LIPID PARAMETER THRESHOLDS: THE DEBATE CONTINUES

María Grau, MD, MPH, PhD

Epidemiology and Cardiovascular Genetics, IMIM Hospital del Mar Medical Research Institute, Barcelona, Spain

Consortium for Biomedical Research in Epidemiology and Public Health, Barcelona, Spain

University of Barcelona

Correspondence: IMIM Hospital del Mar Medical Research Institute ; #88 Dr. Aiguader Street 08003 Barcelona (Spain); mgrau@imim.es

The prevention of atherosclerotic cardiovascular diseases is a paramount priority of the public health agenda because these diseases are the main cause of death in the developed world and an increasing concern in developing countries.[1] Many individual attitudes about health are shaped by community attitudes, and the recommendations given in the clinical practice guidelines for the control of cardiovascular diseases affect not only the individual at risk, but the population as a whole. We might consider, for example, the current and future impact on National Health System sustainability of the recommended treatment needed to prevent a given number of atherosclerotic cardiovascular events from occurring. In primary prevention, the recommendation relies on the patient's overall cardiovascular risk profile according to clinical practice guidelines.[2,3]

Lipid profile management has traditionally played a key role in cardiovascular prevention (Figure 1). From the inception of the National Cholesterol Education Program, promoted by the National Heart, Blood and Lung Institute, the strategy has been focused on the reduction of low-density lipoprotein (LDL) cholesterol in an attempt to move its distribution toward the left of the population scale, thus obtaining a reduction in total risk. In primary prevention, LDL cholesterol threshold is guided by the individual cardiovascular risk profile, whereas in secondary prevention, the current LDL cholesterol goal (i.e. <70 mg/dl) is far from being attained for most patients.[4,5]

In the current volume of the Journal, Wang et al. make an appeal for a critical appraisal of clinical practice guidelines when applying the recommendations in populations where interventions have not been properly tested.[6] For instance, high quality evidence is scarce in Asian populations about the significance of a given lipid parameter on overall cardiovascular outcomes as a hard end-point in clinical trials with guaranteed

representativeness and adequate sample size. Thus, most clinical recommendations applied in Asian countries are derived from guidelines based on clinical trials performed in majority Caucasian populations of America and western Europe.[2,3]

The manuscript by Wang et al. highlights the need to adapt and rigorously evaluate in a recipient population the clinical recommendations developed from evidence observed in a different population.[6] For example, results from two Asian countries, China and Japan, diverged greatly when the IMPACT model was applied to ascertain the role of lifestyles and treatments in the changes observed in coronary heart disease mortality. China had an increasing mortality trend, explained by rises in total cholesterol reflecting an increasingly "Western" diet, while Japan showed a decreasing trend explained by policies designed to reduce blood pressure and smoking and encourage evidence-based treatment for coronary heart disease.[7,8]

In addition, as part of the adaptation process, Wang et al. defend the need to rigorously carry out clinical trials with adequate sample size in the very heterogeneous Asian populations, not only to ascertain the efficacy of statins treatment but also to extract information about patient safety.[6] The scientific community agrees that conclusions drawn from well-performed clinical trials provide the highest quality of evidence (A grade recommendation equivalent). However, clinical trials have known limitations, particularly the challenge of representativeness and a short follow-up that does not allow assessment of patient safety and the observation of long-term outcomes (i.e. hard end-points). These could be remedied in part by pharmacoepidemiology studies using real-world data. For instance, two studies conducted in the same electronic medical record database from Catalonia (Spain) showed that, in this population, LDL cholesterol reduction with statins should remain a priority in primary prevention for individuals at

high 10-year coronary risk (10–19.9%) aged 35 to 74 years because of the clear absolute benefit in reducing myocardial infarction or ischemic stroke [number-needed-to-treat to prevent 1 outcome = 62].[9] The authors also point out that their results do not support the current clinical practice guidelines[2,3] recommending statin treatment without exception in patients older than 75 years. In their population, statin treatment in patients aged 75 or older without type 2 diabetes was not associated with a reduction in atherosclerotic cardiovascular disease or in all-cause mortality, even when the incidence of atherosclerotic cardiovascular disease was significantly higher than the risk thresholds proposed for statin use.[10] Both studies had an adequate and representative sample size from the Catalan community (617,850 and 46,864 individuals, respectively), long-term follow-up (13 and 10 years) and showed that statins did not increase adverse effects in the long term.[9,10]

As emphasized by the most current clinical practice guidelines and also by Wang et al.,[2,3,6] the promotion of a healthy lifestyle and risk-factor reduction early in life is key to achieve an effective prevention of atherosclerotic cardiovascular diseases.[2,3] While the worldwide public health agenda must focus on this point, individual countries should apply high-quality scientific evidence to validate the guidelines promoted by international scientific societies in their own populations.

