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Current treatment of hypertriglyceridemia

Tratamiento actual de la hipertrigliceridemia

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INTRODUCTION

Hypertriglyceridemia (HTG) and triglyceride-rich lipoproteins (TRL) such as chylomicrons or very-low-density lipoproteins (VLDL) have been associated with an increased danger of cardiovascular disease (CVD) and remain elevated in up to 25% of patients with established CVD.[1-4] A severe elevation (> 500 mg/dL) of triglycerides (TG) increases the risk of pancreatitis due to the toxic effects of free fatty acids released by pancreatic lipase, requiring reduction through lifestyle changes and pharmacotherapy, in addition to correcting precipitating etiological factors.[1]

Statin medication aims to minimize low-density cholesterol (LDL-c) and has been shown to improve atherosclerotic CVD damage. Despite this, the residual peril of new events persists,[1,2,4] partly attributed to a mild to moderate HTG by several studies, behaving as an independent risk factor for CVD. However, clinical trials data for managing raised triglycerides taking drugs including fibrates, omega-3 fatty acids, and niacin showed no definitive evidence of the reduced danger of new cardiovascular incidents. The purpose of this review is to examine the role that triglycerides play in cardiovascular hazards and their potential drug administration.

Treatment. The goals of this action are to reduce the risk of pancreatitis in sick individuals with severe HTG and to decrease CVD perils in those experiencing mild to moderate HTG.[1,5-7]

Two fundamental parameters will always guide the care of hypertriglyceridemia: the elevation level of triglycerides and the calculated threat of atherosclerotic disease at ten years.[6] In patients enduring mild to moderate hypertriglyceridemia, LDL-c continues to be the primary treatment target in lipid diminution therapy, and secondary targets being non-HDL cholesterol (non-HDL-c), apolipoprotein B (Apo B), and finally, TG reduction. According to medical guidelines, it is always necessary to reach the recommended goals in the described order.[1,7,8]

Lifestyle changes. To begin with, secondary causes of TG elevation should be excluded, and the corrections appropriate to each case must be carried out.[1,5-7,9-11] Once these tasks are accomplished, the central therapeutic intervention for the treatment of increased TG will be lifestyle modifications, for example, reducing overweight or obesity, decreasing carbohydrate intake, limiting alcohol intake, performing regular physical activity, and attaining adequate glucose control in sick individuals suffering type two diabetes *mellitus*.[5,6,11] It is noteworthy that the most significant impact on HTG is achieved via weight loss and limiting alcohol intake. A decrease of TG up to 80% was reported in ill persons with alcohol abuse who can significantly limit alcoholic ingestion *(Table 1)*.[1]

Pharmacological treatment. Once lifestyle adjustments have been attained, medications will be prescribed according to TG blood concentrations and calculated cardiovascular risk category.[6] In *Figure 1*, the authors propose a simplified flowchart for treatment.

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Indications:

1. For CVD prevention: patients with triglycerides of 150-499 mg/dL.
   a) **Low risk:** lifestyle changes.
   b) **Intermediate risk:** assessing statin use.
   c) **High risk or with established CVD:** use high potency statin until reaching the LDL-c target. If raised TH concentrations persist, preferably assess the use of either or both icosapent ethyl and fibrates.
   d) **For the avoidance of pancreatitis: triglycerides > 500 mg/dL:** coupled to lifestyle alterations, pharmacologic approach with fibrates, niacin, and omega-3 fatty acids should be initiated. In case the patient has cardiovascular disease, these drugs ought to be added to statin therapy.

DRUGS FOR THE TREATMENT OF HTG

1. **Statins, ezetimibe, and PCSK9 inhibitors:** mainly decreasing C-LDL and additionally slightly lessening the TG concentration about 5-15%, but having a significant impact on reducing cardiovascular events.[1,6]
2. **Fibrates, niacin, and omega-3 fatty acids**: achieve a triglyceride reduction of 25-50%, but the impact on reducing cardiovascular incidents is still questioned *(Table 2)*.[1,6]
   Fibrates: these drugs act as binders for the regulator of the nuclear transcription of the alpha receptor activated by proliferated peroxisome (α-PPAR), causing an increase in the synthesis of the enzyme lipoprotein-lipase (LPL), which is responsible for the catabolism of VDLD and chylomicrons (molecules composed primarily of TG). The released free fatty acids (FFA) are the main fuels for every tissue except neurons and blood red cells. The FFA not used for internal combustion, mainly by the striated skeletal muscle, are stored in adipose tissue and the liver, in the form of TG (lipogenesis). They are metabolized by cytochrome P450 isoenzyme 2C9 (CYP2C9) and are excreted via the kidneys.[12]
   Niacin: inhibits the synthesis and esterification of fatty acids by shrinking TG production and also stimulating LPL, so increasing TG cleavage from chylomicrons and VLDL in a way such that it modifies the endogenous and exogenous metabolism of lipids.
   Omega-3 fatty acids: diminish serum TG by decreasing VLDL synthesis through various mechanisms, including changes in the n-6/n-3 ratio of fatty acids, incrementing β-oxidation, lowering hepatic lipogenesis, and increasing degradation of intracellular apolipoprotein B.
3. **Others:** epanova, pemafibrate, evinacumab, volanesorsen, AKSEA APO CIII (apolipoprotein C III), alipogene, ionis angptl3-Lrx.[12-14]

