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: Bir lipit kohortunun gerçek yaşam verileri

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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.

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

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*

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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