight Cardiovascular Institute, Oregon Health and Science University, Portland, OR, USA; [15]Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX, USA; [16]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; [17]Research Unit of Lipids and Atherosclerosis, University Rovira i Virgili, C. Sant Llorenç 21, Reus 43201, Spain; [18]South Australian Health and Medical Research Institute, University of Adelaide, Adelaide, Australia; [19]Department of Clinical Biochemistry and The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Denmark; [20]Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; [21]The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Denmark; [22]Department of Pediatrics, Molecular Genetics Section, University of Groningen, University Medical Center Groningen, Antonius Deusinglaan 1, Groningen AV 9713, The Netherlands; [23]Helsinki University Central Hospital and Research Programs' Unit, Diabetes and Obesity, Heart and Lung Centre, University of Helsinki, Helsinki, Finland; [24]Hacettepe University, Ankara, Turkey; [25]Department of Cardiology, Charité-Universitätsmedizin Berlin (CBF), Hindenburgdamm 30, Berlin 12203, Germany; [26]Berlin Institute of Health (BIH), Deutsches Zentrum für Herz-Kreislaufforschung (DZHK), Berlin, Germany; [27]Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg, Saar, Germany; [28]Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden; [29]Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; [30]European Atherosclerosis Society, Gothenburg, Sweden; [31]INSERM, Dyslipidemia and Atherosclerosis Research, and University of Pierre and Marie Curie, Pitié-Sâlpetrière University Hospital, Paris, France; and [32]Department of Pharmacological and Biomolecular Sciences, University of Milan and IRCCS Multimedica, Milan, Italy

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author. Tel:+1 313 745 1410, Fax: +1 313 745 5565, Email: bference@med.wayne.edu

† These authors contributed equally as senior authors.

Aims	To appraise the clinical and genetic evidence that low-density lipoproteins (LDLs) cause atherosclerotic cardiovascular disease (ASCVD).
Methods and results	We assessed whether the association between LDL and ASCVD fulfils the criteria for causality by evaluating the totality of evidence from genetic studies, prospective epidemiologic cohort studies, Mendelian randomization studies, and randomized trials of LDL-lowering therapies. 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. Separate meta-analyses of over 200 prospective cohort studies, Mendelian randomization studies, and randomized trials including more than 2 million participants with over 20 million person-years of follow-up and over 150 000 cardiovascular events demonstrate a remarkably consistent dose-dependent log-linear association between the absolute magnitude of exposure of the vasculature to LDL-C and the risk of ASCVD; and this effect appears to increase with increasing duration of exposure to LDL-C. Both the naturally randomized genetic studies and the randomized intervention trials consistently demonstrate that any mechanism of lowering plasma LDL particle concentration should reduce the risk of ASCVD events proportional to the absolute reduction in LDL-C and the cumulative duration of exposure to lower LDL-C, provided that the achieved reduction in LDL-C is concordant with the reduction in LDL particle number and that there are no competing deleterious off-target effects.
Conclusion	Consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL causes ASCVD.
Keywords	Atherosclerosis • Cardiovascular disease • Low-density lipoprotein • Mendelian randomization • Clinical trials • Statin • Ezetimibe • PCSK9 • Causality • Recommendations

Introduction

Atherosclerotic cardiovascular disease (ASCVD) and its clinical manifestations, such as myocardial infarction (MI) and ischaemic stroke, are 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.[1] The most extensively studied of these exposures by far is low-density lipoprotein (LDL). Multiple lines of evidence have established that cholesterol-rich LDL 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.[2]

Despite this extensive body of evidence, however, some still express scepticism of the causal nature of the relationship between LDL and the development of ASCVD.[3] With the availability of new, highly efficacious LDL-lowering agents and the development of additional novel lipid-lowering agents with prolonged duration of action, there is a need for a consensus as to whether LDL causes ASCVD in order to inform treatment guidelines and help shape regulatory agency guidance for the approval of new medicines.

This Consensus Statement, the first of two that evaluates the case for LDL causality, appraises evidence from genetic, epidemiologic, and clinical intervention studies. The second paper discusses the evidence for LDL causality based on the current understanding of the pathophysiology of ASCVD. While our focus is on LDL, this does not diminish the importance of the role of other apoB-containing lipoproteins on the development of ASCVD nor does it exclude potential atherogenic actions of the individual components of the lipidome and proteome of LDL beyond cholesterol and apoB.

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.[4] Therefore, to avoid this type of selection bias, we have based our conclusions on the totality of evidence from separate meta-analyses of genetic studies, prospective epidemiologic studies, Mendelian randomization studies, and randomized clinical trials. 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. Together these studies provide remarkably consistent and unequivocal evidence that LDL causes ASCVD as summarized in *Table 1*.

Pathophysiology of atherosclerosis

The key events in the initiation of ASCVD are the retention and accumulation of cholesterol-rich apoB-containing lipoproteins within the arterial intima at sites of predilection for plaque formation.[5–9] Notably, LDL and other apoB-containing lipoproteins <70 nm in diameter (including VLDL, their remnants, IDL, and Lp(a)) efficiently enter and exit the arterial intima.[9,10] At what is now considered physiologically relevant levels of LDL cholesterol [LDL-C; ~0.5–1.0 mmol/L (20–40 mg/dL), typical of newborns[11] and a wide range of mammalian species[12]], the probability of LDL particle retention and the risk of developing atherosclerosis is low.[6] However, as the concentration of LDL-C increases above this level, the probability of intimal retention of LDL leading to the initiation and progressive

Table 1   Criteria for causality: low-density lipoprotein (LDL) and atherosclerotic cardiovascular disease (ASCVD)

Criterion (modified from reference[5])	Evidence grade	Summary of the evidence (references)
1. Plausibility	1	LDL and other apolipoprotein (apo) B-containing lipoproteins (very low-density lipoprotein their remnants, intermediate-density lipoprotein and lipoprotein(a)) are directly implicated in the initiation and progression of ASCVD; experimentally induced elevations in plasma LDL and other apoB-containing lipoproteins lead to atherosclerosis in all mammalian species studied.[2,5–12]
2. Strength	1	Monogenic and polygenic-mediated lifelong elevations in LDL lead to markedly higher lifetime risk.[13–20,27–31,40,43]
3. Biological gradient	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials uniformly demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[13–22,27–36,38–40,42–47]
4. Temporal sequence	1	Monogenic lipid disorders and Mendelian randomization studies demonstrate that exposure to elevated LDL precedes the onset of ASCVD[13–20,27–31,40,43]
5. Specificity	1	Mendelian randomization studies and randomized intervention trials both provide unconfounded randomized evidence that LDL is associated with ASCVD independent of other risk factors[28,31–33,40,43]
6. Consistency	1	Over 200 studies involving more than 2 million participants with over 20 million person-years of follow-up and more than 150 000 cardiovascular events consistently demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[13–22,27–36,38–40,42–47]
7. Coherence	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[15–18,21,22,28,30–32,35,36,43,44,47]
8. Reduction in risk with intervention	1	More than 30 randomized trials involving over 200 000 participants and 30 000 ASCVD events evaluating therapies specifically designed to lower LDL (including statins, ezetimibe, and PCSK9 inhibitors) consistently demonstrate that reducing LDL cholesterol (LDL-C) reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C[32–34,38,39,42,45–47]

Criteria are graded by a modification of the quality criteria adopted by the European Society of Cardiology system.
For reference, see http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelinesdevelopment/Writing-ESC-Guidelines (31 January 2017).
These are defined as follows:
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.
Class 3: Evidence or general agreement that the criterion for causality is not fulfilled.

development of atherosclerotic plaque increases in a dose-dependent manner.[2] This topic will be discussed in detail in the second Consensus Statement on this topic.
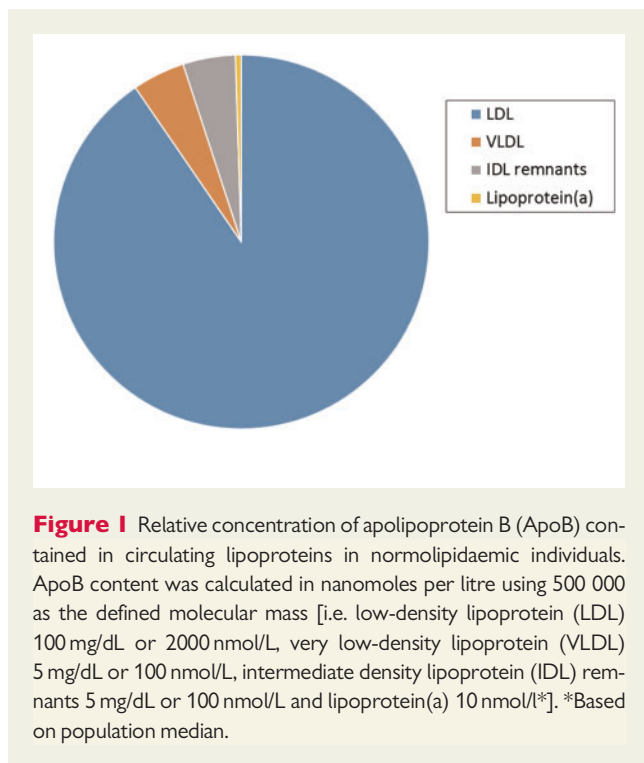
Cholesterol, LDL, and LDL-C

