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**VIEWPOINT**
*Dyslipidaemias*

# The year in cardiovascular medicine 2023: the top 10 papers in dyslipidaemias

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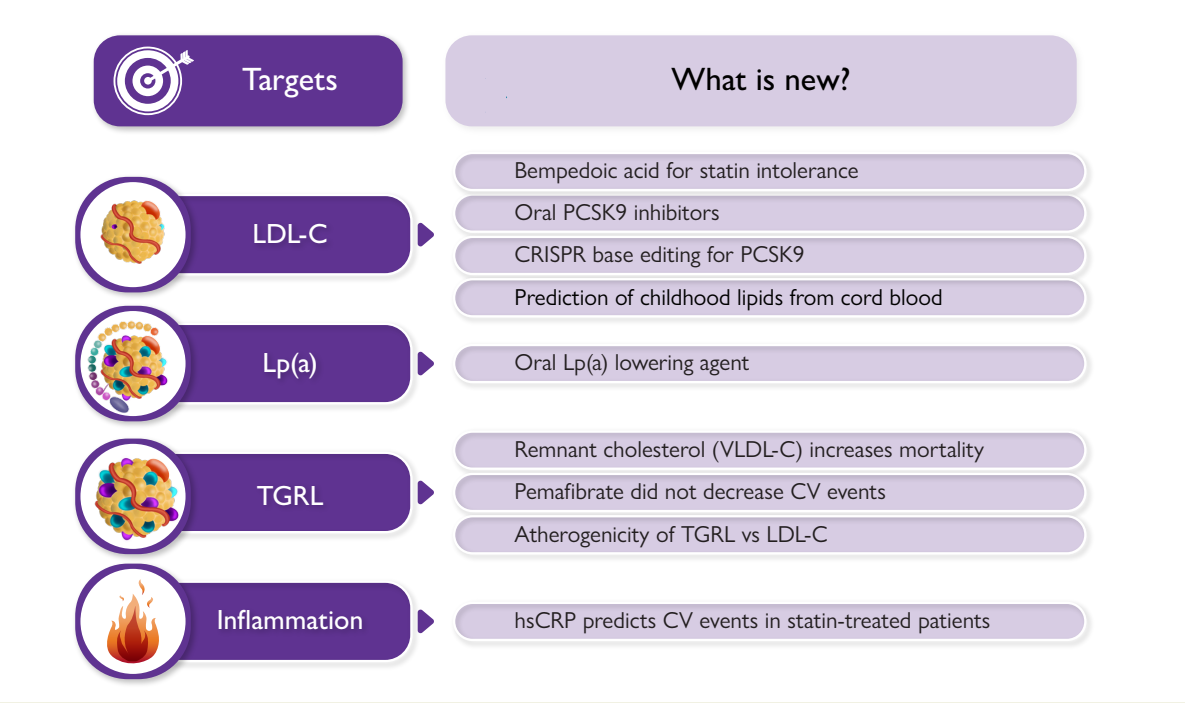
## Graphical Abstract




New insights and treatment options for dyslipidemia and atherosclerotic cardiovascular disease. CV, cardiovascular; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; TGRL, triglyceride-rich lipoprotein; VLDL-C, very low-density lipoprotein cholesterol.

Our understanding of the complex relationship between dyslipidaemia and atherosclerotic cardiovascular disease (ASCVD) was further improved this year by exciting new studies (*Graphical Abstract*). The Copenhagen Baby Heart Study database, which included 13 354 umbilical cord blood samples and parallel venous blood samples from children and parents at birth ($n = 444$), 2 months ($n = 364$), and 14–16 months ($n = 168$), was interrogated to determine lipid parameters during the first 14–16 months of life, and their capability to predict high concentrations at 2 and 14–16 months.[1] All the lipid/lipoprotein parameters increased stepwise from birth to 2 months to 14–16 months. Concentrations of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and lipoprotein(a) [Lp(a)] above the 80th percentile at birth were associated with significantly higher concentrations at 2 and 14–16 months. Other factors contributed to differences in lipid concentrations such as sex, gestational age, birth weight, breastfeeding, and parental lipid concentrations.

