Long-Term Benefits of a Holistic Approach on Dyslipidaemia Management

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Meeting Summary

Prof Banach introduced the concept of adding nutraceuticals to treatment regimens to achieve therapeutic low-density lipoprotein cholesterol (LDL-C) targets. He described the components, effects, and safety of red yeast rice (RYR) extract, and highlighted the potential usefulness of RYR extract in reducing LDL-C levels and cardiovascular (CV) events in different patient populations. Prof Schiele addressed how new LDL-C goals for acute coronary syndromes (ACS) can be achieved in real life, and how the registries help. He outlined the European Society of Cardiology (ESC) guidelines and therapeutic targets, considered the transition from theory to real life and insights from registries, and proposed changes in practice, such as early prescription, optimisation, and maintenance. Dr Morieri discussed the CV benefit of treating hypertriglyceridaemia, highlighted precision medicine

approaches to improve CV disease (CVD) prevention strategies, and considered how and when to treat hypertriglyceridaemia to reduce CVD. He then presented the similarities and differences between fenofibrate and eicosapentaenoic acid (EPA), as well as the pharmacogenomics of fenofibrate.

Low-Dosage Red Yeast Rice Supplementation in Cholesterol Control: Review and Expert Opinion by the International Lipid Expert Panel (ILEP)

Professor Maciej Banach

Prof Banach explained that current lipid-lowering therapy (LLT) with statins, ezetimibe, and proprotein convertase subtilisin/kexin Type 9 inhibitors (PCSK9I) is not effective, with many patients not achieving the 2016, or the more stringent 2019, ESC lipid targets; this is a great challenge.[1] Adherence to LLT is low, but good adherence is required for effective treatment outcomes and may reduce all-cause mortality by up to 45%.[2] Reasons for low adherence include statin intolerance, physician inertia (suitable doses or combination therapy are not prescribed), and reimbursement criteria. Statins, ezetimibe, and PCSK9I are introduced in a step-wise manner in the attempt to achieve LDL-C targets.[3] Early intervention in patients with dyslipidaemia to reach target LDL-C levels helps to reduce (by as much as 25% after 5 years) and/or delay the risk of atherosclerotic CVD events.[4-6] Based on the above, it is not only important for 'the lower, the better', but also 'the earlier, the better' and 'the longer, the better'.[6]

Adding nutraceuticals to treatment regimens may help to achieve therapeutic targets.[7] The 2017 International Lipid Expert Panel (ILEP) guidelines focussed on nutraceuticals with lipid-lowering properties that may have the potential to reduce LDL-C levels.[7] The lipid-lowering component of RYR extract is the natural lovastatin monacolin K, the main ingredient of nutraceutical formulations, usually in combination with low dosages of other natural products with potential synergic effects. Other nutraceuticals may contain sterols/stanols, low dosages of omega-3, or other components. Considering the above-mentioned nutraceutical combinations, the effects of RYR extract may be enhanced by the synergic compounds and may thus be greater than expected from an equivalent low dose of lovastatin. RYR extract inhibits synthesis of liver cholesterol, cholesterol esters, and micelles; reduces absorption of intestinal cholesterol; and enhances cholesterol excretion.[4,7,8]

RYR extract at a 3–10 mg/day (monacolin K) dose is a Class 1A recommendation in the 2017 ILEP guidelines and is expected to give a 15–25% reduction in LDL-C; other properties of this extract include reducing apolipoprotein B and inflammation, and improving endothelial function.[7] A network meta-analysis, presented by Prof Banach at the American Heart Association (AHA) Annual Congress in 2019, of comparative effects of nutraceuticals showed the high efficacy of RYR extract in reducing LDL-C and triglycerides (TG).[8] Other potential properties of RYR extract, such as reducing inflammation and improving endothelial function, have been shown in studies of nutraceutical combinations.[9,10]

For most of the nutraceuticals on the market, there are no CV outcomes trials to evaluate the consequence of reducing LDL-C. Prof Banach considered such trials unnecessary because there is so much evidence to show that LDL-C reductions (e.g., with statins) are associated with a reduction in CV events. RYR extract and omega-3, however, are two nutraceuticals for which there are data showing that reduction in LDL-C is associated with reduced CV outcomes.[11]