The terms 'cholesterol', 'LDL', and 'LDL cholesterol (LDL-C)' are frequently conflated or used interchangeably, potentially leading to confusion. Cholesterol is an essential component of cell membranes and a precursor of bile acids and steroid hormones. Importantly, cholesterol of both exogenous and endogenous origin is transported to peripheral cells largely by the apoB-containing lipoproteins in plasma. In most people, LDL particles constitute ~90% of circulating apoB-containing lipoproteins in fasting blood (Figure 1). However, in clinical practice, the plasma LDL level is generally not measured directly but instead is estimated from its cholesterol concentration—LDL-C—a measure of the total amount of cholesterol contained in LDL particles. As a result, calculated plasma LDL-C has become the focus for assessing cardiovascular risk and for evaluating therapeutic benefit in randomized clinical trials.

Under most conditions, LDL-C concentration and LDL particle number are highly correlated, and therefore plasma LDL-C is a good surrogate for LDL particle concentration. However, in certain conditions (e.g. the metabolic syndrome, diabetes, and hypertriglyceridaemia), plasma LDL-C and LDL particle concentration can become discordant as a result of the predominance of small, dense cholesterol-poor LDL, and therefore plasma LDL-C may not accurately reflect LDL particle concentration or its effect on cardiovascular risk. Under these conditions, direct measurement of LDL particle number or apoB concentration (recognizing that each LDL particle contains a single apoB molecule) may more accurately reflect the causal effect of LDL on ASCVD. In this Consensus Statement, we assess the evidence that LDL causes ASCVD by critically appraising the clinical evidence, with the understanding that the majority of clinical studies have used LDL-C as an estimate of LDL concentration.

Evidence from inherited disorders of lipid metabolism

Familial hypercholesterolaemia (FH) is an autosomal co-dominant disorder that usually results from a loss-of-function (LOF) mutation in the LDL receptor (LDLR) gene, or less commonly, from LOF mutations in the APOB gene that reduce the binding of apoB-containing lipoproteins to the LDL receptor or a gain-of-function (GOF)

Figure I Relative concentration of apolipoprotein B (ApoB) contained in circulating lipoproteins in normolipidaemic individuals. ApoB content was calculated in nanomoles per litre using 500 000 as the defined molecular mass [i.e. low-density lipoprotein (LDL) 100 mg/dL or 2000 nmol/L, very low-density lipoprotein (VLDL) 5 mg/dL or 100 nmol/L, intermediate density lipoprotein (IDL) remnants 5 mg/dL or 100 nmol/L and lipoprotein(a) 10 nmol/l*]. *Based on population median.

mutation in the *PCSK9* gene. Regardless of the underlying genetic defect, FH is characterized by markedly elevated levels of LDL-C and premature atherosclerosis, particularly coronary artery disease.[13,14]

In the most common form of FH, a mutation in the *LDLR* gene causes decreased LDL receptor function leading to a markedly increased concentration of circulating LDL particles and the cholesterol carried by those particles (i.e. LDL-C). Heterozygous FH (HeFH) affects between 1:200 and 1:300 people worldwide[15,16] and when untreated is characterized by LDL-C levels in the range of 4.5–12 mmol/L and a marked increase in risk of ASCVD.[13] Homozygous FH (HoFH) is a much rarer condition, with an extreme phenotype characterized by untreated plasma LDL-C levels often in excess of 13 mmol/L from birth and almost universal development of ASCVD in childhood or early adolescence.[14] Although the phenotypic expression of FH is variable, the extent of atherosclerosis and the risk of cardiovascular events in both HeFH and HoFH is proportional to both the absolute magnitude and the duration of exposure to elevated LDL-C levels.[15,17,18]

Within any affected family, each child has an equal and random 50% probability of inheriting a mutation that causes FH. The fact that siblings who inherit an FH mutation have markedly elevated plasma LDL-C levels and a corresponding dose-dependent markedly elevated lifetime risk of ASCVD as compared to their unaffected siblings provides powerful evidence that LDL causes ASCVD.[19] This conclusion is substantially strengthened by the complementary observations that GOF mutations in *PCSK9* result in a markedly elevated LDL-C concentration and a corresponding markedly elevated risk of ASCVD, while LOF mutations in *PCSK9* result in a lower LDL-C concentration and a corresponding markedly lower lifetime risk of ASCVD.[20]

Evidence from prospective epidemiologic studies

Several large meta-analyses of prospective observational epidemiologic studies using individual participant data have consistently reported a continuous log-linear association between the absolute magnitude of exposure to plasma LDL-C levels and the risk of ASCVD.

The Emerging Risk Factors Collaboration (ERFC) reported the results of a meta-analysis of individual participant data from 302 430 persons without prevalent vascular disease at the time of enrolment in 68 prospective studies during which 8857 non-fatal MI and 928 coronary heart disease (CHD) deaths accrued over 2.79 million person-years of follow-up.[21] In these studies, plasma LDL-C concentration was log-linearly associated with increased risk of non-fatal MI or CHD death. Although the authors reported the association between non-HDL-C concentration and risk of CHD in the primary analysis, all studies included in this meta-analysis measured total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides and reported the calculated LDL-C concentration as estimated by the Friedewald equation. The ERFC authors point out that any regression model that includes terms for non-HDL-C, HDL-C, and triglycerides is a simple mathematical rearrangement of a model that includes terms for calculated LDL-C, HDL-C, and triglycerides. Therefore, in the ERFC analysis, the effect of LDL-C is exactly equal to the effect of non-HDL-C on the risk of CHD by definition in the analysis. The authors confirmed this fact by demonstrating that in a subsample of 8 studies involving 44 234 individuals, the effect of directly measured LDL-C on the risk of CHD was nearly identical to the effect of non-HDL-C (and calculated LDL-C) per millimole per litre.

Similarly, the Prospective Studies Collaboration reported a meta-analysis of individual participant data on 892 337 persons without cardiovascular disease at baseline who had been enrolled in 61 prospective cohort studies during which 33 744 ischaemic heart disease deaths accrued over nearly 12 million person-years of follow-up. This meta-analysis reported a strong, graded log-linear association between total plasma cholesterol and the risk of ischaemic heart disease mortality.[22] Importantly, in a subsample of 153 798 participants for whom HDL-C measurements were available, the effect of non-HDL-C on the risk of ischaemic heart disease mortality was nearly identical to the effect of total cholesterol per millimole per litre.

Together, these meta-analyses of prospective epidemiologic cohort studies provide coherent and consistent evidence that plasma LDL-C concentration is strongly and log-linearly associated with a dose-dependent increase in the risk of incident ASCVD events (*Figure 2*).