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These findings increase our knowledge of how lipid traits develop over the first 14–16 months of life and set the basis to identify the optimal child age for universal familial screening including familial hypercholesterolaemia.

Knowing the worldwide distribution atherogenic lipid levels can inform national policies and health system approaches to mitigate lipid-mediated risk of ASCVD. The Global Diagnostics Network recently reported the lipid distributions results of clinical laboratory testing from 461 888 753 patients aged 20–89 years in 17 countries on five continents from 2018 through 2020.[2] Lipids showed wide variation by country/region, sex, and age. In most countries, total cholesterol and LDL-C peaked at 50–59 years in females and 40–49 years in males. Sex- and age-group adjusted mean total cholesterol levels ranged from 4.58 mmol/L (177.1 mg/dL) in the Republic of Korea to 5.40 mmol/L (208.8 mg/dL) in Austria. Total cholesterol average levels exceeded the World Health Organization goal in Japan, Australia, North Macedonia, Switzerland, Germany, Slovakia, and Austria. North Macedonia had the highest proportions of LDL-C results ≥ 4.91 mmol/L (≥190 mg/dL). This study sheds light on the intercountry variability in lipid levels reflecting differences in genetics, lipid testing, and lifestyle habits. Pharmacologic treatment was not reported, and correction for treatment would have added further strength to these observations.

## What is new in LDL-C lowering?

The CLEAR Outcomes trial randomized 13 970 subjects with either established or at high risk for ASCVD with reported inability or unwillingness to take statins to either bempedoic acid 180 mg daily or placebo.[3] Of note is that 22%–23% of the enrollees in both groups were taking low intensity statins and the use of other lipid-lowering agents was permitted. The primary endpoint was four component major adverse cardiovascular events (MACE) that included death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and coronary revascularization. The median follow-up was 40.6 months. Compared to placebo, the group taking bempedoic acid had a significantly lower incidence of MACE (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.79 to 0.96; $P = .004$). At 6 months of follow-up, the bempedoic acid group had a lower LDL-C (21.7% vs. −0.6) and hs-CRP (−22.2% vs. +2.4%). Bempedoic acid therapy was associated with no increase in the incidence of myalgias, although cholelithiasis, gout, and increased liver enzymes were observed more frequently than with placebo. In a prespecified subgroup ($n = 4206$) of primary prevention subjects, the group receiving bempedoic acid had a 21.3% and 21.5% reduction in LDL-C and hs-CRP, respectively, and a significant risk reduction for the primary endpoint (HR 0.70 [95% CI, 0.55–0.89]).[4]

The cardioprotective value of injectable PCSK9 monoclonal antibodies for statin-treated patients with high-risk ASCVD is supported by large trials. However, patient reluctance to use injectable therapies, cost, and access obstacles has resulted in the search for oral PCSK9-lowering therapies. Administration of a single dose of an investigational orally bioavailable, renally excreted, macrocyclic peptide, MK-0616, an agent that binds to PCSK9, was shown in a phase 1 study to be associated with a >60% reduction in plasma LDL-C. More recently, MK-0616 was evaluated for efficacy and safety in a phase 2b, randomized double-blind placebo-controlled trial of 375 adults with a variety of ASCVD risk.[5] Employing doses of 6, 12, 18, and 30 mg, MK-0616 given daily for 8 weeks was associated with a significant ($P < .001$) reduction vs. placebo in mean percentage reduction in LDL-C of 41.2%, 55.7%, 59.1%, and 60.9%, respectively, with concomitant reductions in apo B and non-HDL-C. The incidence of adverse events was the same as placebo with the administration of all doses of MK-0616. These findings support further development of this drug as an oral option for PCSK9 inhibition.

