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L'hypertriglycéridémie est-elle athérogène ?

Is hypertriglyceridemia atherogenic?

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L'hypertriglycéridémie est-elle athérogène ?

■ Key points

ASCVD reduction is based on LDL reduction, especially by statins.
Highly elevated TG could be harmful, especially because of the risk of pancreatitis.
Elevation of TG is mainly due to metabolic disorders and diabetes, alcohol intake and overweight.
Genetic factors have been clearly identified in the most severe cases.
TG have been generally considered as bystanders for cardiovascular diseases (CVD).
Both biological and basic research provide strong data suggesting that TG-rich lipoproteins could be involved in the pathophysiology of CVD.
Recent epidemiological and genetics studies strongly corroborate the causal role of TG in CVD.
This paves the way for new approaches in the management of patients both for primary and secondary prevention.

■ Points essentiels

L'hypertriglycéridémie est-elle athérogène ?

La prévention de la maladie athéroscléreuse est fondée sur la réduction du taux de LDL, particulièrement par l'utilisation de statines.
Des taux élevés de triglycérides (TG) peut être dangereuse, en particulier à cause du risque de pancréatite.
L'augmentation des TG est principalement liée aux anomalies métaboliques et au diabète, la consommation d'alcool et le surpoids. Des facteurs génétiques ont été identifiés dans les cas les plus sévères.
Les TG sont généralement considérés comme des témoins des maladies cardiovasculaires.

Les approches biologiques et la recherche fondamentale apportent des démonstrations suggérant que les lipoprotéines riches en TG pourraient être impliquées dans la physiopathologie des maladies cardiovasculaires.

Des études épidémiologiques et génétiques récentes confortent puissamment le rôle causal des TG dans les maladies cardiovasculaires.

Cela prépare le terrain pour des nouvelles approches thérapeutiques en prévention primaire et secondaire.

Introduction

Atherosclerosis is usually considered as a complex pathophysiological phenomenon involving dyslipidemia, oxidative stress, inflammation [1], etc. Among lipids, cholesterol has been identified for decades as an actor of atherosclerosis, in spite of recent controversies especially in our country [2]. Low-density lipoprotein (LDL) has been clearly identified as the main component determining cardiovascular disease (CVD) risk, with various types of evidences including notably the observation of patients with familial hypercholesterolemia with high LDL levels and premature atherosclerotic cardiovascular disease (ASCVD), leading to the Nobel Prize award to Brown and Goldstein in 1985 and the development of statins [3]. Above all, many large, randomized, double blind trials particularly with statins demonstrated that LDL reduction lead to reduce both LDL cholesterol and clinical events such as ASCVD and all-cause mortality [4].

For all these reasons, in clinical practice, the physician focuses on cholesterol, and more especially LDL cholesterol, because its role has been well established. Further, international guidelines clearly recommend management of dyslipidemia depending on the only plasmatic LDL cholesterol level.

However, not only initial data form the beginning of the lipids story, but also more recent studies suggest that other lipids, including Triglycerides-(TG) rich lipoproteins could be of importance. All together, these data suggest that these lipoproteins are not only bystanders to low high-density lipoproteins (HDL), but could also be actors involved in active pathophysiological pathways of atherosclerosis.

From a clinical point-of-view, the most important is to control and treat a cause of disease. Statins and other treatments lowering LDL have largely demonstrated clinical benefit, corroborating the importance of LDL in the pathophysiology, as a mirror. By contrast, there is no evidence that lowering TG-rich lipoproteins could provide clinical benefit. Importantly, several studies are currently ongoing on this topic.

Definitions

Figure 1 presents briefly what is measured. Remnant cholesterol can be estimated as: "total cholesterol – LDL cholesterol – HDL cholesterol". When plasmatic level of TG is above >4 g/L, LDL cholesterol has to be directly measured.

In the fasting state, remnant cholesterol is mainly present in very low-density lipoprotein (VLDL) and intermediate-density lipoprotein, whereas in the non fasting state, cholesterol is also included in chylomicron remnants.