Evidence from Mendelian randomization studies

Although the association between LDL-C and the risk of ASCVD is strong, graded, and reproducible in meta-analyses of prospective cohort studies, these studies are not randomized and are therefore unavoidably vulnerable to confounding, reverse causation, and other forms of bias. Mendelian randomization studies introduce a randomization scheme into an observational study specifically to assess
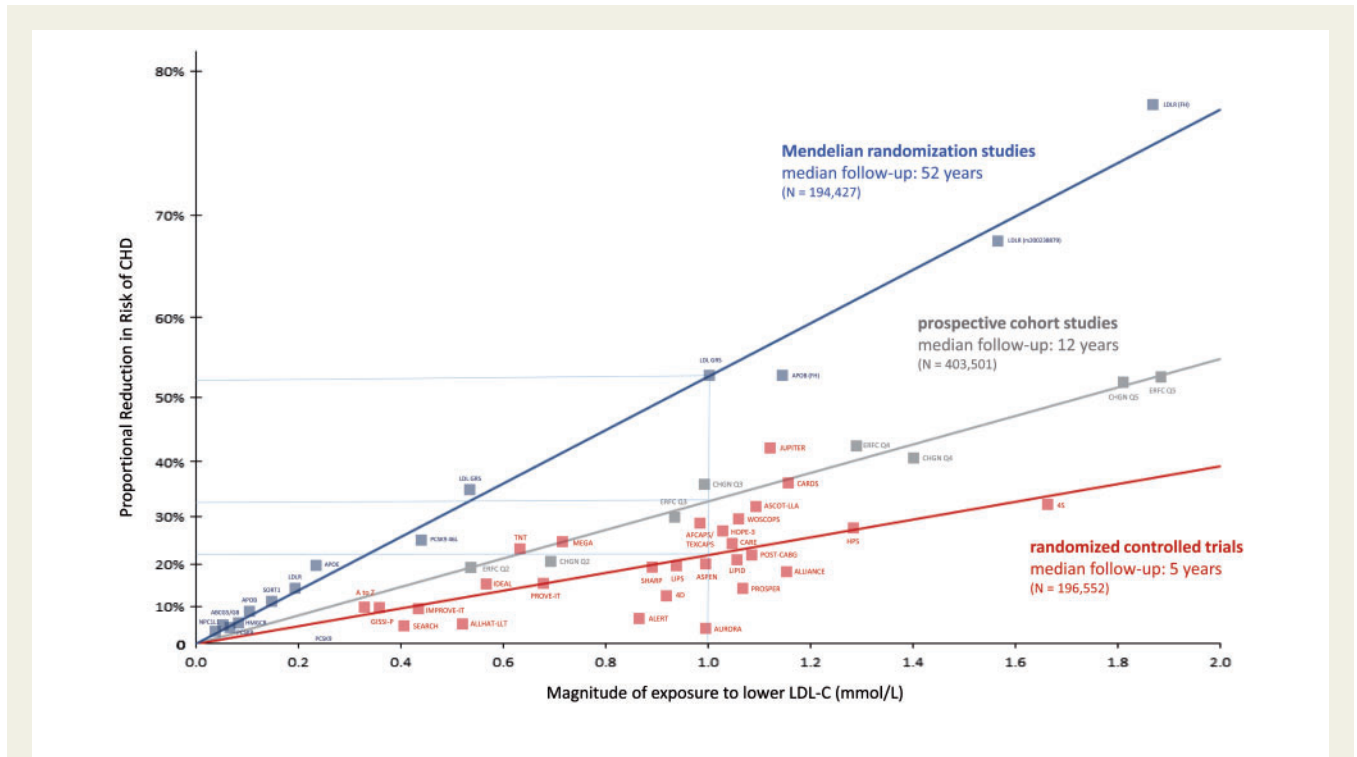
Figure 2 Log-linear association per unit change in low-density lipoprotein cholesterol (LDL-C) and the risk of cardiovascular disease as reported in meta-analyses of Mendelian randomization studies, prospective epidemiologic cohort studies, and randomized trials. The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and a cumulative effect on the risk of cardio-vascular disease. The proportional risk reduction (*y* axis) is calculated as 1-relative risk (as estimated by the odds ratio in Mendelian randomization studies, or the hazard ration in the prospective epidemiologic studies and randomized trials) on the log scale, then exponentiated and converted to a percentage. The included meta-analyses were identified from (i) MEDLINE and EMBASE using the search terms meta-analysis, LDL, and 'cardiovascu-lar or coronary'; (ii) the reference lists of the identified meta-analyses; (iii) public data from GWAS consortia; and (iv) by discussion with members of the EAS Consensus Panel. We included the most updated meta-analyses available, giving preference to meta-analyses that used individual participant data. Trial acronyms: AF/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT, Assessment of LEscol in Renal Transplantation; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid Lowering Trial; ALLIANCE, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus; ASCOT LLA, Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CARE, Cholesterol and Recurrent Events; CARDS, Collaborative Atorvastatin Diabetes Study; CHGN, Community Health Global Network; 4D Deutsche Diabetes Dialyse Studies; ERFC, Emerging Risk Factors Collaboration; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HOPE, Heart Outcomes Prevention Evaluation Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; IMPROVE-IT, Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial; LIPID,, Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; POST-CABG, Post Coronary Artery Bypass Graft; PROSPER, Pravastatin in elderly individuals at risk of vascular disease; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; SHARP, Study of Heart and Renal Protection; TNT, Treating to New Targets; WOSCOPS, West of Scotland Coronary Prevention Study.

whether an observed association between an exposure and an out-come is likely to be causal.[23]

Numerous variants in multiple genes have been reported to be associated with lower LDL-C levels.[24,25] Each of these variants is in-herited approximately randomly at the time of conception in a pro-cess sometimes referred to as Mendelian randomization. Therefore, inheriting an LDL-C lowering allele in one of these genes is analogous to being randomly allocated to treatment with an LDL-C-lowering therapy, while inheriting the other allele is analogous to being ran-domly allocated to 'usual care'. If the variant under study is associated

solely with LDL-C and not with other lipid or non-lipid pleiotropic ef-fects, and if allocation is indeed random, then comparing the risk of ASCVD among persons with and without such a variant should pro-vide an unconfounded estimate of the causal effect of lower LDL-C levels on the risk of ASCVD in a manner analogous to a long-term randomized trial.[26]

