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Editorial
Reaching hypertriglyceridemia goals

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In the January issue of the journal Pintó *et al.*[1] report the achievement of fasting triglyceride (TG) target values ($\leq$2.2 mmol/L; 200 mg/dL) in patients ($n = 929$) attending lipid clinics of the Spanish Arteriosclerosis Society. Those who did not reach the TG goal (56% of the study population) had a poorer lifestyle (in terms of smoking, physical inactivity, weight gain and alcohol intake) than those who achieved adequate control. Independent predictors of treatment failure were the severity of hypertriglyceridemia, low high density lipoprotein cholesterol (HDL-C), as well as high non-HDL-C, alcohol consumption, and higher body mass index (BMI). Surprisingly, drug treatment had no predictive power.

The findings of Pintó *et al.*[1] are of interest because their Spanish population was likely on a Mediterranean diet which has been reported to reduce TG levels[2,3]. However, despite the favorable 'Mediterranean dietary background', 56% of the participants failed to achieve their set TG target[1]. The beneficial effect of the Mediterranean diet extends to post-prandial hypertriglyceridemia, which may predict vascular risk[4–6]. Post-prandial TG levels were not assessed by Pintó *et al.*[1], probably because standardized fat loading tests are time-consuming and more suited to smaller studies[5,6].

Another variable associated with hypertriglyceridemia is an increase in the proportion of small dense low density lipoprotein (sdLDL)[7], which is more atherogenic than buoyant LDL. However, sdLDL is another example of a potential vascular risk predictor where the methodology can be complex and costly as well as not clearly defined[7]. A similar situation is assessing the function, and not just the circulating levels, of high density lipoprotein (HDL)[8]. HDL function is likely to be adversely affected[8] in the hypertriglyceridemic patient population studied by Pintó *et al.*[1]. Unfortunately, at present there is no easy, cheap, rapid, and widely acceptable method to reliably assess HDL function[8].

Liver tests are not reported in the Pintó *et al.*[1] study. This information may have been of interest because their patients are likely to have a high incidence of non-alcoholic fatty liver disease (NAFLD). Indeed, metabolic syndrome (MetS), increased BMI, hypertriglyceridemia, and insulin resistance are associated with NAFLD[9–11]. In turn, a multifactorial lifestyle approach together with statins and weight reduction can improve NAFLD (as assessed by liver tests and ultrasound)[9–11]. NAFLD is relevant because it is likely to be associated with an increased risk of vascular events, type 2 diabetes, and hepatic complications[9–11].

It is likely that combination treatment is necessary to achieve both the LDL-cholesterol (LDL-C) goals as well as lower TG levels; 57.6% of patients were treated with lipid-lowering drugs in monotherapy at the final visit of the Pintó *et al.*[1] study. Ezetimibe was not mentioned in detail by Pintó *et al.*[1] as a treatment option for 'add-on' therapy. In our experience[12], as baseline TG concentrations increase (tertiles: <139, 140–179, and $\geq$180 mg/dl; <1.57, 1.58–2.02, and $\geq$2.02 mmol/L), the fall in TG levels was 0.9, 16.1, and

30.3%, respectively, in patients taking simvastatin + ezetimibe. This finding is especially relevant because this study[12] was carried out in Greece, another Mediterranean country. In another study also carried out in a Mediterranean country (Slovenia) the fall in TG levels with 'add-on' ezetimibe to statin therapy was proportional to baseline TG values[13]. Others also reported a greater fall (up to 25.9%) in TG levels after 'add-on' ezetimibe treatment to a statin in patients with raised baseline TG values[14]. These ezetimibe + statin combination findings are in line with the observations with statin monotherapy where the extent of the fall in LDL-C and higher baseline TG levels were associated with a greater statin-induced fall in TG levels[15]. There is also evidence that ezetimibe can influence post-prandial hypertriglyceridemia[16–19]. This effect may be related to improved glycemic response, decreased chylomicron production and apolipoprotein B48 levels, as well as a fall in remnant-like particles[16–19]. Ezetimibe even as monotherapy may turn out to be a TG-lowering option in patients who cannot tolerate other drugs used to treat dyslipidemias[16–19]. There is a need to clearly establish if ezetimibe can make a clinically-relevant contribution to lowering TG levels, since the current perception may be that it should be exclusively used to lower LDL-C levels.

Pintó *et al.*[1] reported that MetS was more common (48.9 vs 61.9%; $p < 0.001$) in those who did not achieve the TG goals. They[1] used the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition of MetS. A more ideal choice may have been to use the more recent Joint Interim definition of MetS, because it includes the definition of waist circumference based on ethnicity, and several learned societies were involved[20]. More specifically, defining waist circumference according to these more recent diagnostic criteria[20] may be relevant because a Spanish population was studied. Furthermore, we reported considerable variations in the prevalence of MetS in a Greek (i.e., a Mediterranean) population, depending on which definitions were used[21,22].

Pintó *et al.*[1] concluded that a relatively high proportion of patients failed to reach their TG targets despite attending specialized lipid clinics. Based on our experience, we agree that there is a need to alter this situation. In addition to improving adherence with lifestyle measures[1], other factors may contribute to poor control of hypertriglyceridemia. For example, treatment guidelines focus on achieving defined LDL-C levels[23]. The guidelines mention the risk of acute pancreatitis in patients with TG levels > 10 mmol/L (~880 mg/dL) and that this risk increases even at TG values > 5 mmol/L (~440 mg/dL)[23]. Whether the latter information is widely appreciated is not clear, but it certainly does not address lower TG levels. As for the link between hypertriglyceridemia and vascular risk, if the evidence was convincing, then target TG levels would be included in guidelines[23,24]. However, in the context of the Mediterranean diet it is of interest that fasting TG levels were predictive of subsequent vascular events in statin untreated patients in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study[25]. In this trial the statin (mainly atorvastatin)-induced decrease in TG levels was related to a significant reduction in vascular events. This benefit was more evident in patients with coronary heart disease + MetS. However, the value of this finding is limited because it was based on a *post-hoc* analysis[25]. Clearly, if it is proven that lowering TG levels below a threshold value results in a decrease in vascular events, then more aggressive treatment should become widely accepted. Whether such evidence becomes available will depend on if the intervention assessed exclusively influences TG levels. To our knowledge, such an agent is not currently available.

Other potential factors interfering with effective treatment of hypertriglyceridemia may include poor commercial 'promotion' or insufficient scientific/medical interest concerning this topic. If this assumption is correct, then this deficiency can be remedied by often including 'hypertriglyceridemia' in the programs of scientific/educational meetings. Clinicians may also be reluctant to prescribe several lipid lowering drugs concomitantly, especially when elevated TG levels occur with co-morbidities such as diabetes, alcoholism, NAFLD, chronic kidney disease, or if patients are seen as not capable of adhering to complex treatment regimens and regular follow-up visits which may be necessary to ensure safety. These co-morbidities are associated with polypharmacy as well as abnormal kidney and liver function, which can be interpreted as contraindications to adding more medication.

In view of the limited evidence regarding benefit from lowering TG levels that are not markedly raised it seems unreasonable to add medication to achieve a fall in modestly raised TG levels; however, the implementation of lifestyle measures should be strongly recommended and frequently re-enforced in such patients. This approach may avoid unnecessary adverse events and additional cost. However, it may be worth considering achieving LDL-C guideline targets using evidence-based drugs that simultaneously correct raised TG levels.

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