As TG are the main component of chylomicrons and VLDL particles, they are linked to remnant cholesterol. This is an important point that could contribute to explain the involvement of TG in CVD pathophysiology.

Non-HDL cholesterol is calculated or estimated as total cholesterol minus HDL cholesterol and is equivalent to LDL and remnant cholesterol combined. Importantly, the use of non-HDL cholesterol for cardiovascular disease risk prediction has been emphasized.

Preliminary pathophysiological considerations

TG can be used for metabolic functions in all the cells, by contrast with CT (cholesterol). When increased, CT accumulates leading to the deposits in several organs, remaining the well-known cause for ASCVD. CT but not TG has been evidenced in plaques for decades. This is one of the main reasons why TG had not been suspected in ASCVD. Recently, pathophysiological considerations

Glossary

SCVD	Atherosclerotic Cardiovascular Disease
CETP	Cholesteryl Ester Transfer Protein
CT	Cholesterol
CVD	Cardiovascular Diseases
FFA	Free Fatty Acids
HDL	High-Density Lipoprotein
ICAM-1	Intercellular Adhesion Molecule-1
IHD	Ischemic Heart Disease
IL-1	β Interleukin-1 β
LDL	Low-Density Lipoprotein
LPL	Lipoprotein Lipase
MI	Myocardial Infarction
NLRP-1	Nucleotide-Binding Domain-Like Receptor Family Pyrin Domain-Containing Protein 1
NO	Nitric Oxide
ROS	Reactive Oxygen Species
TG	Triglycerides
TNF-α	Tumor Necrosis Factor- α
VCAM-1	Vascular Cell Adhesion Molecule-1
VLDL	Very Low-Density Lipoprotein

Definitions-what is measured?

CT content of TG-rich lipoproteins that is remnant cholesterol =total CT-HDL-LDL

TG : VLDL+intermediate-density+/-chylomicrons

FIGURE 1
Definitions useful for the practitioner. CT: cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; VLDL: very low-density lipoprotein.

have moved to at least consider TG as a marker of high levels of cholesterol in TG-rich lipoproteins. The question regarding its involvement as simple markers or actors remains.

High TG and the risk of pancreatitis

Hypertriglyceridemia has many multifactorial causes summarized in the *figure 2* [5]. Alcohol consumption, high fat intake and hyperglycemia have been identified as possibly reversible causes of elevated TG. As a consequence, lifestyle conditions

Genetic predisposition
Obesity
Type 2 diabetes
Alcohol consumption
Diet high in simple carbohydrates
Renal disease
Hypothyroidism
Pregnancy (physiological triglyceride concentrations double during the third trimester)
Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus
Multiple medications including: <ul style="list-style-type: none"> • Corticosteroids • Oestrogens, especially those taken orally • Tamoxifen • Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides • Isotretinoin • Bile acid-binding resins • Ciclosporin • Antiretroviral regimens (protease inhibitors) • Psychotropic medications: phenothiazines, second generation antipsychotics

ESC 2016

FIGURE 2
HyperTG is multifactorial. Adapted for the ESC guidelines [5], with permission.

have to be modified as first treatment. Independently of the CV risk, the risk of pancreatitis has to be underlined, justifying the dosage of TG per se. Indeed, the cardiologist has to keep in mind the significant risk of pancreatitis in case of severely elevated TG [5] (>10 mmol/L; > 8.80 g/L). This is the reason why the guidelines advise to reduce levels with the aim of reducing the risk of pancreatitis [5], in spite of the lack of randomized trial in the field.

Historical point-of-view

Figure 3 presents the point-of view of the authors [6] on the common concepts on lipoproteins. Importantly, initially before the 90s, both LDL and TG were considered to have a significant role in the ASCVD, because of the post-prandial observations. Hence, it was considered important to treat in parallel both elevated TG and CT. Thereafter, a great interest has raised on elevated LDL and guidelines largely ignored mild-to-moderately elevated TG, even if some guidelines propose additional tables on non-HDL CT.

- This is easily understandable for many reasons:
- the importance of LDL had been largely established;
 - and drug tolerance and interaction might become a problem in case of concomitant treatment of both LDL and TG levels by statin and fibrate association.