Mendelian randomization studies have consistently demonstrated that variants in over 50 genes that are associated with lower LDL-C levels (but not with other potential predictors or intermediates for ASCVD) are also associated with a correspondingly lower risk of
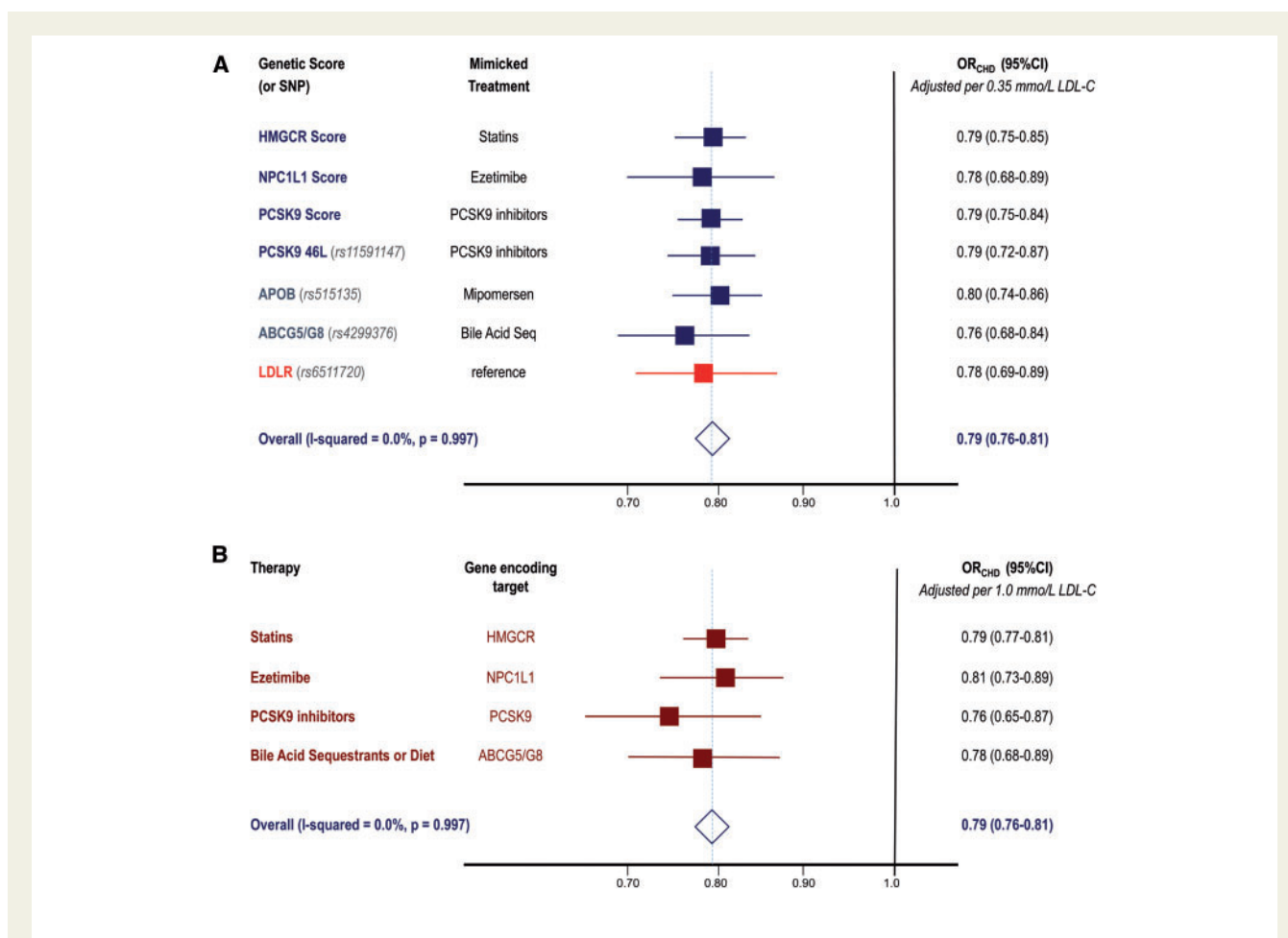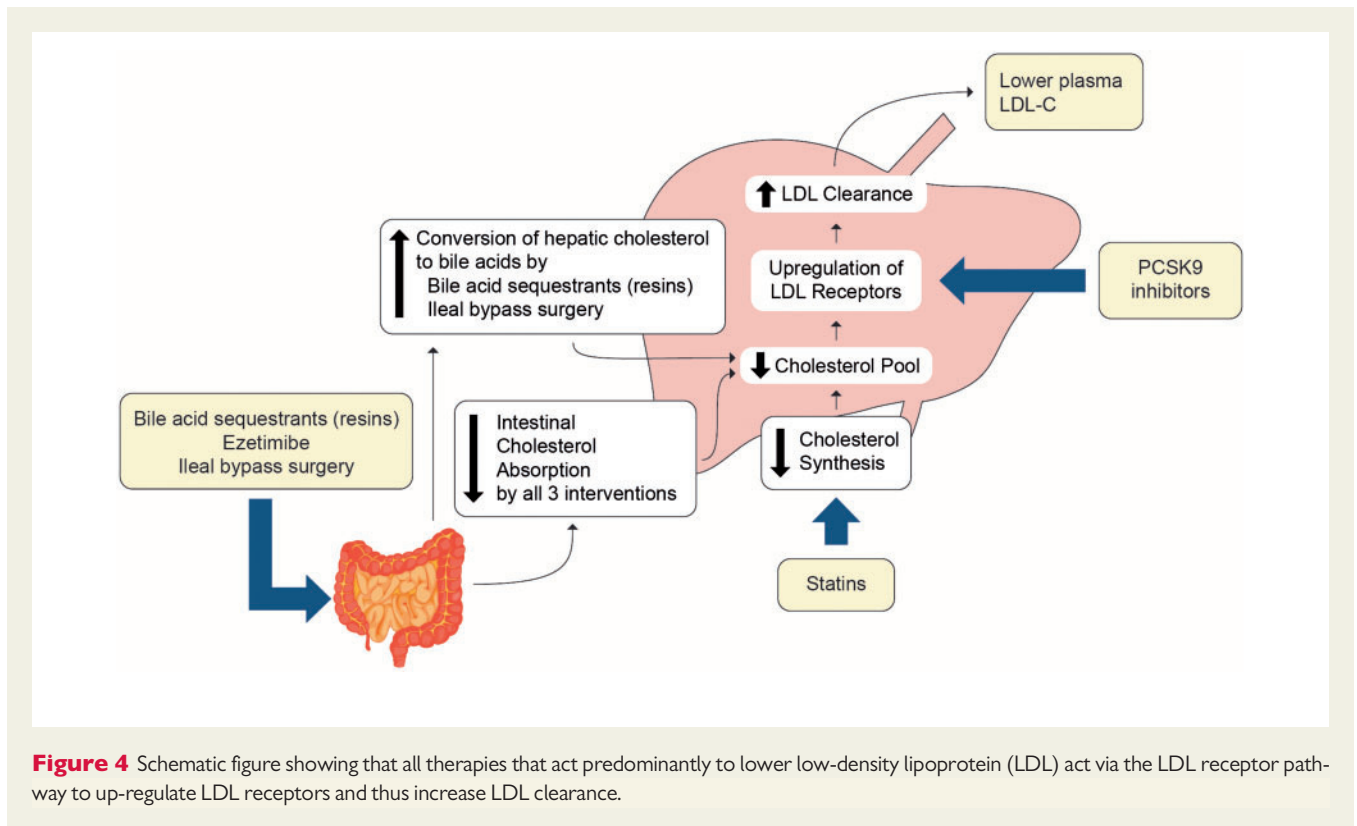
Figure 3 Effect of exposure to lower low-density lipoprotein cholesterol (LDL-C) by mechanism of LDL-C lowering. Panel *A* shows the effect of genetic variants or genetic scores combining multiple variants in the genes that encode for the targets of currently available LDL-C-lowering therapies, adjusted for a standard decrement of 0.35 mmol/L lower LDL-C, in comparison with the effect of lower LDL-C mediated by variants in the LDL receptor gene. Panel *B* shows the effect of currently available therapies that act to primarily lower LDL-C through the LDL receptor pathway, adjusted per millimole per litre lower LDL-C. Both the naturally randomized genetic data in Panel *A* and the data from randomized trials in Panel *B* suggest that the effect of LDL-C on the risk of cardiovascular events is approximately the same per unit change in LDL-C for any mechanism that lowers LDL-C via up-regulation of the LDL receptor where the change in LDL-C (which is used in clinical medicine to estimate the change in LDL particle concentration) is likely to be concordant with changes in LDL particle concentration.

CHD,[20,27–30] thus providing powerful evidence that LDL is causally associated with the risk of CHD. Indeed, when the effect of each LDL-C variant is plotted against its effect on CHD, there is a continuous, dose-dependent, and log-linear causal association between the magnitude of the absolute change in LDL-C level and the lifetime risk of CHD (*Figure 2*).[28,30]

Furthermore, when adjusted for a standard decrement in LDL-C, each of the genetic variants associated with LDL-C has a remarkably similar effect on the risk of CHD per unit lower LDL-C, including variants in the genes that encode the targets of pharmacological agents commonly used to lower LDL-C [i.e. 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), the target of statins; Niemann-Pick C1-like 1 (NPC1L1), the target of ezetimibe; and proprotein convertase subtilisin/kexin type 9

(PCSK9), the target of the monoclonal antibodies alirocumab and evolocumab; see *Figure 3*], with no evidence of any heterogeneity of effect ($I^2 = 0\%$).[28,30,31] This observation strongly implies that the causal effect of these variants on the risk of CHD is mediated essentially entirely through LDL, because it would be implausible that variants in numerous different genes involving multiple distinct biological pathways by which LDL is lowered would each have directionally concordant and quantitatively similar pleiotropic effects on the risk of ASCVD.

Taken together, meta-analyses of Mendelian randomization studies involving more than 300 000 participants and 80 000 CHD cases provide compelling evidence that LDL is causally associated with the risk of ASCVD and that the causal effect of LDL on ASCVD is largely independent of the mechanism by which LDL is 'lowered'.

Figure 4 Schematic figure showing that all therapies that act predominantly to lower low-density lipoprotein (LDL) act via the LDL receptor pathway to up-regulate LDL receptors and thus increase LDL clearance.

Evidence from randomized controlled trials

Perhaps the most compelling clinical evidence for causality is provided by randomized clinical trials evaluating the effect of therapies that reduce LDL-C on the risk of cardiovascular events. (For reference, *Figure 4* shows the principal sites of action of therapeutic interventions that act mainly to lower LDL.) It is important to note, however, that the interpretation of any given individual trial can be substantially affected by its design. In general, studies that are underpowered due to small sample sizes or few accrued events, that do not produce a substantial difference in LDL-C concentration between treatment arms, and those with short-term follow-up (2 years or less) are more likely to produce results that do not show statistically significant differences. Furthermore, some therapies that lower LDL-C (e.g. oestrogen) also have adverse effects that increase the risk of ASCVD which can attenuate or erase the clinical benefit of lowering LDL-C. Over-interpretation of these individual trials may lead to biased conclusions. For that reason, we focus on the totality of the evidence derived from meta-analyses of randomized trials.

In a meta-analysis of individual-participant data from 26 statin trials including almost 170 000 individuals, treatment with a statin was associated with a log-linear 22% proportional reduction in the risk of major cardiovascular events per millimole per litre reduction in LDL-C over a median of 5 years of treatment.[32] The effect was somewhat less during the first year of treatment, followed by a consistent 22-24% proportional reduction in cardiovascular events per millimole per litre reduction in LDL-C during each subsequent year of

treatment.[33] The magnitude of this effect was independent of baseline LDL-C level, similar among persons with and without pre-existing cardiovascular disease at baseline, and remarkably consistent in all subgroups studied.[32,33] This meta-analysis therefore provides powerful evidence that reducing plasma LDL-C levels by inhibiting HMG-CoA reductase with a statin leads to dose-dependent reduction in the risk of major cardiovascular events that is proportional to the absolute magnitude of the reduction in LDL-C (*Figure 2*).

