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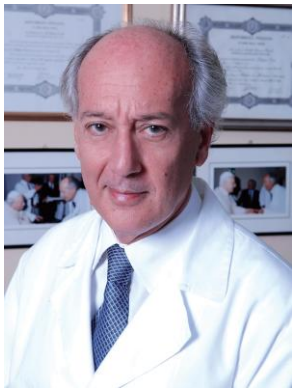
Residual lipidic risk beyond low-density lipoprotein cholesterol: new challenges and opportunities



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This Focus Issue on Dyslipidaemias, diabetes, and metabolic disorders contains the '**2023 ESC Guidelines for the management of endocarditis: Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC)** ***Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM)***' by Victoria Delgado from the Hospital University Germans Trias i Pujol in Badalone, Spain, and colleagues from the ESC Scientific Document Group.[1] Infective endocarditis (IE) is a major public health challenge.[2–5] In 2019, the estimated incidence of IE was 13.8 cases per 100 000 subjects per year, and IE accounted for 66 300 deaths worldwide. Due to the associated high morbidity and mortality (1723 disability-adjusted life years and 0.87 death cases per 100 000 population, respectively), identification of the best preventive strategies has been the focus of research. Since the publication of the *2015 ESC Guidelines for the management of infective endocarditis*, important new data have been published mandating an update of recommendations.

This issue continues with a focus on dyslipidaemias, diabetes, and metabolic disorders starting with the '**2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)**' by Nikolaus Marx from RWTH Aachen University in Germany, and colleagues from the ESC Scientific Document Group.[6] Patients with diabetes are at increased risk of developing cardiovascular disease (CVD) with its manifestations of coronary artery disease, heart failure, atrial fibrillation, and stroke, as well as aortic and peripheral artery diseases.[7–11] In addition, diabetes is a major risk factor for developing chronic kidney disease, which is associated with developing CVD. The combination of diabetes with these cardio-renal comorbidities enhances the risk not only for CVD but also for all-cause mortality. These European Society of Cardiology Guidelines on the management of cardiovascular disease in patients with diabetes are designed to guide prevention and management of the manifestations of CVD in patients with diabetes based on data published up to end of January 2023.

In a Special Article entitled '**Cardiometabolic risk management: insights from a European Society of Cardiology Cardiovascular Round Table**', Francesco Cosentino from the Karolinska Institutet and Karolinska University Hospital in Stockholm, Sweden, and colleagues[12] note that metabolic comorbidities are common in patients with CVD; they can cause atherosclerotic cardiovascular disease (ASCVD), speed its progression, and adversely affect prognosis. Common comorbidities are Type 2 diabetes mellitus (T2DM), obesity/overweight, chronic kidney disease (CKD), and chronic liver disease.[13–15] The cardiovascular system, kidneys, and liver are linked to many of the same risk factors (e.g. dyslipidaemia, hypertension, tobacco use, diabetes, and central/truncal obesity), and shared metabolic and functional abnormalities lead to damage throughout these organs via overlapping pathophysiological pathways (*Figure 1*). The high rates of these comorbidities highlight the need to improve recognition and treatment of ASCVD in patients with obesity, insulin resistance or T2DM, chronic liver diseases, and CKD and equally, to improve recognition and treatment of these diseases in patients with ASCVD. Strategies to prevent and manage cardiometabolic diseases include lifestyle modification, pharmacotherapy, and surgery. There is a need for more programmes at the societal level to encourage a healthy diet and physical activity. Many pharmacotherapies offer mechanism-based approaches that can target multiple pathophysiological pathways across diseases. These include sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, selective mineralocorticoid receptor antagonists, and combined glucose-dependent insulinotropic peptide/glucagon-like peptide-1 receptor agonist. Non-surgical and surgical weight loss strategies can improve cardiometabolic disorders in individuals living with obesity. New biomarkers under investigation may help in the early identification of individuals at risk and reveal new treatment targets.