CLINICAL EFFICACY

Statins

There is excellent scientific evidence about the use of statins in both primary and secondary prevention. This approach would need to be started in all patients exhibiting HTG and great cardiovascular danger of CVD.[1-3] Therefore, the authors certainly need to insist, high potency statins will always be the first-line therapy in HTG to reach the goal of LDL-c, non-HDL-c, and Apo B.

Once the goals have been achieved, if the elevation of TG persists, the use of specific medication with fibrates, omega-3 fatty acids, niacin, icosapent ethyl, or biological agents in the research phase will be assessed.[6]

Table 1: Lifestyle changes suggested for hypertriglyceridemia.

Losing excess weight
Decrease carbohydrate intake
Decrease or avoid alcohol consumption
Increased consumption of polyunsaturated and monounsaturated fat
Increased consumption of omega-3 fatty acids in foods (fish as salmon)
Exercise
Adequate glucose control in patients with diabetes

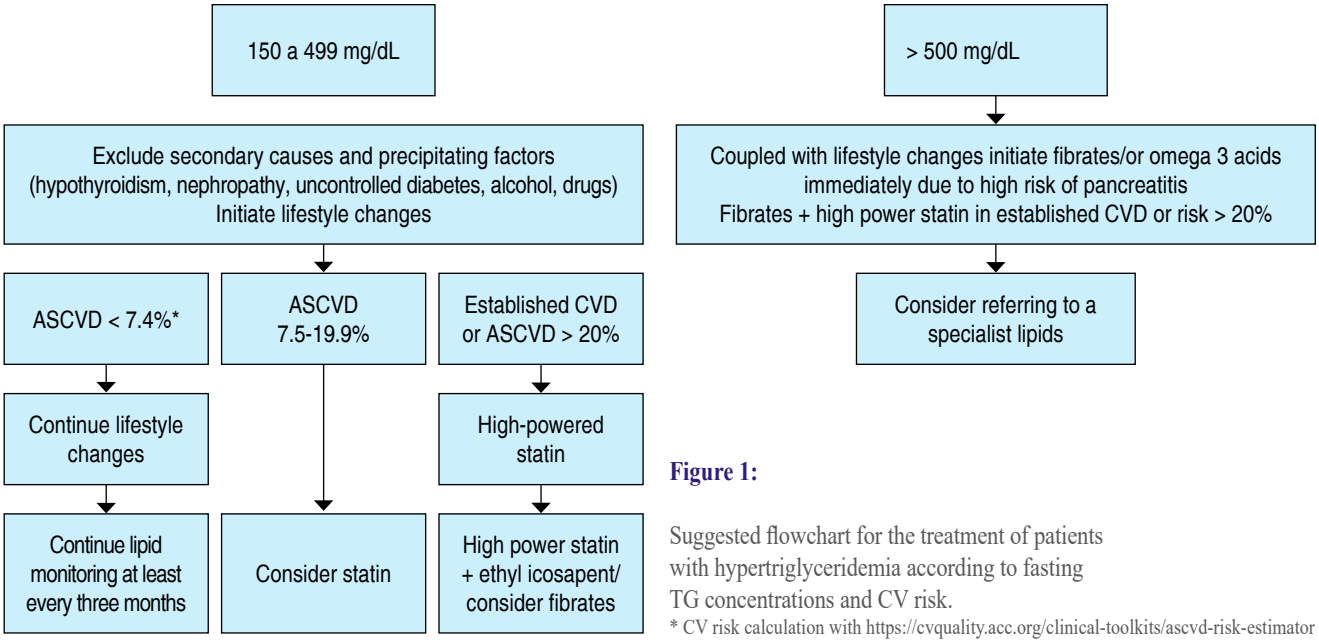

Figure 1:

Suggested flowchart for the treatment of patients with hypertriglyceridemia according to fasting TG concentrations and CV risk.
* CV risk calculation with https://cvquality.acc.org/clinical-toolkits/ascvd-risk-estimator

Fibrates and niacin. Although fibrates and niacin have been the traditional treatment used to lower TG levels in those affected by severe elevation and critical hazard of pancreatitis, it is unclear from what level management should be initiated in primary and secondary prevention and whether it would be sufficient together with the adoption of lifestyle changes.[5,15]

Although multiple studies have been conducted with fibrates, there is not enough evidence to support its use in reducing cardiovascular events.[16] With niacin studies like CDP, AIM HIGH, and HPS2 THRIVE failing to demonstrate effectiveness in lowering occurrences,[5,6] if a fibrate is indicated, the most recommended is fenofibrate.