A recent study described the use in non-human primates and rodents of an investigational base-editing therapy, VERVE 101, composed of a messenger RNA for an adenine base editor and a guide RNA that targets the PCSK9 gene.[6] The therapeutic agent was packaged in a lipid nanoparticle delivery vehicle and was administered systematically as a one-time intravenous infusion. In this study, the authors assessed the safety of this agent in a study of 36 non-human primates followed for at least one year and the potential for germline editing in treated sexually mature male non-human primates and female mice. Their study demonstrated that a single i.v. infusion of VERVE-101 was well tolerated and was associated with an 83% reduction in PCSK9 protein and a 69% lower LDL-C for up to 476 days following the infusion with no germline editing. The safety and efficacy of this technology in humans will be determined with future studies.

## What is new in triglycerides?

PROMINENT was a placebo-controlled randomized clinical trial (RCT) that examined the hypothesis that pemafibrate 0.2 mg twice daily would alter the incidence of the composite endpoint of non-fatal MI, ischaemic stroke, coronary revascularization, or death from cardiovascular causes in individuals with type 2 diabetes, triglycerides 200–499 mg/dL, and HDL-C < 40 mg/dL.[7] Among 10 497 subjects enrolled, one-third had no clinical ASCVD and two-thirds had documented ASCVD. Pemafibrate therapy was associated with significant lowering of triglycerides, VLDL-C, remnant cholesterol, and apo C-3 after 4 months of treatment, but there was no significant reduction in the incidence of the composite endpoint after a median follow-up of 3.4 years, and the study was terminated due to futility. Pemafibrate therapy was associated with a 12.3% increase in LDL-C and a 4.8% increase in apo B levels, a finding that likely contributed to the lack of benefit.

To further clarify the association of elevated remnant cholesterol (measured as VLDL cholesterol) and triglycerides with mortality, a contemporary population-based cohort of 87 192 individuals from the Copenhagen General Population Study aged 20–69 years at baseline was assessed.[8] In individuals with remnant cholesterol ≥ 1.0 mmol/L (≥39 mg/dL) compared with those with levels < 0.5 mmol/L (<19 mg/dL), multivariable-adjusted mortality HRs were 2.2 (95% CI 1.3–3.5) for cardiovascular disease, 1.0 (0.7–1.3) for cancer, and 2.1 (1.4–3.3) for other causes. Exploratory analysis of the cause of death subcategories showed corresponding HRs of 4.4 (1.6–11) for ischaemic heart disease, 8.4 (2.0–34) for infectious diseases, and 9.1 (1.9–43) for endocrinological diseases. A remnant cholesterol of ≥1 mmol/L (39 mg/dL), present in 22% of the population, and plasma triglycerides of ≥2 mmol/L (177 mg/dL), present in 28% of the population, were associated with two-fold increased mortality from cardiovascular and other causes, but not from cancer. The possibility that the so-called remnant cholesterol (VLDL-C) is more atherogenic that LDL-C was raised.

This question has been taken further where the strength of the relationship of triglyceride-rich lipoproteins (TRL) with risk of coronary heart disease (CHD) compared with LDL-C was tested.[9] Single-nucleotide polymorphisms (SNPs) associated with TRL/remnant cholesterol (TRL/remnant-C) and LDL-C in the UK Biobank population were identified. In a multivariable Mendelian randomization analysis, TRL/remnant-C was strongly and independently associated with CHD

in a model adjusted for apolipoprotein B (apoB). Likewise, in a multivariable model, TRL/remnant-C and LDL-C also exhibited independent associations with CHD with odds ratios per 1 mmol/L higher cholesterol of 2.59 [95% CI: 1.99–3.36] and 1.37 [95% CI: 1.27–1.48], respectively. The per-particle atherogenicity of TRL/remnants and LDL was addressed when two clusters of SNPs were identified with differing effects on TRL/remnant-C and LDL-C. The CHD odds ratio per standard deviation was significantly higher for the cluster with the higher TRL/remnant to LDL ratio [1.76, 95% CI: 1.58–1.96 vs. 1.33 (95% CI: 1.26–1.40)]. These findings are consistent with TRL/remnants having a substantially greater atherogenicity per particle than LDLs. What needs to be further clarified is the absolute contribution—not only odds ratio—for these two different lipoprotein classes as well as the quantity.