Notably, in the statin trials, the absolute yearly event rate observed in each randomized treatment arm was strongly and linearly associated with the absolute achieved LDL-C level (*Figure 5A*).[34] In these studies, LDL-C and apoB concentrations had very similar effects on the risk of cardiovascular events per millimole per litre, thus confirming that LDL-C is a satisfactory surrogate for LDL particle number under most circumstances. Furthermore, intravascular ultrasound studies of coronary atherosclerosis involving statin-treated patients have consistently demonstrated that progression of coronary atherosclerotic plaque volume can be substantially arrested at achieved LDL-C levels of ~1.8 mmol/L (70 mg/dL) (*Figure 5B*).[35,36]

Importantly, other therapies that reduce LDL-C without inhibiting HMG-CoA reductase have also been shown to reduce the risk of cardiovascular events in large randomized cardiovascular outcome trials. Ezetimibe inhibits intestinal absorption of cholesterol by binding to the NPC1L1 transporter protein.[37] Among the 18 144 persons with acute coronary syndrome enrolled in the IMPROVE-IT trial, treatment with ezetimibe plus a statin vs. statin monotherapy reduced LDL-C levels by 0.40 mmol/L over the trial duration, and was associated with a 6.5% proportional reduction in major cardiovascular events.[38] Supportive evidence is available from the SHARP
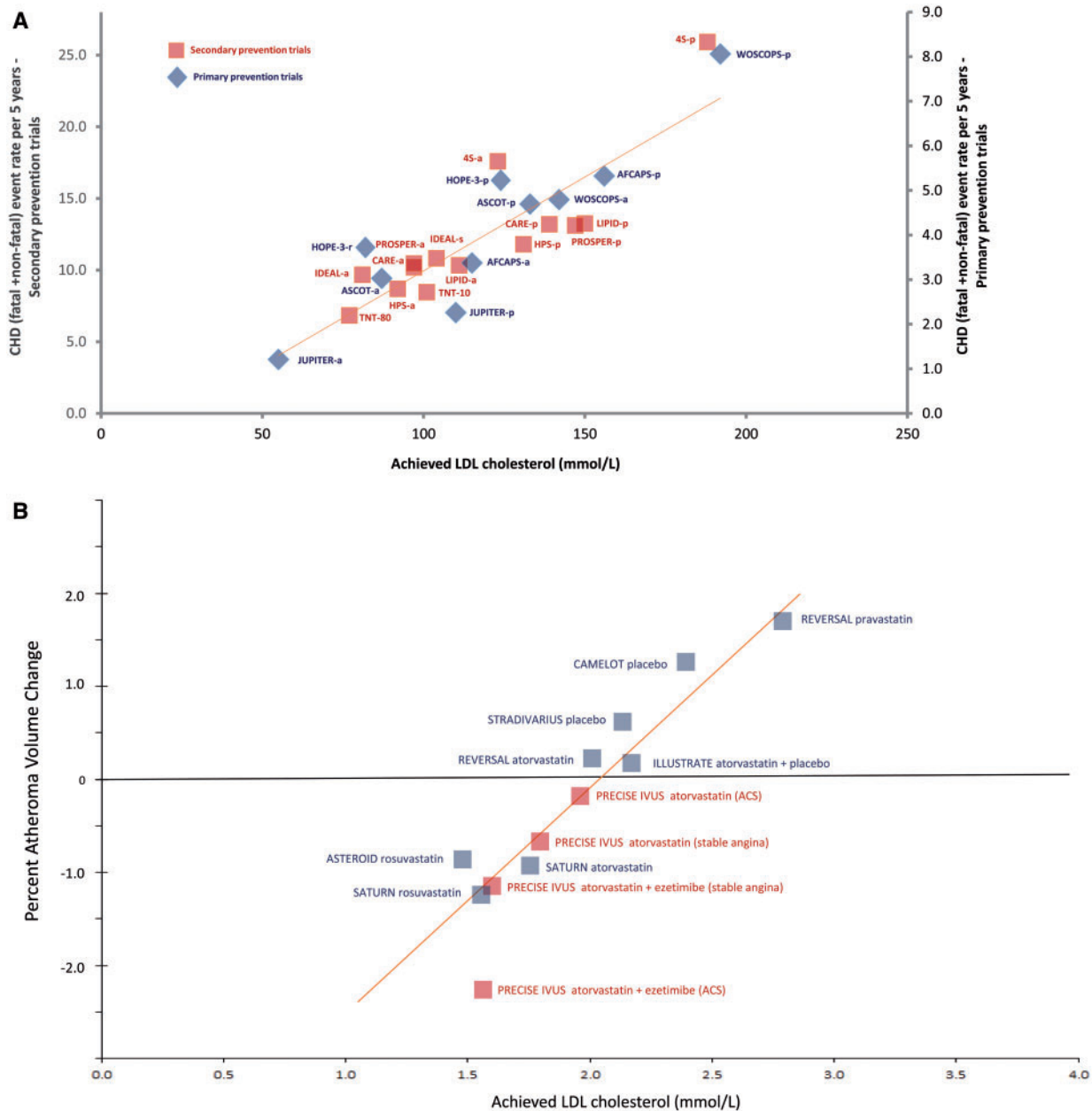
Figure 5 Linear association between achieved low-density lipoprotein cholesterol (LDL-C) level and absolute coronary heart disease (CHD) event rate or progression of atherosclerosis. Panel *A* shows absolute cardiovascular event rates in randomized statin trials and Panel *B* shows progression of atherosclerosis as measured by intravascular ultrasound. In Panel *A*, achieved LDL-C in primary prevention trials and secondary prevention trials in stable CHD patients was related to the end point of CHD events (fatal plus non-fatal myocardial infarction, sudden CHD death) proportioned to 5 years assuming linear rates with time. Trendlines for primary and secondary prevention associations are virtually superimposable. Key: p, placebo; a, active treatment arm, except for IDEAL, where s, simvastatin and a, atorvastatin; and HOPE-3, where r, rosuvastatin; and TNT where reference is made to atorvastatin 10 and 80 mg dose. Trial acronyms: AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; ASCOT, Anglo Scandinavian Cardiac Outcomes Trial; ASTEROID, A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; CARE, Cholesterol and Recurrent Events; CAMELOT, Comparison of Amlodipine vs. Enalapril to Limit Occurrence of Thrombosis; HOPE, Heart Outcomes Prevention Evaluation Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; ILLUSTRATE, Investigation of Lipid Level Management Using Coronary Ultrasound To Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; PRECISE IVUS, Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound; PROSPER, Pravastatin in elderly individuals at risk of vascular disease; REVERSAL, Reversal of Atherosclerosis With Aggressive Lipid Lowering; 4S Scandinavian Simvastatin Survival Study; SATURN, Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs. Atorvastatin; STRADIVARIUS, Strategy To Reduce Atherosclerosis Development InVolving Administration of Rimonabant—the Intravascular Ultrasound Study; TNT, Treating to New Targets; WOSCOPS, West Of Scotland Coronary Prevention Study.

trial in 9270 persons with chronic kidney disease, which compared treatment with the combination of simvastatin and ezetimibe with placebo. Combination treatment reduced LDL-C levels by 0.85 mmol/L (33 mg/dL) and reduced the incidence of major cardiovascular events by 17% relative to placebo.[39] In both trials, the magnitude of the observed proportional risk reduction was consistent with the clinical benefit that would be expected from similar absolute reductions in LDL-C during treatment with statin monotherapy. These data suggest that statins and ezetimibe have therapeutically equivalent effects on the risk of cardiovascular events per unit lower LDL-C (Figure 3B). These findings also agree closely with the naturally randomized genetic data that have demonstrated that variants in the HMGCR and NPC1L1 genes have biologically equivalent effects on the risk of cardiovascular disease per unit lower LDL-C[31,40] (Figure 3A).