Nutraceuticals, as per European and very recent ILEP guidelines,[4,7] may be useful as an early intervention in individuals with elevated plasma cholesterol who do not qualify for treatment with statins because of their global CV risk (low/intermediate). Additionally, clinical studies in patients on statin therapy who are close to target have also shown that addition of nutraceuticals could bring them to target;[7] it has also been suggested that nutraceuticals could be used in patients with statin intolerance.[12-14] It is important to emphasise, however, that use of nutraceuticals in patients for whom a pharmacological treatment had been prescribed goes beyond the guideline-recommended scope

of a nutraceutical,[4] representing empirical use as a potential additional tool for the management of difficult-to-treat patients, under strict medical monitoring. In this context, RYR extract has been tested in patients with statin intolerance; e.g., the Armolipid Plus® (MEDA-Rottapharm S.p.A., Monza, Italy) nutraceutical combination administered to patients, together with ezetimibe, was associated with a significant, additional 25 mg/dL reduction in LDL-C at 12 months (p<0.0001), bringing the patient to the desired target with no increase in adverse effects.[13] In a similar situation, when it was not possible to reach the LDL target in patients who were intolerant to high-intensity statins, coadministration of low-dose statins with Armolipid Plus was shown to achieve a significant additional reduction in LDL-C at 3 months (34 mg/dL; p<0.0001), with 70% of those patients reaching the treatment target (<70 mg/dL).[14]

The safety of nutraceuticals such as RYR extract is just as important as the efficacy. In this context, a large meta-analysis (53 randomised controlled trials, 112 treatment arms, 8,535 patients) of RYR extract safety indicated there were no safety signals for musculoskeletal disorders (odds ratio [OR]: 0.94; 95% confidence interval [CI]: 0.53–1.65), and RYR extract even seemed to be protective for nonmusculoskeletal disorders (OR: 0.59; 95% CI: 0.50–0.69) and serious adverse events (OR: 0.54; 95% CI: 0.46–0.64) versus active controls.[15]

Prof Banach concluded that use of nutraceuticals such as RYR extract is important for reduction of LDL-C and (potentially) of CV events as early intervention in low-to-moderate risk subjects for whom a drug therapy is not yet indicated. Moreover, under strict medical monitoring, they may be useful in the context of clinical management of difficult-to-treat patients, e.g., patients not able to reach the LDL-C target both in primary and secondary prevention and/or with statin intolerance.

Are New LDL-C Goals for Acute Coronary Syndrome Achievable in Real Life? How Could Registries Help?

Professor François Schiele

Prof Schiele explained that there are two main reasons for the LDL-C therapeutic targets defined by the ESC guidelines. The first is the pathological response, which shows how coronary plaque develops in relation to LDL-C level during treatment. Statistical data from studies of coronary plaque progression indicate that at LDL-C levels <50 mg/dL, plaque will not develop.[16] The second reason, which is more important in clinical practice, is that 'treat-to-target' is a much better strategy than 'fire-and-forget'.[17] Results from an observational study showed adherence to statin treatment in treat-to-target patients was significantly better than in patients treated on a fire-and-forget basis (adjusted OR: 2.51; 95% CI: 2.26–2.78). There was also a lower CVD event rate in treat-to-target patients than by fire-and-forget (hazard ratio [HR] of CVD or CV death: 0.41; 95% CI: 0.35–0.48, even after adjustment for adherence and baseline CVD risk).[17]

The 2011 target for very high-risk patients (i.e., patients with ACS) under treatment was LDL-C <70 mg/dL (<1.8 mmol/L) or >50% decrease in baseline LDL-C when the target level could not be reached.[3] The 2016 ESC guidelines include three targets according to LDL-C level at baseline: for <70 mg/dL (<1.8 mmol/L) there is no target, just high-intensity statins; for 70–135 mg/dL (1.8–3.5 mmol/L), the target is >50% LDL-C reduction; and for >135 mg/dL (>3.5 mmol/L), the target is LDL-C <70 mg/dL (<1.8 mmol/L).[18] The 2019 ESC targets are more demanding than those from 2016: LDL-C <55 mg/dL (<1.4 mmol/L) and >50% decrease in baseline LDL-C for secondary prevention for patients at very high risk.[4] Furthermore, if a second CV event occurs within 2 years on statin treatment, the LDL-C goal is <40 mg/dL (<1.0 mmol/L).

