

Cholesterol is Inadequately Treated in Diabetic Patients from Buenos Aires: Independently from the Formula We Use Numbers Do Not Match

El tratamiento del colesterol es inadecuado en pacientes diabéticos de Buenos Aires: independientemente de la fórmula utilizada, las cifras no coinciden

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Type 2 diabetes (T2DM) is associated with at least a 2-fold risk of atherosclerotic cardiovascular disease (ASCVD) compared with the normal population. (1, 2) If risk factors are left uncontrolled up to 70% of T2DM subjects will die of cardiovascular diseases. (3) Among the different factors involved in atherosclerosis development in T2DM, atherogenic dyslipidemia plays a pivotal role. Not only low-density lipoprotein cholesterol (LDL) but also cholesterol-rich remnants of chylomicrons and very low-density lipoproteins (VLDL) are causal of atherosclerotic plaque development and complications. This knowledge comes from robust evaluations of thousands of hundreds of individuals involved in classical prospective observational but most importantly from Mendelian randomization and interventional randomized controlled studies. (4,5)

Considering overwhelming and indisputable evidence, when serious science is concerned, there is consensus from medical societies that apolipoprotein B (ApoB) containing lipoproteins must be adequately reduced to prevent ASCVD in T2DM subjects. Either LDL-cholesterol or the much more intuitive concept of non-HDL-cholesterol (i.e. the cholesterol carried by pro-atherogenic ApoB containing lipoproteins) are used as surrogates of the latter and are targets for therapy. Indeed recent guidelines from Europe and the USA even recommend more aggressive reduction in LDL-cholesterol due to results of ezetimibe and/or PCSK9 inhibitors on top of statins. (6,7)

Implementation of risk factor control, including dyslipidemia, reduces cardiovascular complications in diabetics. (8,9) Unfortunately, despite this indisputable evidence most individuals at high and very high risk of ASCVD including secondary prevention diabetics are not being adequately treated. (10)

In this issue of the Journal Masson et al. (11) show

inadequate treatment of dyslipidemia in high risk subjects from the Buenos Aires region, a fact that unfortunately does not differ very much from Europe, USA or developing countries. (10,12). In their cross-sectional study, the authors clearly show that independently of the mathematical calculation used to estimate LDL-cholesterol (an unfortunately not well quantified parameter despite all advances in clinical chemistry) the latter is severely uncontrolled in T2DM patients at different levels of ASCVD risk. The same applies for non-HDL-cholesterol. In those with a previous ASCVD event, roughly 2/3 present LDL-cholesterol calculated by the Friedewald formula and non-HDL-cholesterol not in accord with Argentinian prevention guidelines (respectively <70 mg/dL and <100 mg/dL). When the formula developed by Martin et al. (13) to better estimate LDL-cholesterol, especially when triglycerides are >150mg/dL or when cholesterol carried by LDL is <100 mg/dL (14), an additional 21% entered the uncontrolled LDL-cholesterol category. In those at primary prevention, but with high ASCVD risk (T2DM with other risk factors or target organ damage), approximately 80% were not at their respective LDL-cholesterol and non-HDL-cholesterol goals. When LDL-cholesterol was estimated by the Martin et al. formula, 28% of those whose LDL-cholesterol was calculated as <70 mg/dL using the Friedewald formula moved to out of goal category. As expected, discrepancy between estimated LDL-cholesterol was greater in those with higher triglyceride levels, where the classical 5:1 molar relationship of triglycerides/cholesterol is no longer valid.

Furthermore, and independently of biochemical and mathematical formulas, statins and doses of these medications that add on average an extra 20% reduction in cardiovascular events (15) are not prescribed

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as recommended by evidence-based guidelines. In the study of Masson et al (11), 23% and 67% of those on secondary prevention were not using any statin or high doses of the latter, respectively. In high risk primary prevention T2DM patients, 38% were not receiving statins, while only 15% were treated at high doses as recommended.