In addition, among 27,564 participants with cardiovascular disease enrolled in the recently reported FOURIER trial, treatment with the PCSK9 monoclonal antibody evolocumab added to a statin reduced LDL-C by 1.4 mmol/L (53.4 mg/dl) to a mean LDL-C level of 0.78 mmol/L (30 mg/dl) and reduced the incidence of cardiovascular death, MI or stroke by 20% during a median of 2.2 years of follow-up.[41,42] When analysed by each year of treatment, evolocumab had nearly identical effects on the risk of multiple different cardiovascular endpoints per millimole per litre reduction in LDL-C compared to treatment with a statin as reported by the Cholesterol Treatment Trialists Collaboration.[31] The results of this trial are remarkably consistent with the results of a recent Mendelian randomization study that showed that variants in the PCSK9 and HMGCR genes have nearly identical effects on the risk of cardiovascular events per unit lower LDL-C, and therefore accurately predicted that PCSK9 inhibitors would reduce the risk of cardiovascular events by approximately the same amount as statins per unit reduction in LDL-C.[43] The results of the FOURIER trial are also consistent with the results of the recent GLAGOV trial in which treatment with evolocumab added to a statin reduced LDL-C levels by 1.45 mmol/L and induced plaque regression that appeared to be directly proportional to the achieved absolute LDL-C level, even at LDL-C levels as low as 0.95 mmol/L (36.6 mg/dl).[44] Taken together, the results of these studies strongly suggest that PCSK9 inhibitors and statins have biologically equivalent effects on the risk of cardiovascular events per unit change in LDL-C.

Furthermore, in the Lipid Research Clinics Coronary Primary Prevention Trial, treatment with the bile acid sequestrant cholestyramine reduced LDL-C by 0.7 mmol/L and reduced the relative risk of cardiovascular death or MI by 19%.[45] Similarly, in the Program on Surgical Control of Hyperlipidemia (POSCH) study, ileal bypass surgery reduced LDL-C by 1.85 mmol/L and reduced the relative risk of cardiovascular death or MI by 35%.[46] In both trials, the observed risk reduction was consistent with the proportional risk reduction per unit lower LDL-C observed during treatment with a statin or with combined statin and ezetimibe therapy (Figure 2). Indeed, in a recent meta-analysis of 49 studies including 312 175 participants and 39 645 major vascular events that compared the effects of 9 different types of lipid-lowering therapies, nearly all of these therapeutic approaches to lowering LDL-C were associated with a consistent 20–25% proportional reduction in vascular events per millimole per litre reduction in LDL-C.[47] These findings are in line with those from the Mendelian randomization studies and demonstrate that the clinical benefit of lowering LDL-C appears to be independent of the mechanism by which LDL-C is lowered (Figure 3).

The one notable exception to this finding is the effect of the cholesteryl ester transfer protein (CETP) inhibitors. In the recently reported ACCELERATE Trial, the CETP inhibitor evacetrapib plus a statin reduced LDL-C by 0.75 mmol/L compared with statin monotherapy but did not reduce the risk of cardiovascular events.[48] To date, we lack a mechanistic explanation for this finding, although deleterious effects on CHD due to a 1.5 mmHg mean increase in systolic blood pressure and/or possible dysfunctional HDL phenotypes on evacetrapib may constitute contributory factors. In addition, the LDL particle-lowering effect of CETP inhibitors appears to become attenuated when a CETP inhibitor is added to a statin, thus leading to discordance between the measured LDL-C and apoB reductions.[48] The ongoing 30 000-person REVEAL trial with the CETP inhibitor anacetrapib will provide more definitive evidence of the effect of adding a CETP inhibitor to a statin on the risk of cardiovascular events.

Criteria for causality

A critical appraisal of the evidence discussed in this review demonstrates that the association between plasma LDL-C concentration and the risk of ASCVD satisfies all the criteria for causality (Table 1).[49] Indeed, the prospective epidemiologic studies, Mendelian randomization studies, and randomized intervention trials all demonstrate a remarkably consistent dose-dependent log-linear association between the absolute magnitude of exposure to LDL-C and the risk of ASCVD, and together demonstrate that the effect of LDL-C on the risk of ASCVD increases with increasing duration of exposure (Figure 2). This concordance between multiple lines of evidence, most notably the remarkable concordance between the unbiased naturally randomized genetic data and the results of numerous randomized intervention trials using multiple different agents to reduce LDL-C, provides overwhelming clinical evidence that LDL causes ASCVD and that lowering LDL reduces the risk of cardiovascular events.

Evidence for the cumulative effect of exposure to LDL on ASCVD

Mendelian randomization studies suggest that long-term exposure to lower LDL-C is associated with up to a three-fold greater proportional reduction in the risk of cardiovascular disease per unit reduction in LDL-C, when compared with shorter term treatment with a statin started later in life after atherosclerosis has developed.[28] This finding suggests that the causal effect of LDL on the risk of ASCVD is determined by both the absolute magnitude and the cumulative duration of exposure to LDL-C. This finding is consistent with increasing benefit observed over time in the long-term follow-up of the WOSCOPS trial.[50]

Because the effect of LDL-C on the risk of ASCVD appears to be both causal and cumulative over time, lowering the plasma LDL-C level earlier than is currently recommended, may result in proportionally greater reductions in the lifetime risk of ASCVD than which is estimated in short-term randomized trials. Integrating the available evidence from Mendelian randomization studies and randomized trials suggests that each millimole per litre reduction in LDL-C reduces

Table 2 Expected proportional risk reduction based on pre-treatment low-density lipoprotein cholesterol (LDL-C), absolute magnitude of LDL-C reduction, and total duration of therapy

Baseline LDL-C (mmol/L)	Absolute reduction LDL-C (mmol/L)	Duration of treatment exposure [expected proportional risk reduction (%)]					Guideline recommended treatment[51,52]
		5 years	10 years	20 years	30 years	40 years	
7	3.5	58	68	81	89	93	Yes (due to markedly elevated LDL-C)
7	3.0	53	62	76	85	90	
7	2.5	46	56	70	79	86	
7	2.0	39	48	61	71	79	
7	1.5	31	39	51	61	69	
5	2.5	46	56	70	79	86	Yes (due to markedly elevated LDL-C)
5	2.0	39	48	61	71	79	
5	1.5	31	39	51	61	69	
5	1.0	22	28	38	46	54	
3	1.5	31	39	51	61	69	Depends on risk of ASCVD
3	1.0	22	28	38	46	54	
3	0.5	12	15	21	27	32	
2	1.0	22	28	38	46	54	Depends on risk of ASCVD
2	0.5	12	15	21	27	32	

Recommendations for treatment: expected clinical benefit per unit reduction in LDL-C expressed as the expected proportional risk reduction (%). The proportional reduction in short-term risk is based on an expected 22% reduction in risk per millimole per litre reduction in LDL-C over 5 years as estimated from randomized trials and is calculated as $[(1-0.78^{(\text{absolute reduction in LDL-C in mmol/L})}) \times 100]$. The proportional reduction in long-term risk is based on an expected 54% reduction in risk per millimole per litre reduction in LDL-C over 40 years of exposure as estimated from Mendelian randomization studies and is calculated as $[(1-0.46^{(\text{absolute reduction in LDL-C in mmol/L})}) \times 100]$. The expected proportional risk reduction per mmol/L reduction in LDL-C for any specific treatment duration is calculated as: $[(1-e^{(-0.249 + (\text{number of years of treatment} - 5) \times (-0.0152))}) \times 100]$.
ASCVD, atherosclerotic cardiovascular disease.

Table 3 Expected short-term absolute risk reduction and number needed to treat based on baseline absolute risk of cardiovascular disease and pre-treatment low-density lipoprotein cholesterol (LDL-C) with 5 years of treatment to lower LDL-C

10-year absolute risk of CVD (%)	Baseline LDL-C mmol/L (mg/dL)	LDL-C after 50% reduction mmol/L (mg/dL)	Proportional risk reduction (%)	10-year Absolute risk (%) after 50% LDL-C reduction	ARR (%)	NNT	Guideline recommended treatment[51,52]
20	5 (200)	2.5 (100)	42.8	11.4	8.6	11.7	Yes (based on 10-
20	4 (160)	2.0 (80)	36	12.8	7.2	13.9	year risk of
20	3 (120)	1.5 (60)	28.4	14.3	5.7	17.6	ASCVD)
20	2 (80)	1.0 (40)	20	16	4	25	
15	5 (200)	2.5 (100)	42.8	8.6	6.4	15.6	Yes (based on 10-
15	4 (160)	2.0 (80)	36	9.6	5.4	18.5	year risk of
15	3 (120)	1.5 (60)	28.4	10.7	4.3	23.4	ASCVD)
15	2 (80)	1.0 (40)	20	12	3	33.3	
10	5 (200)	2.5 (100)	42.8	5.7	4.3	23.4	Yes (based on 10-
10	4 (160)	2.0 (80)	36	6.4	3.6	27.8	year risk of
10	3 (120)	1.5 (60)	28.4	7.2	2.8	35.2	ASCVD)
10	2 (80)	1.0 (40)	20	8	2	50	
5	5 (200)	2.5 (100)	42.8	2.9	2.1	46.8	No (based on 10-
5	4 (160)	2.0 (80)	36	3.2	1.8	55.6	year risk of
5	3 (120)	1.5 (60)	28.4	3.6	1.4	70.3	ASCVD)
5	2 (80)	1.0 (40)	20	4	1	100	

Recommendations for treatment: expected clinical benefit per unit reduction in LDL-C. The proportional reduction in short-term risk is based on an expected 22% reduction in risk per millimole per litre reduction in LDL-C over 5 years as estimated from randomized trials and is calculated as $[(1-0.78^{(\text{absolute reduction in LDL-C in mmol/L})}) \times 100]$. The absolute risk reduction is calculated as [ARR = Column 1 - Column 5], and the number needed to treat is calculated as $[(1 \div ARR) \times 100]$.
CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; ARR, absolute risk reduction; NNT, number needed to treat.

