ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehac750

VIEWPOINT
Dyslipidaemias

The year in cardiovascular medicine 2022: the top 10 papers in dyslipidaemias

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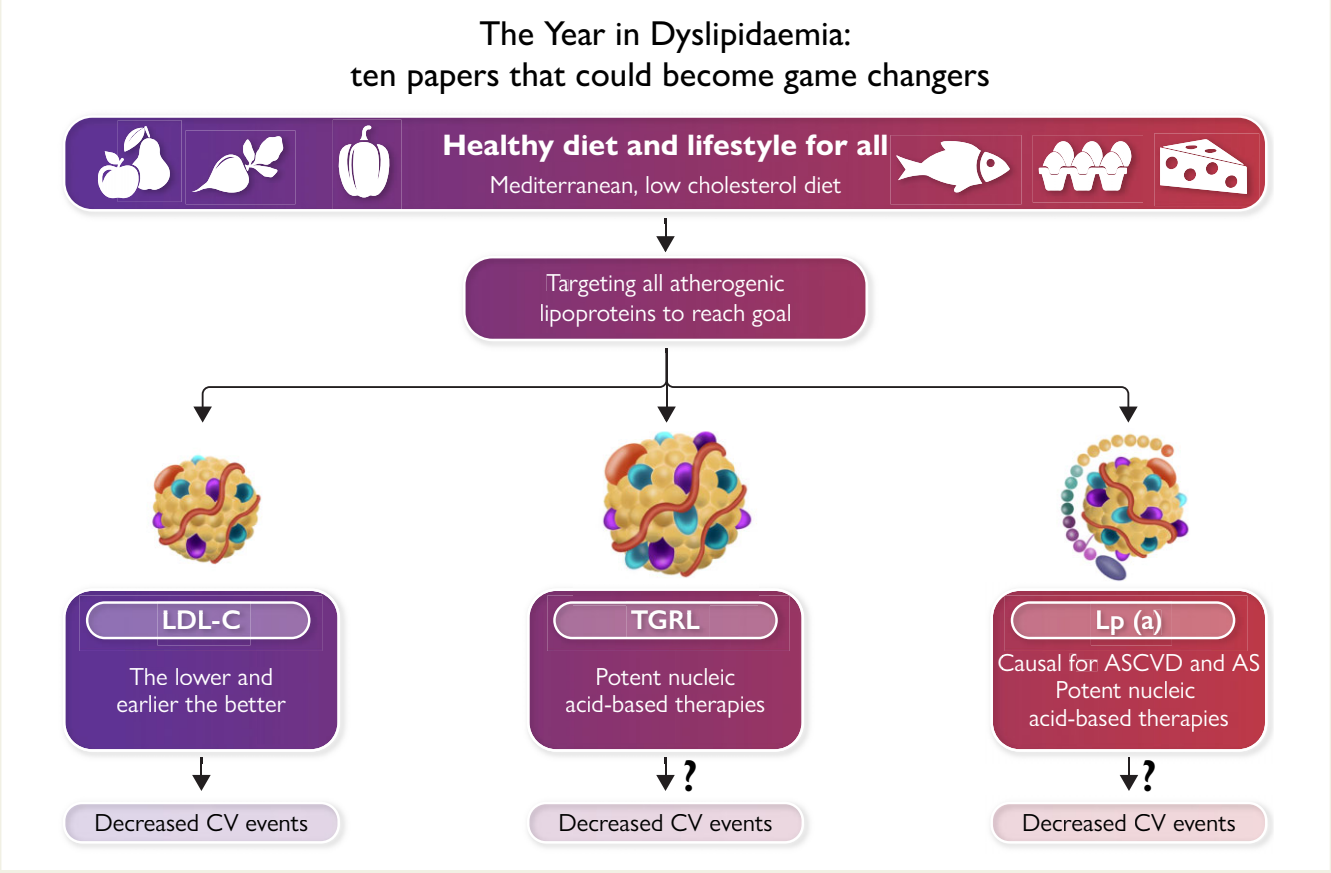
Received 22 September 2022; revised 21 October 2022; accepted 1 November 2022

Graphical Abstract



Dyslipidemia management and evolving therapies in 2022.