Prof Schiele described three classes of LLT with demonstrated clinical benefits in ACS. Median LDL-C levels in the PROVE-IT trial were 62 versus 95 mg/dL with high- versus low-intensity statins (16% relative risk reduction [RRR] in major CV events [MACE]: CV mortality, nonfatal myocardial

infarction, and stroke; p<0.001), with a difference in risk between treatments seen as early as approximately 3 months, indicating the benefit of early use of high-intensity statins irrespective of baseline LDL-C.[19] Addition of the cholesterol absorption inhibitor ezetimibe to statin treatment was shown to be clinically beneficial in IMPROVE-IT, in which median LDL-C levels were 54 versus 69 mg/dL for simvastatin plus ezetimibe versus simvastatin alone (6% RRR in MACE; p<0.001).[20] The PCSK9I alirocumab administered with high-intensity statins was associated with mean LDL-C levels at 12 months of 48 mg/dL versus 96 mg/dL with high-intensity statins alone (15% RRR in MACE) in the ODYSSEY OUTCOMES trial.[21]

How to achieve >50% LDL-C reduction with statins is an important consideration. In the LIPID trial, few of the 3,936 patients on a moderate-intensity statin (pravastatin 40 mg/day) achieved >50% LDL-C reduction.[22,23] High-intensity statin (rosuvastatin 20 mg/day) in the JUPITER trial was associated with >50% LDL-C reduction in only one-half of the 7,783 patients.[22,24] To achieve >50% LDL-C reduction, Prof Schiele explained, a combination of high-intensity statins plus ezetimibe is likely to be needed in ≥50% of patients.

To achieve both components of the LDL-C target (<55 mg/dL and >50% reduction) requires a step-wise strategy for LLT post-ACS: high-intensity statins as soon as possible (plus ezetimibe before discharge when baseline LDL-C >110 mg/dL), then after 4–6 weeks, add ezetimibe and PCSK9I as necessary to achieve the LDL-C target.[4] Long-term effective prevention by LLT requires regular LDL-C monitoring.

Three registries of real-life statin use post-ACS highlight the undertreatment of patients. DYSIS II, an observational study of 3,867 patients with stable coronary heart disease who were hospitalised for an ACS event, showed that the mean ± standard deviation atorvastatin-equivalent statins dosage on admission was 23±17 mg/day, which increased to 37±24 mg/day during the hospital stay, then decreased to 32±21 mg/day at 3 months.[25] Overall, only 18.9% of the ACS cohort had LDL-C <70 mg/dL (2016 target) at 4 months post-ACS, which is far from the new ESC objective. In FAST-MI 2015 (N=4,016), mean admission LDL-C was 119±42 mg/dL, and mean expected LDL-C at discharge was 84±39 mg/dL for the entire cohort.[26] At discharge, 65% were on high-intensity statins, 2% were on ezetimibe, and only approximately 25% of patients had LDL-C <55 mg/dL. EUROASPIRE V, a cross-sectional survey of 8,261 patients with coronary artery events or interventions, showed that when statins were not given at high intensity at discharge (i.e., no LLT or low-/moderate-intensity statins; approximately 50%), an increase in intensity occurred in only 4.6% of patients during follow-up; for high-intensity statins at discharge (approximately 50%), there was a decrease to low-/moderate-intensity in 20% of patients, and only a very low rate of patients post-ACS were at target (males: 32%; females: 23%; <70 mg/dL).[27]

Prof Schiele emphasised that a change in practice is needed regarding early prescription, optimisation with combination therapy in most cases (preferably before discharge), and maintenance of therapy, noting that adherence is a huge issue in long-term LLT, with predictors of nonadherence including younger age, treatment complexity, smoking, sedentary lifestyle, and depression.[21,28-32]

Prof Schiele concluded that the new LDL-C goals are challenging, with current treatments (statins, ezetimibe, and PCSK9I) showing clinical benefit. Initial prescription, optimisation of LLT before discharge, and long-term maintenance can be improved to attain LDL-C targets and encourage treatment adherence.