Table 4 Expected long-term absolute risk reduction and number needed to treat based on baseline absolute risk of cardiovascular disease and pre-treatment low-density lipoprotein cholesterol (LDL-C) with 30 years of treatment (or exposure) to lower LDL-C

30-year Absolute risk of CVD (%)	Baseline LDL-C mmol/L (mg/dL)	LDL-C after reduction mmol/L (mg/dL)	Proportional risk reduction (%)	30-year absolute risk (%) after 50% LDL-C reduction	ARR(%)	NNT	Guideline recommended treatment[51,52]
60	5 (200)	2.5 (100)	82.3	10.6	49.4	2	Individualized (based
60	4 (160)	2.0 (80)	75	15	45	2.2	on lifetime risk of
60	3 (120)	1.5 (60)	64.6	21.2	38.9	2.6	ASCVD)
60	2 (80)	1.0 (40)	50	30	30	3.3	
45	5 (200)	2.5 (100)	82.3	8	37	2.7	Individualized (based
45	4 (160)	2.0 (80)	75	11.3	33.8	3	on lifetime risk of
45	3 (120)	1.5 (60)	64.6	15.9	29.1	3.4	ASCVD)
45	2 (80)	1.0 (40)	50	22.5	22.5	4.4	
30	5 (200)	2.5 (100)	82.3	5.3	24.7	4	Individualized (based
30	4 (160)	2.0 (80)	75	7.5	22.5	4.4	on lifetime risk of
30	3 (120)	1.5 (60)	64.6	10.6	19.4	5.2	ASCVD)
30	2 (80)	1.0 (40)	50	15	15	6.7	
15	5 (200)	2.5 (100)	82.3	2.7	12.3	8.1	Individualized (based
15	4 (160)	2.0 (80)	75	3.8	11.3	8.9	on lifetime risk of
15	3 (120)	1.5 (60)	64.6	5.3	9.7	10.3	ASCVD)
15	2 (80)	1.0 (40)	50	7.5	7.5	13.3	

Recommendations for treatment: expected clinical benefit per unit reduction in LDL-C. The proportional reduction in long-term risk is based on an expected 54% reduction in risk per millimole per litre reduction in LDL-C over 40 years of exposure as estimated from Mendelian randomization studies and is calculated as $[(1-0.46^{(\text{absolute reduction in LDL-C in mmol/L})}) \times 100]$. The absolute risk reduction is calculated as [ARR = Column 1 - Column 5], and the number needed to treat is calculated as $[(1 \div ARR) \times 100]$.

CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; ARR, absolute risk reduction; NNT, number needed to treat.

the relative risk of ASCVD events by ~10% during the first year of treatment, by ~16% after 2 years of treatment and by ~20% after 3 years of treatment, presumably related to the stabilization of any existing underlying plaque burden.[33] Each subsequent year of treatment after the third might then be expected to result in a further 1.5% proportional reduction in ASCVD events per millimole per litre per year (*Tables 2–4*). Therefore, 5 years of treatment with a lipid-lowering agent should reduce the relative risk of ASCVD by ~20–25% per millimole per litre reduction in LDL-C, while 40 years of treatment (or approximately equivalently 40 years of exposure to lower LDL-C) would be expected to reduce ASCVD events by ~50–55% per millimole per litre lower LDL-C (*Figure 2*).

Recommendations for treatment

The evidence clearly indicates that reducing LDL-C by increasing the numbers of hepatic LDL receptors can reduce ASCVD (*Figure 4*). Because reducing LDL-C should have a constant effect on the risk of ASCVD per unit absolute reduction in LDL-C, and because LDL-C has both a causal and a cumulative effect on the risk of ASCVD, the proportional reduction in risk that a person can expect from reducing LDL-C will depend on their baseline LDL-C level, the absolute magnitude of the reduction in LDL-C, and the duration of therapy. Similarly, the absolute risk reduction that a person can expect from reducing LDL-C will depend on their baseline risk of ASCVD, baseline LDL-C level, the absolute magnitude of the reduction in LDL-C, and the duration of LDL-C-lowering therapy.

Tables 2–4 provide estimates of the potential clinical benefit that can be achieved by lowering plasma LDL-C concentration based on a person's baseline risk of ASCVD, baseline LDL-C, and the duration of lipid-lowering therapy, expressed as both expected proportional and absolute risk reductions. Physicians can use this information to discuss with their patients about the potential benefits of lowering LDL-C based on the causal effect of LDL on the risk of ASCVD.

Impact of other exposures on the casual effect of LDL on ASCVD

In addition to LDL, multiple other exposures have been reported to be associated with the risk of ASCVD including elevated systolic blood pressure, diabetes, and tobacco smoking.[1] Both the Mendelian randomization studies and the meta-analyses of randomized trials demonstrate that changes in LDL-C have a very consistent proportional effect on the risk of ASCVD across different levels of various risk factors. As a result, a given absolute reduction in LDL-C is associated with the same proportional reduction in the risk of ASCVD, regardless of the presence or absence of other risk factors. However, because persons with more risk factors have a higher absolute rate of ASCVD in comparison with persons with fewer risk factors, the constant proportional reduction in risk per millimole per litre reduction in LDL-C will translate into greater absolute risk reductions for persons with increasing numbers of risk factors or among persons who are at a higher risk of cardiovascular disease more generally.

Finally, an important area for future research is to identify persons who are most likely to benefit from LDL-C-lowering therapies. The probability that LDL will be retained within the arterial intima leading to the development and growth of atherosclerotic plaque increases with increasing concentration of circulating LDL particles.[6] Because retention of LDL particles is a probabilistic event, one would expect, therefore, that people with similar LDL-C level will have a distribution of underlying atherosclerotic plaque burdens. Genetic factors may influence whether a person is more or less likely to retain LDL-C within the arterial intima or influence the degree to which retention of LDL particles triggers the inflammatory process or oxidative changes that influence the rate of plaque growth and the propensity for plaque disruption.

Indeed, many of the genetic variants most strongly associated with ASCVD in GWAS are in genes that encode for components of the arterial wall, which may modify susceptibility to retaining LDL or modify responses to the accumulated LDL within the artery wall.[27] This hypothesis is consistent with the results of a meta-analysis of statin trials that reported that persons with the highest tertile of a genetic ASCVD risk score derived a greater proportional reduction in the risk of cardiovascular events per millimole per litre reduction in LDL-C than did persons with the lowest tertile of the genetic risk score.[53] The genetic score used in this study may have included variants that lead to a greater susceptibility to retain LDL particles. Identifying genetic and other factors that influence the likelihood of retaining LDL particles within the intima is an active area of ongoing research and may eventually help to personalize the prevention of cardiovascular disease by identifying persons who are most vulnerable to the deleterious effects of LDL-C and therefore are most likely to benefit from therapies that lower LDL-C.

Conclusions

Considered together, the strong and consistent evidence from the genetic studies, prospective epidemiologic cohort studies, Mendelian randomization studies, and randomized intervention trials discussed here, supported by mechanistic evidence to be presented in the second Consensus Statement on LDL causality, establishes that LDL is not merely a biomarker of increased risk but a causal factor in the

pathophysiology of ASCVD. The key implications for this conclusion are presented in *Box 1*.

References

1. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937–952.

2. Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell* 2015;**161**:161–172.

3. DuBroff R. Cholesterol paradox: a correlate does not a surrogate make. *Evid Based Med* 2017;**22**:15–19.

4. Ravnskov U, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B, Hynes N, Kendrick M, Langsjoen PH, Malhotra A, Mascitelli L, McCully KS, Ogushi Y, Okuyama H, Rosch PJ, Schersten T, Sultan S, Sundberg R. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open* 2016;**6**:e010401.

