



# How to prevent cardiovascular events from recurring

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A substantial body of evidence from different types of clinical and genetic studies has consistently and unequivocally established a causal role of low-density lipoprotein (LDL) particles in atherosclerotic cardiovascular disease (ASCVD).<sup>1</sup> Consistent with this notion, lowering levels of LDL cholesterol (LDL-C) pharmacologically reduced the risk of cardiovascular events proportional to the absolute magnitude of LDL-C reduction in numerous randomized clinical trials.<sup>1</sup> As a result of these relationships, lowering of LDL-C is recommended as a cornerstone of ASCVD prevention, with treatment targets depending on overall risk.<sup>2</sup> Of concern, the translation of guideline recommendations into clinical practice appears to be inefficient. Results from the European Society of Cardiology EUROASPIRE V registry – a large cross-sectional survey that aimed to determine whether the Joint European Societies' guidelines on cardiovascular prevention were implemented in everyday practice – demonstrated that 71% of patients did not reach their targets for LDL-C (<70 mg/dL) and one fifth were not on statin therapy at all six months or after coronary artery events or interventions.<sup>3</sup>

In a past issue of the *European Journal of Preventive Cardiology*, Lassenius et al.<sup>4</sup> presented real-life data from an Amgen-financed, retrospective, register-based study encompassing a cohort of 28,625 adult patients from Southwest Finland who had survived a cardiovascular event between 2004 and 2016. First, the authors reported the association of cardiovascular event rates with LDL-C levels and statin adherence/intensity as estimated by statin purchases. Second, Lassenius et al. evaluated the timing of event recurrence. In line with EUROASPIRE V, they demonstrated that LDL-C treatment targets (<70 mg/dL), as defined by the guidelines of the European Society of Cardiology at the time of this study, were accomplished by only 18% of the cohort in the year following the index event and that high-intensity statins were used by only 22% of the cohort six months after the index event. Low statin adherence was associated with an increased risk of event recurrence. Furthermore, of little surprise, each additional event increased the likelihood of subsequent

events (1.2–1.9-fold per consecutive event). The key statement made by the authors was that more attention should be directed towards ensuring long-term adherence to statin therapy and to LDL-C treatment goals in real-life clinical settings.<sup>4</sup>

Clinical trials, but less so registry data, often fail to reflect the aging and multi-morbid population that our health services care for. The cohort of the study by Lassenius et al., with a mean age of 73 years, is representative of the patients we care for on a day-to-day basis and, thus, complements the information provided by randomized clinical trials.<sup>4</sup> Furthermore, Lassenius et al. assessed up to five recurring cardiovascular events, adding important information on long-term risk reduction by statins.<sup>4</sup> In this regard, it is worth noting that clinical trials that end with the index event tend to underestimate the cumulative benefit of statin use over time.<sup>5</sup> One limitation that should be considered when interpreting the results of these data is the fact that patients that comply with pharmacological therapy are also more likely to have a low-risk lifestyle. This *healthy user bias* is a confounder and difficult to quantify, but has to be considered when interpreting the evidence presented by Lassenius et al. Interestingly, upon stratification by sex (as depicted in the Cox model of recurrent events in Table 3), levels of LDL-C were no longer significantly associated with event recurrence in males.<sup>4</sup> While this may be attributable to a loss of power caused by the splitting of the groups, these data align with data by Vergallo et al.,<sup>6</sup> where the expression of markers of atherogenic dyslipidaemia, but not

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LDL-C, discriminated between patients with multiple recurrent acute coronary syndromes and long-standing clinical stability, as outlined in further detail below.<sup>7,8</sup>

Taken together, Lassenius et al. showed in a large cohort representing real life that a substantial number of patients did not reach their LDL-C goal and that statin adherence decreased over time. This was associated with an increased risk of recurrent events. The results of this study reiterate the importance of motivating patients to adhere to statin therapy for event reduction.<sup>4</sup>

We would like to build upon the important data reported by Lassenius et al.<sup>4</sup> by highlighting the paramount role of residual risk. Despite optimal statin therapy, which lowers LDL-C and inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) by about the same magnitude,<sup>9,10</sup> significant lipoprotein- and non-lipoprotein-associated sources of ASCVD risk remain.<sup>11</sup> The lipoprotein pattern referred to as atherogenic dyslipidaemia is a prominent lipid trait associated with metabolic syndrome and ASCVD.<sup>12</sup> Interestingly, in a recent study by Vergallo et al.,<sup>6</sup> neither LDL-C level nor statin use discriminated between patients with multiple recurrent acute coronary syndromes and long-standing clinical stability.<sup>7</sup> Conversely, global inflammatory burden (hsCRP levels) and the expression of atherogenic dyslipidaemia were higher in the recurrent acute coronary syndrome group compared with the long-standing stable angina group, with high-density lipoprotein cholesterol (HDL-C) levels showing statistical significance.<sup>7</sup> A secondary analysis furthermore demonstrated that the triglyceride-to-HDL-C (TG/HDL-C) ratio, a metabolic index indicative of atherogenic dyslipidaemia, was significantly higher in patients with high-risk fibroatheromas.<sup>8</sup> This reiterates the role of lipid markers beyond LDL-C for identifying patients that are candidates for intensified preventive measures. Elevated plasma triglycerides with or without low levels of HDL-C are often accompanied by visceral adiposity, non-alcoholic fatty liver disease, metabolic syndrome and type 2 diabetes mellitus, and thus constitute a key modifiable component in cardiovascular disease prevention.<sup>12–14</sup> This coordinated cluster of high-risk metabolic traits might, in part, be seen as a consequence of just a handful of basic lifestyle factors such as poor diet quality, including a deficit in long-chain omega-3 polyunsaturated fatty acids,<sup>15</sup> sedentarism, a failure to cope with distress, sleep deprivation and exposure to environmental stressors such as ambient air pollution/noise.<sup>16</sup>