Fenofibrate and EPA: Are They Equal When It Comes to Hypertriglyceridaemia Management?

Doctor Mario Luca Morieri

Dr Morieri explained that LDL-C and non-high-density lipoprotein-cholesterol (non-HDL-C; calculated by total-C minus HDL-C, and corresponding to LDL-C plus remnant-C) are usually highly correlated; however, in the presence of hypertriglyceridaemia there is less correlation (as TG increase, so does remnant-C but not LDL-C).[33] TG are not a target for CVD prevention

in the ESC guidelines but it is important to identify hypertriglyceridaemia because TG are a marker of remnant cholesterol (very-LDL-C plus intermediate-density lipoprotein-cholesterol) and TG-rich lipoprotein concentrations. Experimental models and epidemiologic and genetic studies support the causal link between TG-rich lipoproteins and their remnants, as well as CVD.[34]

The first goal for CVD prevention when treating atherogenic dyslipidaemia (AD) is to stratify patients according to CV risk and to identify the LDL-C target. For each LDL-C target there is also a non-HDL-C target (LDL-C plus 30 mg/dL [plus 0.8 mmol/L]); therefore, if the patient is not on LDL-C target, they are also not on non-HDL-C target. Considering the non-HDL-C target (as LDL-C plus remnant-C) and the fixed ratio between TG and cholesterol in very-LDL-C, a patient on LDL-C target who has mild hypertriglyceridaemia (TG >150 mg/dL) will have a remnant-C >30 mg/dL and is likely not on non-HDL-C CVD prevention targets.

LDL-C-lowering and TG-lowering approaches differ, with the latter requiring a precision medicine approach. For patients at high CV risk, the approach for all patients is LDL-C-lowering (treat-to-target with statins, ezetimibe, and PCSK9I). In contrast, the TG-lowering approach requires identification of patients who will benefit from treatment (fenofibrate or EPA).

Fenofibrate is an agonist of peroxisome proliferator-activated receptor (PPAR)α, which decreases TG, increases HDL-C, increases LDL size (making it less atherogenic), and reduces inflammation.[35]

In the ACCORD-Lipid trial, 5,518 patients with Type 2 diabetes mellitus (T2DM) at high CV risk were randomised to statins and either fenofibrate or placebo.[36] There was a reduction in TG and increase in HDL-C with fenofibrate compared to placebo; however, the trial did not achieve the primary outcome of reduction in MACE (CV mortality, nonfatal myocardial infarction, and stroke), in the overall population (HR: 0.92; 95% CI: 0.79–1.08; p=0.32).[36]

Meta-analysis of results from ACCORD-Lipid and other clinical trials in fibrates showed a 10% reduction in risk of MACE (relative risk: 0.90; 95% CI: 0.82–1.00; p=0.048) in unselected patients.[37] In contrast, in patients with AD (low HDL-C and high TG), fibrates were associated with a 35% RRR of MACE (95% CI: 22–46%),[38] which matched observations in patients with AD in ACCORD-Lipid who received fenofibrate with a statin (RRR: 31%; p=0.032).

Further evidence of the effectiveness of fenofibrate in preventing CVD events is provided by the ACCORDION trial, a long-term follow-up to ACCORD.[39] Although only 4.3% of patients continued previously allocated fenofibrate in the follow-up period in ACCORDION, the benefit of adding fenofibrate to statins in patients with AD (TG >204 mg/dL, HDL-C <34 mg/dL) was confirmed after 9.7 years (combined treatment plus follow-up: 4.7 plus 5.0 years), with a 27% RRR of MACE (95% CI: 5–44%).