5. Camejo G, Lopez A, Vegas H, Paoli H. The participation of aortic proteins in the formation of complexes between low density lipoproteins and intima-media extracts. *Atherosclerosis* 1975;**21**:77–91.

6. Skålén K, Gustafsson M, Rydberg EK, Hultén LM, Wiklund O, Innerarity TL, Borén J. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. *Nature* 2002;**417**:750–754.

7. Schwenke DC, Carew TE. Initiation of atherosclerotic lesions in cholesterol-fed rabbits. II. Selective retention of LDL vs. selective increases in LDL permeability in susceptible sites of arteries. *Arteriosclerosis* 1989;**9**:908–918.

8. Frank JS, Fogelman AM. Ultrastructure of the intima in WHHL and cholesterol-fed rabbit aortas prepared by ultra-rapid freezing and freeze-etching. *J Lipid Res* 1989;**30**:967–978.

9. Tabas I, Williams KJ, Borén J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation* 2007;**116**:1832–1844.

10. Nordestgaard BG, Zilversmit DB. Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits. *J Lipid Res* 1988;**29**:1491–1500.

11. Descamps OS, Bruniaux M, Guilmot PF, Tonglet R, Heller FR. Lipoprotein concentrations in newborns are associated with allelic variations in their mothers. *Atherosclerosis* 2004;**172**:287–298.

12. Chapman MJ. Animal lipoproteins: chemistry, structure, and comparative aspects. *J Lipid Res* 1980;**21**:789–853.

13. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. *Eur Heart J* 2013;**34**:3478–3490.

14. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjærg-Hansen A, Watts GF, Averna M, Boileau C, Borén J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;**35**:2146–2157.

15. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, Morrison AC, Brody JA, Gupta N, Nomura A, Kessler T, Duga S, Bis JC, van Duijn CM, Cupples LA, Psaty B, Rader DJ, Danesh J, Schunkert H, McPherson R, Farrall M, Watkins H, Lander E, Wilson JG, Correa A, Boerwinkle E, Merlini PA, Ardissino D, Saleheen D, Gabriel S, Kathiresan S. Diagnostic yield of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol* 2016;**67**:2578–2589.

16. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J* 2016;**37**:1384–1394.

17. Raal FJ, Pilcher GJ, Waisberg R, Buthelezi EP, Veller MG, Joffe BI. Low-density lipoprotein cholesterol bulk is the pivotal determinant of atherosclerosis in familial hypercholesterolemia. *Am J Cardiol* 1999;**83**:1330–1333.

18. Schmidt HH, Hill S, Makariou EV, Feuerstein IM, Dugi KA, Hoeg JM. Relationship of cholesterol-year score to severity of calcific atherosclerosis and tissue deposition in homozygous familial hypercholesterolemia. *Am J Cardiol* 1996;**77**:575–580.

19. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Borén J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Steinhagen Thiessen E, Stroes ES, Taskinen MR, Tybjærg-Hansen A, Wiklund O; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015;**36**:2425–2437.

20. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;**354**:1264–1272.

21. Emerging Risk Factors C, Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundström J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RP, Assmann G, D'agostino RB Sr, Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gómez-de-la-Cámara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FG, Casiglia E, Hofman A, Salomaa V, Barrett-Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw KT, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J. Lipid-related markers and cardiovascular disease prediction. *JAMA* 2012;**307**:2499–2506.

22. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;**370**:1829–1839.

23. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* 2008;**27**:1133–1163.

24. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, König IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Döring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA Jr, Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe

PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010;**466**:707–713.

25. Global Lipids Genetics Consortium. Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013;**45**:1274–1283.

26. Ference BA. Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps. *Curr Opin Lipidol* 2015;**26**:566–571.

27. CARDIoGRAMplusC4D Consortium. A comprehensive 1000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet* 2015;**47**:1121–1130.

28. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA Sr, Flack JM. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol* 2012;**60**:2631–2639.

29. Linsel-Nitschke P, Götz A, Erdmann J, Braenne I, Braund P, Hengstenberg C, Stark K, Fischer M, Schreiber S, El Mokhtari NE, Schaefer A, Schrezenmeier J, Rubin D, Hinney A, Reinehr T, Roth C, Ortlepp J, Hanrath P, Hall AS, Mangino M, Lieb W, Lamina C, Heid IM, Doering A, Gieger C, Peters A, Meitinger T, Wichmann HE, König IR, Ziegler A, Kronenberg F, Samani NJ, Schunkert H. Lifelong reduction of LDL-cholesterol related to a common variant in the LDL-receptor gene decreases the risk of coronary artery disease: a Mendelian Randomisation study. *PLoS One* 2008;**3**:e2986.

30. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Swerdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, UCLEB Consortium, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almoguera B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karczewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimäki M, Lawlor DA, Dudbridge F, Samani NJ, Keating BJ, Hingorani AD, Casas JP. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J* 2015;**36**:539–550.

31. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 x 2 factorial Mendelian randomization study. *J Am Coll Cardiol* 2015;**65**:1552–1261.

32. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.

33. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD5, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;**388**:2532–2561.

34. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, Hitman GA, Welch KM, DeMicco DA, Zwinderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM Jr, Ridker PM, Kastelein JJ. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012;**307**:1302–1309.

35. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM. ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;**295**:1556–1565.

36. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011;**365**:2078–2087.

37. Garcia-Calvo M, Lisnock J, Bull HG, Hawes BE, Burnett DA, Braun MP, Crona JH, Davis HR Jr, Dean DC, Detmers PA, Graziano MP, Hughes M, Macintyre DE, Ogawa A, O'neill KA, Iyer SP, Shevell DE, Smith MM, Tang YS, Makarewicz AM, Ujjainwalla F, Altmann SW, Chapman KT, Thornberry NA. The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). *Proc Natl Acad Sci USA* 2005;**102**:8132–8137.

38. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.

39. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano

M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–2192.

40. Lauridsen BK, Stender S, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Genetic variation in the cholesterol transporter NPC1L1, ischemic vascular disease and gallstone disease. *Eur Heart J* 2015;**36**:1601–1608.

41. Sabatine MS, Giugliano RP, Keech A, Honarpour N, Wang H, Liu T, Wasserman SM, Scott R, Sever PS, Pedersen TR. Rationale and design of the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) Trial. *Am Heart J* 2016;**173**:94–101.

42. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR. FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1615664.

43. Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, Voros S, Giugliano RP, Davey Smith G, Fazio S, Sabatine MS. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med* 2016;**375**:2144–2153.

44. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of evolocumab on progression of coronary disease in statin-treated patients. The GLAGOV randomized clinical trial. *JAMA* 2016;**316**:2373–2384.

45. Lipid Research Clinics Program. The Lipid Research Clinics coronary primary prevention trial results: reduction in the incidence of coronary artery disease. *JAMA* 1984;**251**:351–364.

46. Buchwald H, Varco RL, Matts JP, Long JM, Fitch LL, Campbell GS, Pearce MB, Yellin AE, Edmiston A, Smink RD, Sawin HS, Campos CT, Hansen BJ, Tuna N, Karnegis JN, Sanmarco ME, Amplatz K, Castaneda-Zuniga WR, Hunter DW, Bissett JK, Weber FJ, Stevenson JW, Leon AS, Chalmers TC; The POSCH Group. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med* 1990; **323**:946–955.

47. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;**316**:1289–1297.

48. Lincoff AM for the ACCELERATE Trial Investigators. Lipid levels and cardiovascular outcome with cholesteryl ester transfer protein (CETP) inhibition by evacetrapib in the ACCELERATE Trial. Late Breaking Clinical Trials, ESC Congress 2016, Rome. http://congress365.escardio.org/Search-Results?vgnextkeyword=evacetrapib&Years=C365YEAR2016#.WCm9LoXXJjo (8 February 2017).

49. Hill AB. The environment and disease. Association or causation? *Proc R Soc Med* 1965;**58**:295–300.

50. Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of West of Scotland Coronary Prevention Study. *Circulation* 2016;**133**:1073–1080.

51. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL; on behalf of Authors/Task Force Members. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.

52. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation* 2014;**129**(25 Suppl 2):S1–S45.

53. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, Nordio F, Hyde CL, Cannon CP, Sacks FM, Poulter NR, Sever PS, Ridker PM, Braunwald E, Melander O, Kathiresan S, Sabatine MS. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet* 2015;**385**:2264–2271.