The lipid-lowering landscape is rapidly evolving and several trials published this year provided new insights. The CORDIOPREV Trial was a Spanish single center randomized controlled trial in which 1002 patients, mean age 59.5 years, 82.5% men, with established coronary heart disease were assigned to either a low-fat, high complex carbohydrate diet (<30% total fat and <10% saturated fat) or a Mediterranean diet (≥35% total fat, 22% monounsaturated fat) and both had cholesterol restriction to <300 mg/day.[1] The primary outcome was a composite

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of myocardial infarction (MI), revascularization, ischemic stroke, peripheral artery disease, and cardiovascular disease. The median follow-up was 7 years. The primary outcome occurred in 198 participants, with 87 in the Mediterranean diet group and 111 in the low-fat group (crude rate 28/1000 person-years in the Mediterranean group and 38/1000 in the Mediterranean diet group, log rank $P = 0.039$). The event curves split at approximately 3 years. Multi-variable adjusted hazard ratios using different models consistently favored the Mediterranean diet.

A long-standing question related to diet has been egg consumption and atherosclerotic cardiovascular disease (ASCVD) risk. This was addressed in a primary prevention observational trial (the Alpha-Tocopherol, Beta-Carotene Cancer Study) on 27 078 Finnish male smokers.[2] Information on dietary sources of cholesterol was collected from food frequency questionnaires focusing on consumption of eggs and other cholesterol-containing foods over the preceding 12 months and 31-year absolute mortality risk differences were calculated. In addition, an updated systematic review and meta-analysis of cohort studies was performed. The authors reported increased mortality among men who consumed higher amounts of cholesterol at baseline, with each additional 300 mg/day associated with a 10% higher risk of all-cause death. However, using a model that included total cholesterol consumption, the relationship was no longer significant. Thus, mortality in this population is probably more closely linked to their background dietary cholesterol intake to which, egg consumption contributes.

Statin intolerance remains an important clinical challenge, and it is associated with an increased risk of cardiovascular events. A large meta-analysis to determine the prevalence of statin intolerance according to various definitions was performed.[3] A total of 176 studies [112 randomized controlled trials (RCTs); 64 cohort studies] encompassing more than 4 million patients were included. The overall reported prevalence of statin intolerance was 9.1% (95% CI 8.0%–10%). The prevalence was quite similar when defined using National Lipid Association, International Lipid Expert Panel, and European Atherosclerosis Society criteria [7.0% (6.0%–8.0%), 6.7% (5.0%–8.0%), 5.9% (4.0%–7.0%), respectively]. The prevalence of statin intolerance in RCTs was significantly lower compared with cohort studies (4.9% vs. 17%). The prevalence of statin intolerance in studies including both primary and secondary prevention patients was much higher than when primary or secondary prevention patients were analyzed separately (18%, 8.2%, 9.1%) respectively. Age, female gender, Asian and Black race, obesity, diabetes mellitus, hypothyroidism chronic liver disease, and renal failure were significantly associated with statin intolerance in the meta-regression model. Antiarrhythmic agents, calcium channel blockers, alcohol use, and increased statin dose were also associated with a higher risk of statin intolerance. These results support that the prevalence of statin intolerance might often be overestimated and highlight the need for the careful assessment of patients with symptoms related to statin intolerance, a significant public health problem.