This study clearly shows that there is a gap between theory and practice, which widens by using the contemporary and robust Martin et al. formula for LDL-cholesterol estimation. (13). Certainly, the greatest explanation for the study findings is inadequate use of statins at correct doses. This phenomenon unfortunately occurs everywhere despite widespread availability, low cost and access to these lifesaving medications. The authors should be commended by their study since real world evidence is very important to plan programs to improve clinical practice. The study of Masson et al.(11) clearly shows that independently of the formula used the numbers unfortunately do not match where cholesterol control is concerned and as physicians we need to improve our mathematics.

Conflicts of interest

RDS has received honoraria related to consulting, research and/or speaker activities from: Ache, Amgen, Astra Zeneca, Esperion, Kowa, Novo-Nordisk, Merck, MSD, Pfizer, PTC and Sanofi/Regeneron.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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REFERENCES

- American Diabetes Association. Standards of Medical Care in Diabetes-2019 Abridged for Primary Care Providers. *Clin Diabetes* 2019;37:11-34. <https://doi.org/10.2337/cd18-0105>
- Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-22. [https://doi.org/10.1016/S0140-6736\(10\)60484-9](https://doi.org/10.1016/S0140-6736(10)60484-9)
- Bertoluci MC, Moreira RO, Faludi A, Izar MC, Schaan BD, Valerio CM, et al. Brazilian guidelines on prevention of cardiovascular disease in patients with diabetes: a position statement from the Brazilian Diabetes Society (SBD), the Brazilian Cardiology Society (SBC) and the Brazilian Endocrinology and Metabolism Society (SBEM). *Diabetol Metab Syndr* 2017;9:53. <https://doi.org/10.1186/s13098-017-0251-z>
- Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E. 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;38:2459-72. <https://doi.org/10.1093/eurheartj/ehx144>
- Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, et al. Association of Triglyceride-Lowering LPL Variants and LDL-C-Lowering LDLR Variants With Risk of Coronary Heart Disease. *JAMA* 2019;321:364-73. <https://doi.org/10.1001/jama.2018.20045>
- Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285-e350. <https://doi.org/10.1016/j.jacc.2018.11.004>
- Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, 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;41:111-88. <https://doi.org/10.1093/eurheartj/ehz455>
- Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med*. 2014;370:1514-23. <https://doi.org/10.1056/NEJMoa1310799>
- Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2018;379:633-44. <https://doi.org/10.1056/NEJMoa1800256>
- Blom DJ, Santos RD, Daclin V, Mercier F, Ruiz AJ, Danchin N; ICLPS study group. The challenge of multiple cardiovascular risk factor control outside Western Europe: Findings from the International Cholesterol management Practice Study. *Eur J Prev Cardiol* 2019;2047487319871735. <https://doi.org/10.1177/2047487319871735>
- Masson WH, Huerin M, Lobo M, Masson G, Webmaster D, Fernández N, et al. Lipid Goals in Diabetic Patients. Clinical Implications after Application of a New Formula for LDL-cholesterol Calculation. *Rev Argent Cardiol* 2020;88:42-48.
- Santos RD. Inadequate control of atherosclerotic cardiovascular disease risk factors in Europe: EUROASPIRE repeats itself. *Eur J Prev Cardiol* 2019;26:820-3. <https://doi.org/10.1177/2047487319831476>
- Martin SS, Blaha MJ, Elshazly MB, Toth PP, Kwiterovich PO, Blumenthal RS, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *Jama* 2013;310:2061-8. <https://doi.org/10.1001/jama.2013.280532>
- Martin SS, Giugliano RP, Murphy SA, Wasserman SM, Stein EA, Ceška R, et al. Comparison of Low-Density Lipoprotein Cholesterol Assessment by Martin/Hopkins Estimation, Friedewald Estimation, and Preparative Ultracentrifugation: Insights From the FOURIER Trial. *JAMACardiol*. 2018;3:749-53. <https://doi.org/10.1001/jamacardio.2018.1533>
- Cholesterol Treatment Trialists C, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; 376:1670-81. [https://doi.org/10.1016/S0140-6736\(10\)61350-5](https://doi.org/10.1016/S0140-6736(10)61350-5)