Cardiovascular disease is the leading cause of death in women and men globally, mostly due to ASCVD. In a Special Article entitled

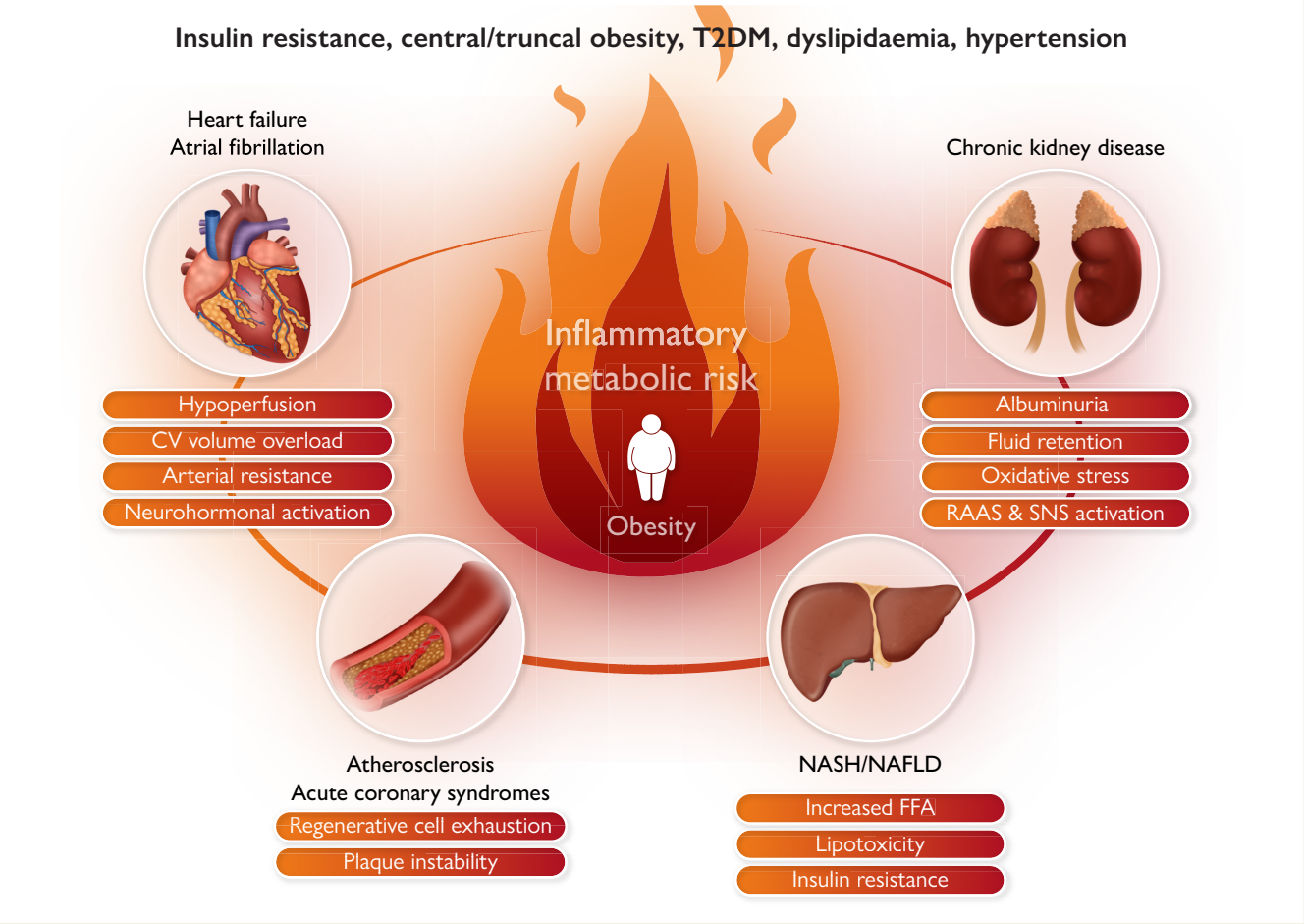

Figure 1 Obesity, particularly ectopic fat accumulation, has been linked to chronic inflammation and insulin resistance, which are linked to multiple pathways of cardiovascular risk. CV, cardiovascular; FFA, free fatty acid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; T2DM, Type 2 diabetes mellitus.[12]

'**Women, lipids, and atherosclerotic cardiovascular disease: a call to action from the European Atherosclerosis Society**', Jeanine Roeters van Lennep from the Erasmus Medical Center in Rotterdam, the Netherlands, and colleagues indicate that despite progress during the last 30 years, ASCVD mortality is now increasing, with the fastest relative increase in middle-aged women.[16] Missed or delayed diagnosis and undertreatment do not fully explain this burden of disease. Sex-specific factors, such as hypertensive disorders of pregnancy, premature menopause (especially primary ovarian insufficiency), and polycystic ovary syndrome are also relevant, with good evidence that these are associated with greater cardiovascular risk. This position statement from the European Atherosclerosis Society focuses on these factors, as well as sex-specific effects on lipids, including lipoprotein(a), which impact ASCVD risk. Women are also disproportionately impacted (in relative terms) by diabetes, chronic kidney disease, and auto-immune inflammatory disease. All these effects are compounded by sociocultural components related to gender. This panel stresses the need to identify and treat modifiable cardiovascular risk factors earlier in women, especially for those at risk due to sex-specific conditions, to reduce the unacceptably high burden of ASCVD in women.