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REFERENCES

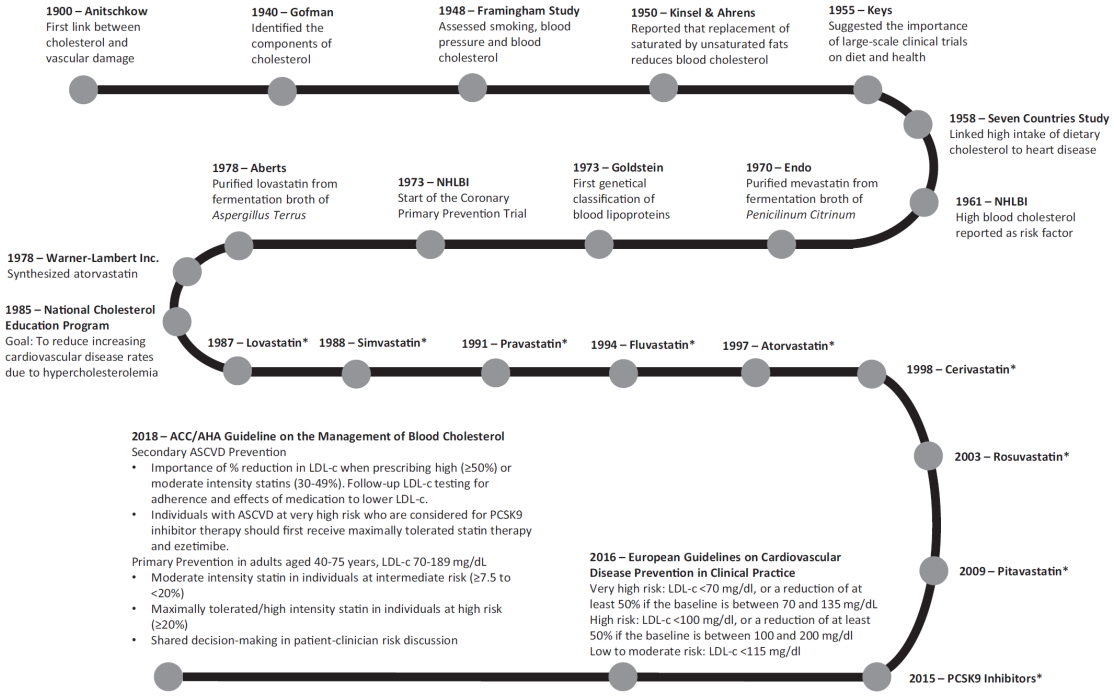
1. World Health Statistics [Homepage on the internet]. Geneva: World Health Organization. 2019 https:// apps. who. int/ infobase/ (Cited 27 March 2019).
2. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. *Circulation* 2018:CIR0000000000000624.
3. 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. *Eur J Prev Cardiol* 2016;23(11):NP1-NP96.
4. Ferrieres J, De Ferrari GM, Hermans MP, et al. Predictors of LDL-cholesterol target value attainment differ in acute and chronic coronary heart disease patients: Results from DYSIS II Europe. *Eur J Prev Cardiol* 2018;25(18):1966-1976.
5. Poh KK, Ambegaonkar B, Baxter CA, et al. Low-density lipoprotein cholesterol target attainment in patients with stable or acute coronary heart disease in the Asia-Pacific region: results from the Dyslipidemia International Study II. *Eur J Prev Cardiol* 2018;25(18):1950-1963.
6. Wang Y, Yan BP, Tomlison B, Lee VWY. Is lipid goal one-size-fits-all: A review of evidence for recommended low-density lipoprotein treatment targets in Asian patients. *Eur J Prev Cardiol* 2019
7. Critchley J, Liu J, Zhao D, Wei W, Capewell S. Explaining the increase in coronary heart disease mortality in Beijing between 1984 and 1999. *Circulation* 2004;110:1236-44.

8. Ogata S, Nishimura K, Guzman-Castillo M, et al. Explaining the decline in coronary heart disease mortality rates in Japan: Contributions of changes in risk factors and evidence-based treatments between 1980 and 2012. *Int J Cardiol* 2019. pii: S0167-5273(18)34148-2.
9. Garcia-Gil M, Comas-Cufí M, Blanch J, et al. Effectiveness of Statins as Primary Prevention in People With Different Cardiovascular Risk: A Population-Based Cohort Study. *Clin Pharmacol Ther* 2018;104:719-732.
10. Ramos R, Comas-Cufí M, Martí-Lluch R, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *BMJ* 2018;362:k3359.

FIGURE LEGENDS

Figure 1. Historical evolution of blood lipid management, according to strategies supported by the American and European clinical guidelines.

Figure 1.



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