Evidence of fenofibrate CV effectiveness has also been derived from real-world studies, such as ECLIPSE-REAL, in which fenofibrate plus statin was associated with 26% RRR of MACE in patients with metabolic syndrome at approximately 2.5 years' follow-up.[40]

EPA and docosahexaenoic acid (DHA) are very-long-chain omega-3 fatty acids that activate PPAR, mainly target TG, and are effective only at high doses (>2 g/day EPA/DHA; 4 g/day EPA). Meta-analyses of EPA/DHA in 77,917 patients of mixed CVD history and statin background showed no clear benefit on MACE in this unselected population (RR: 0.97; 95% CI: 0.93–1.01; p=0.10).[41] However, in a selected population of 8,179 patients with CVD or T2DM and hypertriglyceridaemia (TG >150–200 mg/dL) on statins in the REDUCE-IT trial, high-dose EPA (icosapent ethyl 4 g/day) showed benefit of MACE compared to placebo (HR: 0.74; 95% CI: 0.65–0.83; p<0.001).[42]

In REDUCE-IT, beneficial CV effects of EPA were equivalent, regardless of baseline TG level, and patients achieved target TG levels during the study.[42] Patients with AD had greater benefit from EPA than those without AD; however, this was not explainable by considering only the lipid profile. Dr Morieri suggested that anti-inflammatory and antiplatelet actions of EPA may have contributed to this increased benefit.

Meta-regression exploring the role of achieved lipid concentration on the effectiveness of fibrates indicated CV efficacy is proportional to

TG reduction; however, this reduction only partly explains fibrate CV effectiveness.[37,43] Dr Morieri postulated that the anti-inflammatory effect of fenofibrate might also be involved. Fenofibrate also reduces progression of albuminuria associated with T2DM by 14% (95% CI: 2–25%) and diabetic retinopathy by 37% (95% CI: 19–51%), independently of lipid response.[37,43]

Dr Morieri described a pharmacogenetic approach to identify patients with T2DM who carry a genetic variant associated with better CV response to fenofibrate even in the absence of AD. This approach focussed on the *PPARA* gene, which codes for the pharmacological target of fibrates, PPARα.[35] Data from ACCORD-Lipid[36] were used to identify a common variant at the PPARα locus (rs6008845, C/T) that identifies patients who benefit from fenofibrate in terms of reduced MACE.[44] T/T homozygotes (36% of participants) experienced a 51% MACE reduction in response to fenofibrate (HR: 0.49; 95%: CI 0.34–0.72), whereas no benefit was observed for other genotypes. Interestingly, among patients with AD, fenofibrate's beneficial effect on CVD was observed across all genotypes. Moreover, among patients without AD, i.e., those who did not derive CVD reduction with fenofibrate, the presence of the T/T genotype induced a nearly 50% reduction in MACE.[44] Thus, genotypes may identify patients who derive CV benefit from fenofibrate that goes beyond the induced changes in lipid profile; however, this needs replication and validation before reaching clinical practice.

Dr Morieri concluded that a comprehensive CVD prevention approach should include evaluation of hypertriglyceridaemia. Fenofibrate and EPA reduce CVD events in selected populations, with patients with AD identified as benefitting from these therapies. A precision medicine approach can be used to identify patients who may have a relevant reduction in CVD risk with TG-lowering therapy and, for fenofibrate, this may include pharmacogenetics.

References

1. Ray KK et al. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. Eur J Prevent Cardiol. 2020;DOI:10.1093/eurjpc/zwaa047.
2. Chowdhury R et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940-8.
3. Reiner Ž et al. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769-818.
4. Mach F et al.; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.
5. Ference BA et al. 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. Eur Heart J. 2017;38(32):2459-72.
6. Penson P et al. LDL-C: lower is better for longer - even at low risk. BMC Med. 2020;18(1):320.
7. Cicero AFG et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an international lipid expert panel. Nutr Rev. 2017;75(9):731-67.
8. Morze J et al. A network meta-analysis on the comparative efficacy of nutraceuticals on lipid profile. Circulation. 2019;140(Suppl 1):A13360.
9. Zhao SP et al. Xuezhikang, an extract of cholestin, protects endothelial function through anti-inflammatory and lipid-lowering mechanisms in patients with coronary heart disease. Circulation. 2004;110(8):915-20.
10. Pirro M et al. Effects of a nutraceutical combination on lipids, inflammation and endothelial integrity in patients with subclinical inflammation: a randomized clinical trial. Sci Rep. 2016;6:23587.
11. Lu Z et al. Effect of xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. Am J Cardiol. 2008;101(12):1689-93.
12. Banach M et al. The role of nutraceuticals in statin intolerant patients. J Am Coll Cardiol. 2018;72(1):96-118.
13. Marazzi G et al. Usefulness of nutraceuticals (armolipid plus) versus ezetimibe and combination in statin-intolerant patients with dyslipidemia with coronary heart disease. Am J Cardiol. 2015;116(12):1798-801.
14. Marazzi G et al. Comparison of low-dose statin versus low-dose statin + armolipid plus in high-intensity statin-intolerant patients with a previous coronary event and percutaneous coronary intervention (ADHERENCE Trial). Am J Cardiol. 2017;120(6):893-7.
15. Fogacci F et al. Safety of red yeast rice supplementation: a systematic review and meta analysis of randomized controlled trials. Pharmacol Res. 2019;143:1-16.
16. Nicholls SJ et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA. 2007;297(5):499-508.
17. Wei L et al. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study. Pharmacoepidemiol Drug Saf. 2007;16(4):385-92.
18. Catapano AL et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37(39):2999-3058.
19. Cannon CP et al. Intensive versus moderate lipid lowering with statins