It is unclear whether higher triglyceride metabolism *per se* contributes to mortality separate from elevated triglyceride-rich lipoproteins and body mass index.[17–19] In a Clinical Research article entitled '**From plasma triglycerides to triglyceride metabolism: effects on mortality in the Copenhagen General Population Study**', Mia Johansen from the Copenhagen University Hospital in Denmark, and colleagues tested the hypotheses that higher triglyceride metabolism, measured as higher plasma glycerol and β-hydroxybutyrate, is associated with increased all-cause, cardiovascular, cancer, and other mortality.[20] This study included 30 000 individuals nested within 109 751 individuals from the Copenhagen General Population Study. During a median follow-up of 10.7 years, 9897 individuals died (2204 from cardiovascular, 3366 from cancer, and 2745 from other causes), while none were lost to follow-up. In individuals with glycerol >80 μmol/L (highest fourth) vs. individuals with glycerol <52 μmol/L (lowest fourth), the multivariable adjusted hazard ratio (HR) for all-cause mortality was 1.31. In individuals with β-hydroxybutyrate >154 μmol/L (highest fourth) vs. individuals with β-hydroxybutyrate <91 μmol/L (lowest fourth), the multivariable adjusted HR for all-cause mortality was 1.18. Corresponding values for higher plasma glycerol and β-hydroxybutyrate were 1.37 and 1.18 for cardiovascular mortality,

