ESC European Society of Cardiology
European Heart Journal (2020) **41**, 1–3
doi:10.1093/eurheartj/ehz960

'The lower the better' revisited: the new lipid targets in high risk patients

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Ever since Nikolai Nikolaiaevich Anitchkow's seminal experiments,[1] lipids have been associated with atherosclerotic cardiovascular disease (ASCVD). Although the Framingham Study confirmed this relationship in humans,[2] a causal relationship between LDL cholesterol (LDL-C) and complications of ASCVD such as myocardial infarction, stroke, and sudden death was only convincingly proven by the 4S trial.[3] From then on, lipid lowering became part of the management of most patients with CVD. However, the amount of LDL-C lowering required remained debatable, but overall LDL-C target levels became lower and lower over time.

In spite of increasingly aggressive measures in primary and secondary prevention, CVD remains the most important cause of morbidity and mortality. As outlined in the comprehensive '**European Society of Cardiology: cardiovascular disease statistics 2019**' by Adam Timmis and colleagues,[4] the contemporary analysis of CVD statistics across 56 member countries, with particular emphasis on international inequalities in disease burden and healthcare delivery overall, confirms this fact (*Figure 1*). The statistics are drawn from the ESC Atlas, which is a repository of CVD data from a variety of sources including the World Health Organization, the Institute for Health Metrics and Evaluation, as well as the World Bank. The Atlas also includes novel ESC-sponsored data on human and capital infrastructure and cardiovascular healthcare delivery obtained by an annual survey of the national societies of ESC member countries.

The prognostic role of hypertriglyceridaemia in patients with ASCVD has been debated over decades,[5] but gained importance following the publication of the REDUCE-IT trial,[6] showing benefit with icosapent ethyl in such patients. In their FAST TRACK entitled '**Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies**', Patrick Ryan Lawler and colleagues from the Toronto General Hospital in Ontario, Canada quantified the real-world risk of ASCVD in hypertriglyceridaemia, and estimated icosapent ethyl eligibility in 2 424 865 adults in Ontario.[7] Increasing triglycerides was associated with a progressively higher hazard of ASCVD events. Twenty-five per cent of individuals with ASCVD had hypertriglyceridaemia and controlled LDL-C; these patients were demographically similar to those in REDUCE-IT with comparable event rates. Thus, among patients with ASCVD, hypertriglyceridaemia is common and is associated with higher event rates across a range of triglycerides, and as many as one in four patients may be candidates for emerging therapies. These findings, which are relevant for clinical practice, are put into context in a thought-provoking **Editorial** by Chris J. Packard from the Western Infirmary in Glasgow, UK.[8]

This issue is further discussed in a '**Clinical review on triglycerides**' by Ulrich Laufs and colleagues from the Universitat Leipzig in Germany.[9] The authors confirm not only that is hypertriglyceridaemia common, but that epidemiological and genetic studies have established triglyceride-rich lipoproteins and their remnants as important contributors to ASCVD. In addition, severe hypertriglyceridaemia raises the risk of pancreatitis. While LDL-C is the primary treatment target for lipid-lowering therapy, secondary targets that reflect the contribution of triglyceride-rich lipoproteins such as apolipoprotein B and non-HDL-C are recommended for risk assessment in the current ESC Guidelines. Reduction of severe triglyceridaemia is primarily of importance to avert or reduce the risk of pancreatitis. However, managing hypertriglyceridaemia is now also an evolving target in patients with ACVD (see *Figure 2*). Current remedies include diet and lifestyle and established treatments such as fibrates and omega-3 fatty acids as well as emerging therapies, including various biological agents such as antisense oligonucleotides.

Finally, this Focus Issue on lipids contains the '**2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)**' by Francois Mach and colleagues from the ESC Scientific Document Group[10] which updates the previous ESC/EAS

With thanks to Amelia Meier-Batschelet for help with compilation of this article.

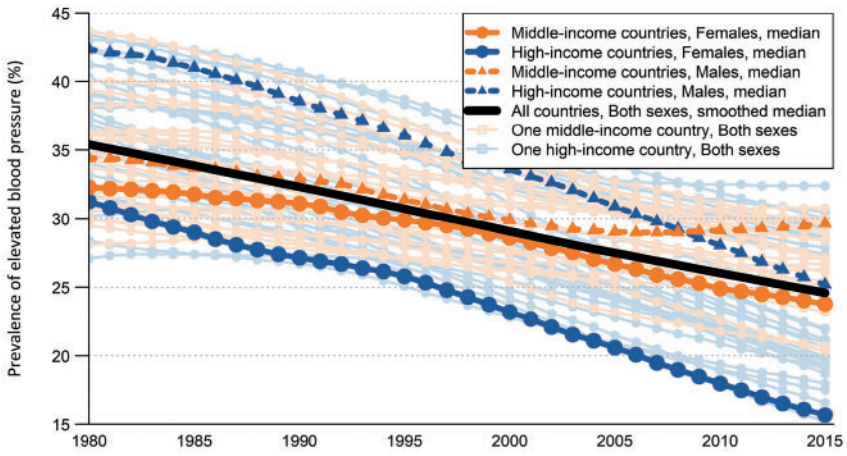

Figure 1 Prevalence of elevated blood pressure among adults (%) in ESC member countries (1980–2015). *Data source*: WHO, http ://apps.who.int/gho/data/node.main.A875STANDARD?lang=en. *Data not available*: Republic of Kosovo and Republic of San Marino (Supplementary file: S4.xlsx). Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, de Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P; European Society of Cardiology. European Society of Cardiology: Cardiovascular Disease Statistics 2019. See pages 12–85)