after acute coronary syndromes. N Engl J Med. 2004;350(15):1495-504.

20. Cannon CP et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387-97.
21. Schwartz GG et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097-107.
22. Boekholdt SM et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol. 2014;64(5):485-94.
23. Simes RJ et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? Circulation. 2002;105(10):1162-9.
24. Hsia J et al. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol. 2011;57(16):1666-75.
25. Gitt AK et al. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: results from the Dyslipidemia International Study II. Atherosclerosis. 2017;266:158-66.
26. Schiele F et al. Patients eligible for proprotein convertase subtilisin/kexin type9 inhibitors (pcsk9i) after acute myocardial infarction. The ESC position applied to patients included in the FAST-MI 2015 registry. Abstract 468. ESC Congress, 31 August–4 September, 2019.
27. Kotseva K et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019;26(8):824-35.
28. Schiele F et al. A consensus statement on lipid management after acute coronary syndrome. Eur Heart J Acute Cardiovasc Care. 2018;7(6):532-43.
29. Buonvino et al. An innovative lipid-lowering approach to enhance attainment of low density lipoprotein cholesterol goals. Eur Heart J Acute Cardiovasc Care. 2020:DOI:10.1177/2048872620912639.
30. Landmesser U et al. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin Type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. Eur Heart J. 2018;39(14):1131-43.
31. Khunti K et al. Association of a combined measure of adherence and treatment intensity with cardiovascular outcomes in patients with atherosclerosis or other cardiovascular risk factors treated with statins and/or ezetimibe. JAMA Netw Open. 2018;1(8):e185554.
32. Castellano JM et al. A polypill strategy to improve adherence: results from the FOCUS project. J Am Coll Cardiol. 2014;64(20):2071-82.
33. Varbo A et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol. 2013;61(4):427-36. Erratum in: J Am Coll Cardiol. 2019;73(8):987-8.
34. Varbo A et al. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. Circulation. 2013;128(12):1298-309.
35. Noonan JE et al. An update on the molecular actions of fenofibrate and its clinical effects on diabetic retinopathy and other microvascular end points in patients with diabetes. Diabetes. 2013;62(12):3968-75.
36. ACCORD Study Group et al. Effects of combination lipid therapy in Type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563-74.
37. Jun M et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta analysis. Lancet. 2010;375(9729):1875-84.
38. Sacks FM et al. Combination lipid therapy in Type 2 diabetes. N Engl J Med. 2010;363(7):692-4.
39. Elam MB et al. Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with Type 2 diabetes. JAMA Cardiol. 2017;2(4):370-80. Erratum in: JAMA Cardiol. 2017;2(4):461.
40. Kim NH et al. Use of fenofibrate on cardiovascular outcomes in statin users with metabolic syndrome: propensity matched cohort study. BMJ. 2019;366:l5125.
41. Aung T et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals. JAMA Cardiol. 2018;3(3):225-34.
42. Bhatt DL et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380(1):11-22.
43. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626-35.
44. Morieri ML et al. *PPARA* polymorphism influences the cardiovascular benefit of fenofibrate in Type 2 diabetes: findings from ACCORD-Lipid. Diabetes. 2020;69(4):771-83.