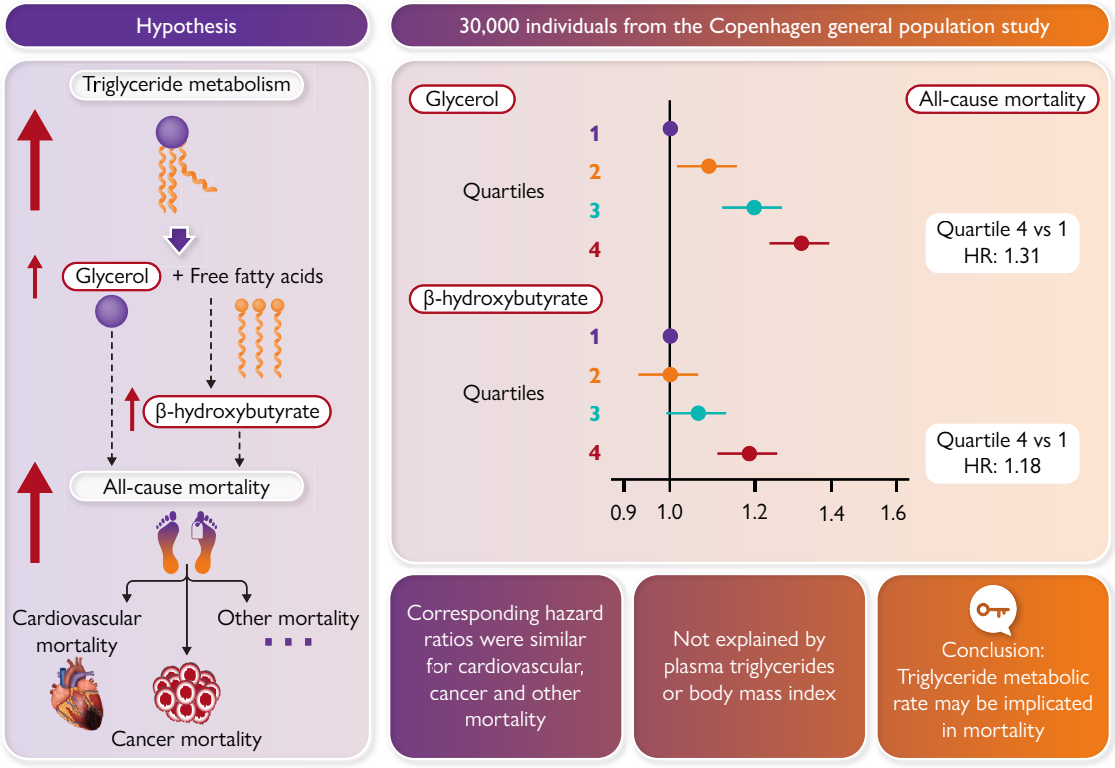

Figure 2 Risk of mortality by higher triglyceride metabolism marked by higher plasma glycerol and β-hydroxybutyrate. Studied in 30 000 individuals selected for metabolic profiling nested within 109 751 individuals from the Copenhagen General Population Study. HR, hazard ratio (95% confidence intervals) after multivariable adjustment. Parts of the figure were created using Biorender.com.[20]

1.24 and 1.16 for cancer mortality, and 1.45 and 1.23 for other mortality, respectively (*Figure 2*). Results were robust to exclusion of first year of follow-up, to stratification for covariates including plasma triglycerides and body mass index, and to further adjustments.

The authors conclude that their study indicates an increased risk of all-cause, cardiovascular, cancer, and other mortality with higher triglyceride metabolism. This is not explained by higher plasma triglycerides and body mass index. The contribution is accompanied by an Editorial by Lale Tokgözoğlu from the Hacettepe University Medical Faculty in Istanbul, Turkey, and colleagues.[21] The authors note that many alternative explanations exist for the correlations described by the authors, the increased TG turnover being one possibility. However, until a direct physiological study demonstrates that individuals with elevated glycerol and β-hydroxybutyrate have increased catabolism of plasma lipoproteins/TGs, the jury is still out and the enigma of the effects of TG-related molecules on morbidity and mortality continues.

The strength of the relationship of triglyceride-rich lipoproteins (TRL) with risk of coronary heart disease (CHD) compared with low-density lipoprotein (LDL) has yet to be resolved.[18,19] In a Clinical Research article entitled '**Triglyceride-rich lipoprotein remnants, low-density lipoproteins, and risk of coronary heart disease: a UK Biobank study**', Elias Björnson from the University of Gothenburg in Sweden, and colleagues identified single-nucleotide polymorphisms (SNPs) associated with TRL/remnant cholesterol (TRL/remnant-C) and LDL cholesterol (LDL-C) in the UK Biobank population. 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 (OR) per 1 mmol/L higher cholesterol of 2.59 and 1.37, respectively. To examine the per-particle atherogenicity of TRL/remnants and LDL, SNPs were categorized into two clusters with differing effects on TRL/remnant-C and LDL-C. Cluster 1 contained SNPs in genes related to receptor-mediated lipoprotein removal that affected LDL-C more than TRL/remnant-C, whereas cluster 2 contained SNPs in genes related to lipolysis that had a much greater effect on TRL/remnant-C. The CHD OR per standard deviation (SD) higher apoB for cluster 2 (with the higher TRL/remnant to LDL ratio) was 1.76, which was significantly greater than the CHD OR per SD higher apoB in cluster 1 (1.33). A concordant result was obtained by using polygenic scores for each cluster to relate apoB to CHD risk.

The authors conclude that distinct SNP clusters appear to impact differentially on remnant particles and LDL. These findings are consistent with TRL/remnants having a substantially greater atherogenicity per particle than LDL. The manuscript is accompanied by an Editorial by Anne Tybjærg-Hansen from the Copenhagen University Hospital Rigshospitalet in Denmark, and colleagues.[22] The authors draw the conclusion that the extremely well thought through and conducted study by Björnson *et al.* together with previous literature implies that future studies aiming at reducing ASCVD by lowering TRLs should reduce both TRL/remnant-C, non-HDL-C, and apoB.

Further, per particle reduction, the beneficial effect will probably be greater for TRLs/remnants than for LDL, most probably because TRLs/remnants per particle carry substantially more cholesterol than LDL.

The issue is also complemented by a Discussion Forum contribution. In a commentary entitled '**The fiction of the obesity paradox**', Maya Guglin from the Indiana University School of Medicine in Indiana, USA comments on the recent publication '**Anthropometric measures and adverse outcomes in heart failure with reduced ejection fraction: revisiting the obesity paradox**' by Jawad H Butt from the University of Glasgow, and colleagues.[23,24]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

Dr. Crea reports speaker fees from Abbott, Amgen, Astra Zeneca, BMS, Chiesi, Daiichi Sankyo, Menarini outside the submitted work.

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