In light of recent trials, the guidelines are recommending lower low-density lipoprotein-cholesterol (LDL-C) goals for cardiovascular prevention. There is also emerging evidence that not only lower but earlier LDL-C lowering is beneficial, especially in the setting of acute coronary syndromes. The PACMAN-AMI was a double-blind, placebo-controlled, randomized clinical trial enrolling 300 patients undergoing percutaneous coronary intervention for acute MI.[4] The aim was to determine the effect of subcutaneous biweekly 150 mg alirocumab added to statin therapy and initiated within 24 h of intervention on plaque burden and composition. Intravascular ultrasonography, near-infrared spectroscopy, and optical coherence tomography were serially performed in the two non-infarct-related coronary arteries at baseline and after 52 weeks. There was a significant decrease in mean per cent atheroma volume [−2.13% with alirocumab vs. −0.92% with placebo [difference, −1.21; 95% confidence interval (CI), −1.78 to −0.65%; *P*, 0.001] and maximum lipid core burden index (−79.42 vs. −37.60) and an increase in minimal fibrous cap thickness (62.67 μm vs. 33.19 μm) at week 52. This study along with the HUYGENS study confirms that early and intensive lipid-lowering therapy leads to benefits in terms of plaque regression and stabilization in the acute setting of MI; a patient population at increased risk of recurrent events.[5] Whether this will translate into improved clinical outcomes needs to be determined.

The inhibition of cholesteryl ester transfer protein (CETP) activity has been addressed in several trials in the last decade. The lesson learned is that the cardiovascular benefit is present if LDL-C reduction occurs. A post-trial follow-up of survivors of an RCT that examined the effect on major coronary events of the CETP inhibitor, Anacetrapib vs. placebo on 30 449 statin-treated subjects was performed.[6] In total, 26 129 survivors entered a post-trial follow-up period in which they were blinded to original treatment allocation and were followed for the composite of coronary death, MI, or coronary revascularization during the combined in-trial and post-trial follow-up periods. A 20% relative risk reduction (RRR) (95% CI 10%–29%; $P < 0.001$) was noted over the median 2.2 years of extended follow-up in addition to the 9% reported in the original trial. The total absolute risk reduction was 1.8% over a median of 6.3 years. These findings support the importance of long-term treatment and follow-up to avoid underestimating treatment effects in lipid-lowering therapies.

The seminal ASCVD outcomes trial, FOURIER, demonstrated that evolocumab therapy was associated with significant additional ASCVD risk reduction over placebo in a study of 27 564 high-risk, statin-treated subjects followed over a median of 2.2 years FOURIER-OLE [FOURIER Open-Label Extension] enrolled 6635 patients (3355 randomized to evolocumab and 3280 to placebo in the parent study) with a median follow up of 5 years (maximum 8.4 years).[7] At 12 weeks in FOURIER-OLE, median LDL-C was 30 mg/dL. Patients originally randomized in the parent trial to evolocumab had a 15% lower risk of cardiovascular death, MI, stroke, or hospitalization for unstable angina or coronary revascularization [hazard ratio (HR) 0.85 (95% CI, 0.75–0.96); $P = 0.008$]; a 20% lower risk of cardiovascular death, MI, or stroke [HR 0.80 (95% CI, 0.68–0.93); $P = 0.003$]; and a 23% lower risk of cardiovascular death [HR 0.77 (95% CI, 0.60–0.99); $P = 0.04$] when compared with the placebo-treated patients who only switched to evolocumab once the parent trial was completed. Incidences of serious adverse events, muscle-related events, new-onset diabetes, hemorrhagic stroke, and neurocognitive events with evolocumab were similar to placebo during the parent study and did not increase over time. This study illustrates the importance of early treatment initiation, highlights the lag in clinical benefit and documents the safety of long-term use of evolocumab.

There is renewed interest in triglyceride rich lipoproteins (TGRL) since they are associated with increased risk of cardiovascular events. Genetic studies have suggested new targets for lowering TGRL and novel nucleic acid-based therapies are being developed for these new targets. Two important regulators of TGRL metabolism are Angiopoietin-like 3 (ANGPTL3) and Apoprotein C-III (apoC-III). Vupanorsen is a hepatically targeted antisense oligonucleotide that inhibits ANGPTL3 protein synthesis. To test its efficacy and safety, adults with non-high-density lipoprotein cholesterol (non-HDL-C) ≥ 100 mg/dL and triglycerides 150–500 mg/dL on statin therapy were randomized to placebo or monthly Vupanorsen dose regimens 80–

160 mg.[8] Vupanorsen resulted in significant decreases in non-HDL-C ranging from 22.0% to 27.7% and triglycerides 41.3%–56.8%. A dose-response relationship between ANGPTL3 levels and LDL-C or apolipoprotein B was not seen. Higher doses led to significant increases in liver enzymes and hepatic fat fraction leading to the discontinuation of its development. This is an important warning demonstrating that we need careful evaluation of safety for these new agents.