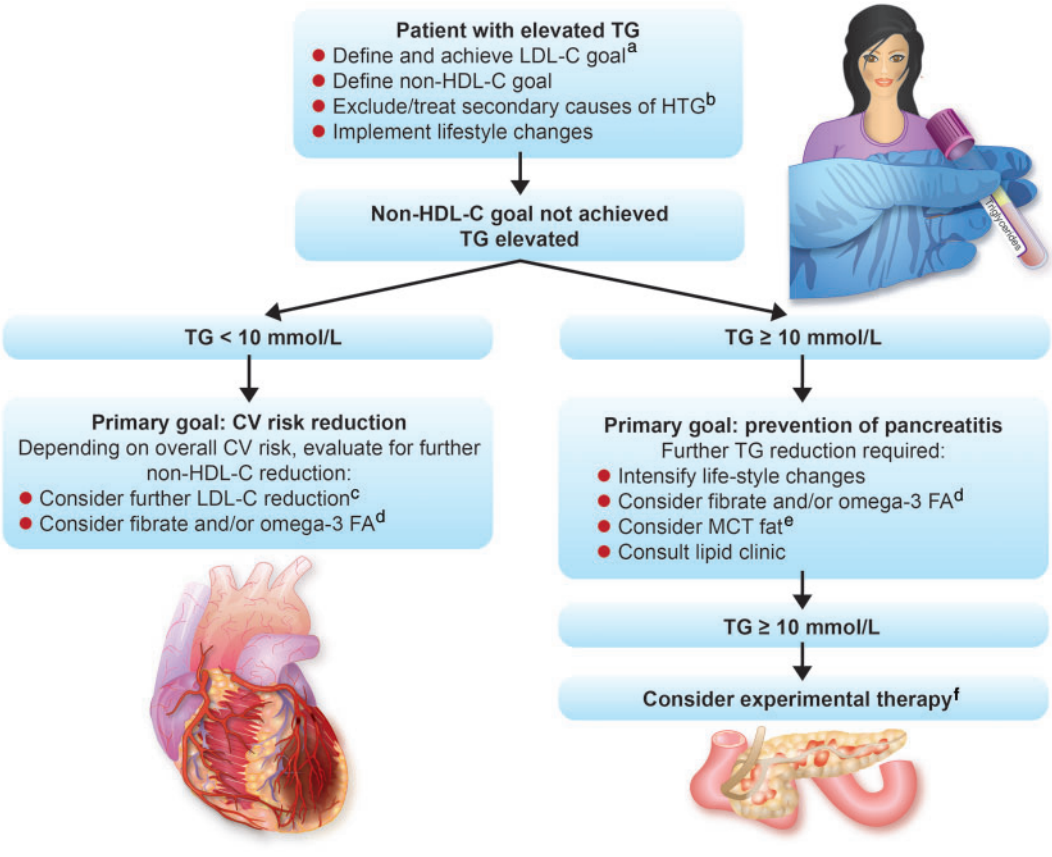

Figure 2 Treatment algorithm for patients with elevated fasting triglycerides. [a]Low-density lipoprotein cholesterol goal depends on absolute cardiovascular risk. [b]Potential secondary causes for hypertriglyceridaemia are listed in *Table 2* of the manuscript (see page 102).[9] [c]Further low-density lipoprotein cholesterol reduction will also help in achieving non-high-density lipoprotein cholesterol goals. [d]Omega-3-FA, omega-3 fatty acids. [e]MCT, fats containing medium-chain fatty acids. [f]Experimental therapies are listed in *Table 6* of the manuscript (see page 107).[9] (Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. See pages 99–109)

lipid Guidelines published in August 2016. The emergence of a substantial body of evidence has required an update. Retention of LDL-C and other cholesterol-rich apolipoprotein B-containing lipoproteins in the arterial wall remains the major driver of ASCVD. Several recent placebo-controlled clinical studies have shown that the addition of ezetimibe and/or anti-proprotein convertase subtilisin/kexin type 9 (PCSK9;[11,12]) monoclonal antibodies to statin therapy provides a further reduction not only of LDL-C, but also of ASCVD risk. Importantly, lower achieved LDL-C values lower the risk of future cardiovascular events, with no apparent lower limit of LDL-C. Importantly, the clinical safety of very low LDL-C values is reassuring.[13] In contrast, therapies raising HDL cholesterol (HDL-C) do not reduce ASCVD risk. Thus, there is no longer an 'LDL-C hypothesis', but rather established facts that increased LDL-C values are causally related to ASCVD, and that lowering LDL particles and other apolipoprotein B-containing lipoproteins as much as possible reduces cardiovascular events with no apparent limit.[14,15] As such, in a bold step, the 2019 ESC Guidelines on the Management of Dyslipidaemias recommend much lower LDL-C target levels of 1.8, 1.4, or even 1.0 mmol/L depending on ASCVD risk.

