



## EDITORIAL COMMENT

## Does lowering triglycerides reduce cardiovascular risk?



## Será que a diminuição dos triglicéridos reduz o risco cardiovascular?

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Triglycerides (TG) have long been the ugly duckling of lipidology. The relationship between TG and cardiovascular (CV) risk has been fraught with multiple issues: from the variability of TG levels, to their inverse association with high-density lipoprotein cholesterol (HDL-C) and whether to measure them in a fasting or non-fasting state. Many large studies have found a significant association between TG and cardiovascular disease (CVD). The Paris Prospective Study, the Lipid Research Clinics Follow-up Study, the Reykjavik study, and the European Prospective Investigation of Cancer (EPIC Norfolk) study showed a relationship between TG levels and CVD, while the Multiple Risk Factor Intervention Trial, the Copenhagen City Heart Study, the Copenhagen General Population Study and the Women's Health Study found an even stronger relationship between non-fasting TG levels and CVD; as most people eat regularly throughout the day, non-fasting lipids may be a better indicator of mean lipid concentrations in the blood, and individuals are exposed to post-prandial TG most of the time.<sup>1,2</sup>

Genome-wide association studies (GWAS) have also found a causal association between TG and CVD. Mutations in at least six different genes including *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, and *GPD1* can substantially increase TG and are identified as monogenic disorders. Some GWAS have clearly linked high TG with increased CV risk, and conversely a significantly reduced risk for ischemic CVD has been found with

genetically reduced TG. The main TG-metabolizing enzyme is lipoprotein lipase (LPL), the function of which is modulated by apolipoproteins A-V (APOA5) and C-III. In this regard, studies have found relative risk reductions of 24% and 46% in ischemic CVD for APOA5 and LPL gain-of-function mutations, respectively (with corresponding reductions of 35-36% in non-fasting TG), compared with non-TG-reducing alleles.<sup>3-6</sup>

No large-scale randomized trials have directly examined the effect of reducing TG on CV risk in people with raised TG. Thus, only secondary subgroup analyses from other trials have been used to assess CV risk in patients with high TG, with or without low HDL-C.<sup>2</sup> The question is whether lowering TG reduces CV risk in clinical trials.

The Scandinavian Simvastatin Survival Study (4S) and Cholesterol and Recurrent Events (CARE) found a greater CV risk reduction in high TG subgroups with statin therapy. By contrast, in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial, the Heart Protection Study and the West of Scotland Coronary Prevention Study (WOSCOPS), CVD reductions were similar across all baseline TG levels, and the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) actually found higher CVD reduction in those without the features of metabolic syndrome. The LIPID study found an 11% decrease in CV risk (14% after adjustment for other risk factors) with each 1 mmol/l decrease in TG with pravastatin, and in the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) trial, each 10 mg/dl decrease in on-treatment TG level was associated with a 1.8% reduction in CVD (1.4% after adjustment for other

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risk factors).<sup>7-16</sup> There are conflicting data concerning the relationship between fibrate therapy and CVD. The Helsinki Heart Study (HHS) (gemfibrozil monotherapy in primary prevention) and the Veterans Affairs HDL Intervention Trial (VA-HIT) (gemfibrozil monotherapy in secondary prevention) found a significant benefit in CV outcomes. However, the Bezafibrate Infarction Prevention trial and others failed to show any significant CVD reduction in secondary prevention in monotherapy. In two trials with fenofibrate in combination with statins, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD Lipid), the benefit was only observed in subgroups with increased baseline TG and low HDL.<sup>17-20</sup> On the other hand, for secondary prevention in patients with established CVD or with diabetes and other risk factors and with fasting TG of 135-499 mg/dl, icosapent ethyl reduced the risk of ischemic events, including CV death.<sup>21</sup>

While there is still controversy concerning the relationship between TG and CVD, the value of non-HDL-C as a CV risk factor is universally accepted. Non-HDL-C is defined as all the cholesterol present in potentially atherogenic lipoprotein particles that include very-low-density cholesterol, intermediate-density cholesterol, lipoprotein(a), and low-density lipoprotein cholesterol (LDL-C). Non-HDL-C is therefore sometimes considered an even better marker than LDL-C. Measurement of non-HDL-C has the advantage of not requiring fasting, and is more practical, reliable, and inexpensive than assessment of other lipid fractions. Non-HDL-C is thus potentially an important risk marker, particularly in patients with diabetes, metabolic syndrome or obesity; the UK National Institute of Health and Care Excellence considers non-HDL-C a better CVD risk indicator than LDL-C.

In some cases, even with the maximum dose of more potent statins, associated with ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, a significant CV risk remains, known as residual risk. It is consensual that non-HDL-C, given its relationship with TG-rich remnant lipoproteins, is one of the main causes of this residual risk. When high non-HDL-C is associated with low HDL-C and high levels of TG and small dense LDL particles, this phenotype, which is characteristic of diabetes, metabolic syndrome and obesity, is known as atherogenic dyslipidemia.<sup>2,22</sup>

The current issue of the *Journal* sees the publication of a multidisciplinary consensus among Portuguese experts on the definition, detection and management of atherogenic dyslipidemia.<sup>23</sup> In the CODAP study, a questionnaire was applied to an expert panel composed of specialists in internal medicine, endocrinology, cardiology and family and general medicine, following a modified Delphi methodology. The panel acknowledged the importance of the atherogenic dyslipidemia phenotype and the role played by LDL-C and HDL-C as risk markers and therapeutic targets. Around 72% of the participants considered that non-HDL-C is a better risk marker for atherogenic dyslipidemia than LDL-C. By contrast, there was no consensus on the role played by TG in CV risk and the therapeutic value of fibrates. So, is the role of TG as a CV risk factor still in doubt? We do not believe this to be the case. Recent studies have shown that high TG levels (200-600 mg/dl) are associated with high levels of remnant lipoproteins and with significant CV risk.<sup>24</sup> In a

substudy of the Copenhagen General Population Study that included 58 547 individuals aged 40-65 years and free of atherosclerotic CVD, diabetes, and statin use at baseline, 14% were definitely statin eligible, 7% were not eligible and had TG $\geq$ 264 mg/l, and 79% were not statin eligible and had TG $<$ 264 mg/l. The estimated 10-year risk of major adverse cardiovascular events was 2.8% and 5.7% in statin non-eligible individuals with TG  $<$ 264 mg/l and  $\geq$ 264 mg/l, respectively.<sup>25</sup>

The authors of the CODAP study conclude that in patients at high or very high cardiovascular risk and atherogenic dyslipidemia, after LDL-C targets have been achieved with a statin, fenofibrate should be associated.<sup>23</sup>

## Conflicts of interest

The author has no conflicts of interest to declare.

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