In conclusion, we share the authors' view that efforts to address risk factors with pharmacotherapy constitute one very important pillar in cardiovascular disease prevention. However, numerous factors modify the causality of lipoprotein-associated risk in ASCVD

and the vast majority of coronary heart disease (CHD) (80%) and total cardiovascular events (70%) are lifestyle related.<sup>17</sup> To meet our patient's needs, financial resources must be made available to assess lifestyle risk factors, inform about them and support the implementation of healthy lifestyle habits.<sup>16,17</sup> This calls for multifactorial prevention strategies, not only detailed in pertinent guidelines,<sup>18</sup> but also delivered by interdisciplinary teams of healthcare professionals addressing the full spectrum of individual risk factor management.<sup>3</sup> A first step towards that goal could be the implementation of *Preventive Cardiology* as a subspecialty of Cardiology, including the delivery of structured training programs that teach all dedicated skills necessary to manage cardiovascular risk.<sup>19,20</sup> We strongly posit that the huge global disease burden of cardiometabolic disease can and must be reduced by structured and competent care.

#### Author contribution

KL conducted the literature search and drafted the manuscript. CvS revised and edited the manuscript. Both authors approved the final version of this manuscript.

#### Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KL has received speaker's honoraria from Sanofi, Amgen and Novo Nordisk. CvS operates Omegamatrix, a laboratory for fatty acid analyses. He also consults for BASF/Pronova and Huntsworth Medical, and received speaker's honoraria from Abbott, DSM and Norsan.

#### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

#### References

1. Ference BA, Ginsberg HN, Graham I, 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: 2459–2472.
2. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; 41: 111–188.
3. Kotseva K, De Backer G, De Bacquer D, 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: 824–835.
4. Lassenius MI, Toppila I, Bergius S, et al. Cardiovascular event rates increase after each recurrence and associate

- with poor statin adherence. *Eur J Prev Cardiol*. [Epub ahead of print] DOI: 10.1177/2047487319869400.
5. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J* 2018; 39: 2526–2539.
  6. Vergallo R, Porto I, D’Amario D, et al. Coronary atherosclerotic phenotype and plaque healing in patients with recurrent acute coronary syndromes compared with patients with long-term clinical stability: an in vivo optical coherence tomography study. *JAMA Cardiol* 2019; 4: 321–329.
  7. Lechner K and Halle M. Are atherogenic lipoprotein phenotype and inflammation indicative of plaque phenotype and clinical stability in coronary artery disease? *JAMA Cardiol* 2019. [Epub ahead of print] DOI: 10.1001/jamacardio.2019.2261.
  8. Vergallo R, Porto I and Crea F. Are atherogenic lipoprotein phenotype and inflammation indicative of plaque phenotype and clinical stability in coronary artery disease?-Reply. *JAMA Cardiol* 2019. [Epub ahead of print] DOI: 10.1001/jamacardio.2019.2231.
  9. Ridker PM and Luscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J* 2014; 35: 1782–1791.
  10. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359: 2195–2207.
  11. Libby P and Everett BM. Novel antiatherosclerotic therapies. *Arterioscler Thromb Vasc Biol* 2019; 39: 538–545.
  12. Grundy SM. Atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance. *Clin Cornerstone* 2006; 8(Suppl 1): S21–S27.
  13. Fruchart JC, Santos RD, Aguilar-Salinas C, et al. The selective peroxisome proliferator-activated receptor alpha modulator (SPPARMalpha) paradigm: conceptual framework and therapeutic potential: a consensus statement from the International Atherosclerosis Society (IAS) and the Residual Risk Reduction Initiative (R3i) Foundation. *Cardiovasc Diabetol* 2019; 18: 71.
  14. Ganda OP, Bhatt DL, Mason RP, et al. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol* 2018; 72: 330–343.
  15. von Schacky C. Omega-3 fatty acids in cardiovascular disease—an uphill battle. *Prostaglandins Leukot Essent Fatty Acids* 2015; 92: 41–47.
  16. Lechner K, von Schacky C, McKenzie AL, et al. Lifestyle factors and high-risk atherosclerosis: pathways and mechanisms beyond traditional risk factors. *Eur J Prev Cardiol* 2019. [Epub ahead of print] DOI: 10.1177/2047487319869400.
  17. Mozaffarian D, Wilson PW and Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. *Circulation* 2008; 117: 3031–3038.
  18. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315–2381.
  19. Lechner K, Lorenz E and Drezner JA. The ‘heart’ of preventive cardiology: lifestyle medicine for the treatment of cardiometabolic diseases. *Eur J Prev Cardiol* 2020. [Epub ahead of print] DOI:10.1177/2047487319899107.
  20. Shapiro MD, Maron DJ, Morris PB, et al. Preventive cardiology as a subspecialty of cardiovascular medicine: JACC Council perspectives. *J Am Coll Cardiol* 2019; 74: 1926–1942.