The issue is also complemented by three *Discussion Forum* contributions. In a first piece '**More consideration of β-cell function and PCSK9/LDLR axis**', Daxin Wang and colleagues from the Clinical Medical College of Yangzhou University in China comment on the recent publication '**PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor**' by Giuseppe Norata and colleagues from the University of Milan in Italy.[16,17] In another piece '**Statins and Lp(a): do not make perfect the enemy of excellent**' Maciej Banach and colleagues from the Medical University of Lodz in Poland comment on the recently published '**Statin therapy increases lipoprotein(a) levels**' by Sotirios Tsimikas and colleagues from the University of California-San Diego in La Jolla, California, USA.[17,18] Tsimikas *et al.* respond in a separate contribution.[19]

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

References

1. Anitschkov NN. A history of experimentation on arterial atherosclerosis in animals. In: Blumenthal HT, Ed., *Cowdry's Atherosclerosis. A Survey of the Problem*, Chalres C. Thomas, Springfield, Ill., 1933, pp. 21–44.
2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Boren J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgozoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano 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**:2459–2472.
3. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–1389.
4. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, de Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P. European Society of Cardiology: cardiovascular disease statistics 2019. *Eur Heart J* 2020;**41**:12–85.
5. Madsen CM, Varbo A, Nordestgaard BG. Unmet need for primary prevention in individuals with hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/European Atherosclerosis Society guidelines: a contemporary population-based study. *Eur Heart J* 2018;**39**:610–619.
6. Bhatt DL. REDUCE-IT. *Eur Heart J* 2019;**40**:1174–1175.
7. Lawler PR, Kotrri G, Koh M, Goodman SG, Farkouh ME, Lee DS, Austin PC, Udell JA, Ko DT. Real-world risk of cardiovascular outcomes associated with hypertriglyceridaemia among individuals with atherosclerotic cardiovascular disease and potential eligibility for emerging therapies. *Eur Heart J* 2020;**41**:86–94.
8. Packard CJ. Triglyceride lowering 2.0: back to the future? *Eur Heart J* 2020;**41**:95–98.
9. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. *Eur Heart J* 2020;**41**:99–109.
10. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
11. Sinnaeve PR, Schwartz GG, Wojdyla DM, Alings M, Bhatt DL, Bittner VA, Chiang CE, Correa Flores RM, Diaz R, Dorobantu M, Goodman SG, Jukema JW, Kim YU, Pordy R, Roe MT, Sy RG, Szarek M, White HD, Zeiher AM, Steg PG. Effect of alirocumab on cardiovascular outcomes after acute coronary syndromes according to age: an ODYSSEY OUTCOMES trial analysis. *Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz809.
12. White HD, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Erglis A, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lopes RD, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Sritara P, Tricoci P, Zeiher AM, Schwartz GG. Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial. *Eur Heart J* 2019;**40**:2801–2809.
13. Guedeney P, Giustino G, Sorrentino S, Claessen BE, Camaj A, Kalkman DN, Vogel B, Sartori S, De Rosa S, Baber U, Indolfi C, Montalescot G, Dangas GD, Rosenson RS, Pocock SJ, Mehran R. Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz430.
14. Gencer B, Mach F. So low… so far so good: neurocognitive impact of lowering LDL-C levels with PCSK9 inhibitors. *Eur Heart J* 2018;**39**:382–384.
15. Harvey PD, Sabbagh MN, Harrison JE, Ginsberg HN, Chapman MJ, Manvelian G, Moryusef A, Mandel J, Farnier M. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized Phase 2 and 3 controlled trials: a meta-analysis of individual patient data. *Eur Heart J* 2018;**39**:374–381.
16. Yang XQ, Mao YQ, Wang DX. More consideration of beta-cell function and PCSK9/LDLR axis. *Eur Heart J* 2020;**41**:189.
17. Da Dalt L, Ruscica M, Bonacina F, Balzarotti G, Dhyani A, Di Cairano E, Baragetti A, Arnaboldi L, De Metrio S, Pellegatta F, Grigore L, Botta M, Macchi C, Uboldi P, Perego C, Catapano AL, Norata GD. PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor. *Eur Heart J* 2019;**40**:357–368.
18. Banach M, Pesen PE. Statins and Lp(a): do not make perfect the enemy of excellent. *Eur Heart J* 2020;**41**:190–191.
19. Tsimikas S, Gordts PLSM, Nora C, Yeang C, Witztum JL. Statin therapy increases lipoprotein(a) levels. *Eur Heart J* 2020;**41**:192–193.