## What is new in Lp(a) lowering?

While clinical trials investigating ASCVD outcomes in those receiving injectable anti-sense oligonucleotides or RNA silencing agents are in progress, a small molecule inhibitor of Lp(a) formation has been developed as a possible oral option. Muvalaplin, a drug that binds to apo(a) and prevents binding between apo(a) and apo B-100, was evaluated in a phase 1 randomized double-blind parallel-design study in which 114 healthy subjects, 55 of whom were a mean age of 29 years and had a median baseline Lp(a) of 10.3 mg/dL, were assigned to a single ascending dose and 59 of whom were a mean age of 32 years and had a baseline Lp() of 58.3 mg/dL to multiple ascending dose study vs. placebo.[10] The dosing range was from 1 to 800 mg daily. In the multiple ascending dose group, the placebo-controlled reduction in Lp(a) on Days 14 and 15 using a dose of ≥100 mg was 63%–65%, returning to baseline by Day 43 in the 100 mg daily dose. Doses of 300 mg and higher were associated with a return of Lp(a) levels to baseline by Day 64. There were no changes in levels of other lipids or lipoproteins, apo B-100, or plasminogen, and the drug was well tolerated. Additional studies in individuals with or at increased risk for ASCVD are needed to further assess the safety, efficacy, and clinical utility of this agent.

## What about inflammation?

The administration of anti-inflammatory therapy with colchicine has been shown to be associated with reduced ASCVD risk when administered within 30 days of a myocardial infarction. Thus, a relevant question is the relative importance of reduction of atherogenic lipoproteins vs. that of inflammation. A collaborate analysis of 31 245 statin-treated patients with clinical ASCVD, or at high risk for ASCVD from three ASCVD outcomes trials of triglyceride-lowering therapies (STRENGTH, REDUCE-IT, and PROMINENT), examined quartiles of increasing baseline high-sensitivity C-reactive protein and quartiles of increasing LDL-C as predictors of the multivariate adjusted risk of MACE, cardiovascular death, and all-cause death.[11] The highest vs. lowest quartiles of hs-CRP were significantly related to cardiovascular and all-cause mortality, whereas LDL-C was not related to incident MACE and was less strongly associated with cardiovascular death and all-cause death. These data support the risk-prediction value of obtaining a baseline measurement of hs-CRP in high-risk, statin-treated patients with hypertriglyceridaemia and a potential role for treatments targeted both at atherogenic lipoproteins and inflammation.

One of the unresolved clinical question is the prediction of recurrent events after an acute coronary syndrome and why some patients remain stable while others experience repeated cardiovascular events. Current approaches with proteomics and lipidomics to better stratify patient's risk have been recently reviewed.[12] Contemporary clinically used risk scores such as the SCORE2 system and the Second Manifestations of Arterial disease 2 have limited predictive power. Multimarker proteomic and lipidomic panels hold the promise to reliably assess risk in a high-throughput routine. When combined with the genetic predisposition captured with polygenic risk scores and the actual ASCVD phenotype observed with coronary artery imaging, proteomics and lipidomics can advance understanding of the complex multifactorial causes underlying an individual's ASCVD risk. This opens the field to machine learning-based approaches for ASCVD risk prediction and individual responses to therapy.

## Declarations

### Disclosure of Interest

L.T. has received honoraria/consulting fees from Abbott, Amgen, Astra Zeneca, Bayer, Daiichi Sankyo, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, Pfizer, and Ultragenyx. C.O. has no disclosures. A.L.C., in the last three years, has received honoraria, lecture fees, or research grants from: Aegerion, Akcea Therapeutics, Amarin, Amgen, Amryt Pharma, AstraZeneca, Daiichi Sankyo, Esperion, Ionis Pharmaceutical, Medscape Education, Menarini, Merck, Mylan, Novartis, Novo Nordisk, PeerVoice, Pfizer, Recordati, Regeneron, Sanofi, The Corpus, and Viatris.

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