Olezarsen is a novel *N* acetyl-galactosamine-conjugated antisense oligonucleotide targeted to hepatic apoC-III mRNA to inhibit apoC-III production. In a randomized, double-blind, placebo-controlled, dose-ranging study, 114 subjects with fasting serum triglycerides 200–500 mg/dL (2.26–5.65 mmoL/L) patients received Olezarsen or placebo subcutaneously for 6–12 months.[9] Treatment with Olezarsen resulted in significant triglyceride reductions of 23%–60%. Furthermore, significant decreases in apoC-III, very low-density lipoprotein cholesterol, non-HDL-C, and apolipoprotein B were also observed. There were no platelet count, liver, or renal function changes. These findings suggest that inhibiting apoC-III may provide a potent approach in lowering triglyceride levels in a population at high risk for or with established ASCVD. Because of its favorable effect on other atherogenic lipoproteins, there may be a potential cardiovascular benefit when added to standard of care.

The European Atherosclerosis Society consensus statement reported an update providing new evidence for the role of lipoprotein(a) (Lp(a)) in ASCVD and aortic valve stenosis.[10] The key observation of an interaction of Lp(a) with global CV risk of an individual sets the stage for a risk guided approach to the levels of intervention with an approach similar to that for other causal risk factors such as LDL-C. The definition of high Lp(a) therefore may vary according to risk. Current novel findings also do not support Lp(a) as a risk factor for venous thrombotic events and impaired fibrinolysis. Very low Lp(a) levels may associate with increased risk of diabetes mellitus meriting further study. Without specific Lp(a) lowering therapies available, early intensive risk factor management is recommended, targeted according to a global cardiovascular risk evaluation that includes Lp(a). Trials of specific Lp(a)-lowering treatments are critical to confirm clinical benefit for cardiovascular disease and aortic valve stenosis.

In a recent trial, the authors aimed at assessing safety and tolerability of a short interfering RNA (siRNA) designed to reduce hepatic production of apolipoprotein(a) and changes in plasma concentrations of Lp(a). A single ascending dose study of SLN360, an siRNA targeting apolipoprotein(a) synthesis enrolled adults with Lp(a) plasma concentrations of 150 nmol/L (roughly 65 mg/dL) or greater.[11] Participants were randomized to receive placebo or single subcutaneous doses of SLN360 at 30–600 mg. Maximal median percentage changes in Lp(a) were from −46% to −98% for the 30–600-mg SLN360 groups, respectively. The duration of Lp(a) lowering was dose dependent, persisting for at least 150 days after administration. The siRNA was well tolerated, and a dose-dependent large lowering of plasma Lp(a) concentrations was observed. If confirmed in Phase 2 and 3 studies, these findings will provide further evidence for a rapid and durable decrease of Lp(a).

Funding

All authors declare no funding for this contribution.

Conflict of interest: L.T. has received consulting fees or honoraria from Abbott, Amgen, Astra Zeneca, Bayer, Daiichi Sankyo, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Recordati, Sanofi, and Servier. A.C. has received contracts, consulting fees or honoraria from Aegerion, Amarin, Amgen, Amryt, Astra Zeneca, Daiichi Sankyo, Eli Lilly, Esperion, Inois Pharmaceutical, Ionis Pharmaceutical, Kova, Medscape, Menarini, Merck, Mylan, Novartis, Sandoz, Sanofi, Sanofi Regeneron, Peer Voice, Pfizer, Recordati, Regeneron, and The Corpus. C.E.O. has no disclosures to report.

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