Invited Editorial / *Davetli Editöryal Yorum*

The long-term safety and efficacy of fibrates in patients with hypertriglyceridemia: Real-life data from a lipid clinic cohort

Hipertrigliseridemisi olan hastalarda fibratların uzun-dönem güvenliği ve etkinliği: Lipit kliniği kohortunun gerçek yaşam verileri

Alberto Zambon, M.D.

Department of Medicine, University of Padova School of Medicine, Padova, Italy

Robust and extensive evidence from epidemiologic, genetic, and clinical intervention studies has unequivocally shown that low-density lipoprotein cholesterol (LDL-C) is causal in the atherothrombotic process and an important determinant of the risk of cardiovascular (CV) events.[1] Yet, despite an intensive LDL-C-lowering approach, there is a remarkable residual risk of CV events, even at extremely low LDL-C levels (i.e., LDL-C 0.8 mmol/L or 30 mg/dL).[2] Recent evidence from clinical, genetic, and Mendelian randomization studies supports the hypothesis that triglyceride-rich lipoproteins (TRL) are a causal risk factor for CV disease, highlighting a similar per-particle atherogenic potential for all the apolipoprotein B (Apo-B)-containing lipoproteins (LDL, TRL and their remnants).[3] Statins, ezetimibe, and the new monoclonal antibodies against PCSK9 are highly effective in lowering LDL-C, but have a marginal, and often not significant, effect on triglycerides (TG) and TRL. Fibrates and omega n-3 fatty acids are recognized by current guidelines as effective at lowering plasma TG levels. Although measurement of Apo-B represents the gold standard to estimate the actual number of atherogenic particles circulating in our patients and a primary target for CV event reduction, as suggested by the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines,[4] Apo-B measurement is not widely available in all our hospital and clinical laboratories and requires extra costs for patients and healthcare systems. A recognized clinical surrogate for Apo-B is the measurement of non-high-density lipoprotein cholesterol (non HDL-C), which, as with Apo-B, provides an estimate of all the atherogenic lipoproteins (LDL and TRL), does not require fasting blood sampling, and is supported by national and international guidelines.[4] Unlike Apo-B, however, non HDL-C analysis is widely available and inexpensive (it is calculated by subtracting HDL-C from total plasma cholesterol). Recent evidence supports the role of non HDL-C as a better risk factor and treatment target than LDL-C, particularly in patients with diabetes, metabolic syndrome, or insulin-resistance. However, there are no real-life studies on the impact of therapeutic approaches focusing on TRL and non HDL-C with long follow-up.

Abbreviations:

Apo-B	*Apolipoprotein B*
CV	*Cardiovascular*
LDL-C	*Low-density lipoprotein cholesterol*
Non HDL-C	*Non-high-density lipoprotein cholesterol*
TG	*Triglycerides*
TRL	*Triglyceride-rich lipoproteins*

The study performed by Kayikcioglu et al.[5] is clinically extremely relevant and informative and contributes to filling this gap by providing a retrospective, real-life report of the efficacy and safety of a recognized TG-lowering approach with fibrates in a large cohort of hypertriglyceridemic patients with long-term

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Correspondence: Dr. Alberto Zambon. Department of Medicine DIMED, University of Padova, Padova, Italy.
Tel: +39.049.8212150 e-mail: alberto.zambon@unipd.it

follow-up at a specialized lipid clinic center. A mean 5.3-year-use of fibrates, primarily fenofibrate, often in combination with a statin, demonstrated a significant and remarkable reduction of 88.2% in TG levels and 73.2% in non-HDL-C levels without severe adverse effects. Of clinical relevance for our daily practice is the finding of a significantly lower frequency of side effects in long follow-up, much lower than that reported in large, randomized, controlled trials.

The key point of the study, however, is the introduction of the innovative concept of the non HDL-C cumulative burden, described here for the first time, as a measurement of non HDL-C over time, after fibrate therapy. The essential clinical relevance of this parameter arises from the evolution of the original concept of "the lower the LDL-C the better" to "the longer the lower LDL-C is maintained the better," based on strong, evidence-based observations in the past 5-10 years. Long-term, possibly lifetime, knowledge of LDL-C levels, and thereby non HDL-C levels, are critical parameters to evaluate the individual risk of CV events and the expected response to lipid-lowering therapy.[1] The non HDL-C cumulative burden is a key clinical upgrade of the LDL-C burden, since it includes all of the atherogenic Apo-B-containing lipoproteins, LDL, and TG-rich particles that are elevated in patients with diabetes or metabolic syndrome. Kayikcioglu et al.[5] highlight the need to address all of the atherogenic lipoproteins, LDL, and TRL, to effectively reduce the cumulative non HDL-C burden, and thereby the risk of CV events. This concept translates into more patients being considered for a combination of lipid-lowering agents active on LDL-C, i.e., statins and ezetimibe, and TG-lowering drugs, such as fenofibrate, which was shown in this study to be safe and effective, or omega n-3 fatty acids, particularly in cases of mild to moderate hypertriglyceridemia. Tailored lipid-lowering therapy is important for successful CV risk reduction. The non HDL-C cumulative burden is a comprehensive and recognized CV risk predictor and a clinically relevant target to monitor therapeutic effectiveness. Kayikcioglu et al.[5] have paved the way for future, population-based, prospective trials examining the relevance of non HDL-C cumulative burden as a simple, effective predictor of CV disease and a target for our lipid-lowering strategies.

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