Omega-3 fatty acids. Pharmacological interest in omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the deterrence of CVD is due to a lower incidence of CVD seen in populations consuming large amounts of fish oil. Short-term studies have revealed how omega-3 fatty acids (2-4 g/day) can reduce TG levels.

Omega-3 EPA fatty acids (without DHA) improve lipid levels beyond the lessening of TG, and in addition diminish non-HDL-c, Apo B, LDL-c, and the number of atherogenic particles. In addition to atherogenic control, EPA improves inflammation, as manifested by a lower C-reactive protein activity and greater concentration of adiponectin.[5,6] Regression of the atheromatous plaque and improvement of endothelial dysfunction has also been demonstrated. However, in systematic reviews, none of the omega-3 fatty acids have been shown to decrease cardiovascular incidents consistently, so its use in the primary prevention of cardiovascular disease is not recommended.[5] The recent STRENGTH study, which included 13,078 persons with omega-3 fatty acid supplementation in HTG patients, was prematurely discontinued because the formulation did not decrease major cardiovascular events in diseased persons at notorious cardiovascular risk.[17-19] The exception is icosapent ethyl in the REDUCE-IT study, which included those with elevated TG concentrations and a high cardiovascular threat or with proven CVD. Oral administration of four grams daily of this drug demonstrated a 25% reduction in CVD.[20-22] Decreased revascularizations have also become evident in ill people treated with this drug.[4] However, estimating a cost-benefit ratio with this substance is necessary to evaluate whether the intervention is cost-effective.[6]

Emerging therapies: omega-3-carboxylic acid, pemafibrate, AKSEA, APO CIII inhibitors such as volanesorsen, alipogene to treat lipoprotein lipase deficit, ANGPTL3 inhibitor antibody (evinacumab), ANGPTL4 inhibitors, and ANGPTL8 inhibitors-1.[1,13,14,23]

What do dyslipidemia treatment guidelines recommend? US American and European guidelines suggest that first-line therapy promotes statins in people with moderate to severe hypertriglyceridemia. These guidelines consider adding ethyl of icosapent or fibrates in those with TG > 500 mg/dL or high VLDL or chylomicrons. Contrariwise, European guidelines consider icosapent ethyl in TG > 135 mg/dL despite treatment with statins in subjects at significant cardiovascular risk. Fibrates are not recommended in primary prevention.[4,8,22,23]

Managing hypertriglyceridemia in the COVID-19 pandemic. Significant elevations of TG have been reported in sick ones treated with tocilizumab. No interactions of statins, fibrates, or omega-3 fatty acids were publicized in clinical trials for the therapy of COVID-19, so they must be continued unless there is a specific contraindication for administration.[24]

Discussion and conclusions. In patients suffering verified CVD, a residual risk of new episodes persists. In the case of having a high TG serum concentration, it is proposed that once optimized, the management with statin and the control of LDL-c are attained. Here is an area of opportunity managing TRL with new potential remedies. The main objective of HTG care is to reduce cardiovascular risk and the onset of pancreatitis. However, to date, there is little evidence that the addition of fibrates, omega-3 fatty acids, or niacin to a prescription decreases said events. There is also no convincing evidence of lipid-reducing treatment diminishing the risk of pancreatitis.

The REDUCE-IT study showed that in those at lifted cardiovascular risk who show elevated triglycerides despite statin use and adequate levels of LDL-c, icosapent ethyl at a dose of four grams daily reduces cardiovascular instances, so its use should be considered in this type of patients. Several emerging therapies are currently under study.

Table 2: Hypertriglyceridemia treatment: key messages.

The use of omega-3 fatty acids, niacin and fibrates for cardiovascular disease prevention is not supported
In patients with established or high cardiovascular risk CVD consider adding to statin therapy, icosapent ethyl at a dose of 4 g daily
In patients with severe HTG and high risk of pancreatitis consider fibrates, niacin, and omega-3 fatty acids at a dose of 2 to 4 g daily
For patients with pancreatitis, hypertriglyceridemia > 1,000 mg/dL and hyperglycaemia consider insulin and plasmapheresis infusion, in addition to fibrates, niacin, and omega-3 fatty acids

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