In addition to positive randomized, double blind trials (that lack until now regarding TG treatment), several publications provide useful information on epidemiology, genetics, and biology. Taking all these data into account, guidelines were updated and recommend the clinician not to neglect the TG. Indeed, from the beginning of the 2010s, new concepts have progressively emerged, underlining the role of TG and the interest to control them to lower the cardiovascular risk [7-10].

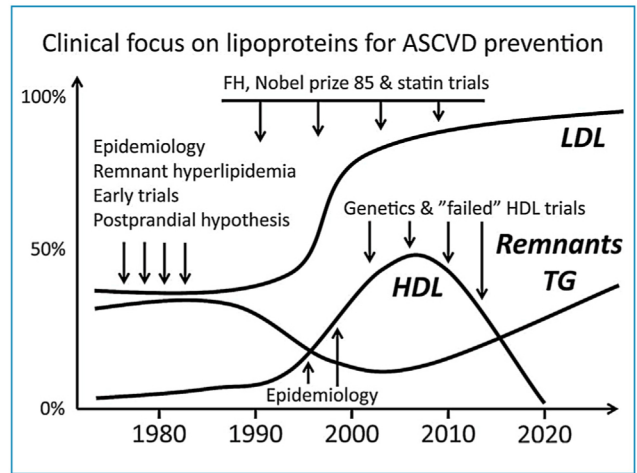


FIGURE 3
Hypertriglyceridemia: an old wine in new bottle. Adapted with permission from [6].

Despite this interest, their treatment is not really consensual in clinical practice, as most of trials with fibrates are generally considered as negative regarding clinical outcomes.

Increasing HDL was considered as promising to struggle the CV risk. Unfortunately, in spite of encouraging epidemiological approaches, genetic studies and above all negative large clinical trials with CETP-modulators [11,12] as well as niacin [13] failed to confirm this enthusiasm. There is only one study; the REVEAL study that shows positive results in term of cardiovascular events reduction, using the anacetrapib [14]. It has been suggested that the positive impact could be driven at least partly by the effect on LDL. Unfortunately, the development of the drug was stopped various reasons including commercial ones. Therefore, low HDL has been proposed as rather a bystander or long-term marker of high levels of TG-rich lipoproteins, hence a new interest on TG that could be the real actor. Nevertheless regarding CETP-modulator, promising pharmacological and pharmacogenomics studies [15,16] suggested to better select the patients that could draw benefits and a large clinical pharmacogenomics study: the dal-genE-the first in cardiology- is actually conducted (NCT02525939).

Consistently, as already mentioned long time ago [17], it is actually hypothesized that atherogenesis could take place prominently as a non fasting phenomenon, that is caused by high levels of TG-rich lipoproteins [17].

A large study on 84,177 individuals (see figure 4) described the distribution of non fasting plasma TG and showed that 27% of adults have mild-to-moderately elevated TG (1.76–8.80 g/L), whereas only 0.1% of adults have severely elevated TG (>8.80 g/L) [6].

The first generally admitted modifiable causes of elevated TG are diabetes, alcohol consumption and overweight. Recently, genetic factors have been confirmed to participate to mild-to-moderately elevated TG. Further, these genetic factors are the main cause of severely elevated TG (mutations in *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, and *GPD1* genes)[10], paving the way to target therapeutic approaches in these rare but severe patients.

Similarly, 21% of adults have elevated remnant cholesterol >1 mmol/L (0.4 g/L).

High levels of TG have been shown to be independently correlated with more elevated risk of ASCVD [18] and even all-cause mortality [19]. Indeed, in the general population (low risk of ASCVD), non fasting TG > 4.40 g/L versus < 0.88 g/L were associated with 17- and 5-fold risk of MI in women and men and for all-cause mortality 4- and 2-fold in women and men (figure 5).

Pathophysiology

TG could be involved at various levels in the pathophysiology of ASCVD, as shown in figure 6.

TG enter easily into the arterial intima, in the heart of the atherosclerotic plaque. It should be noticed that isolated

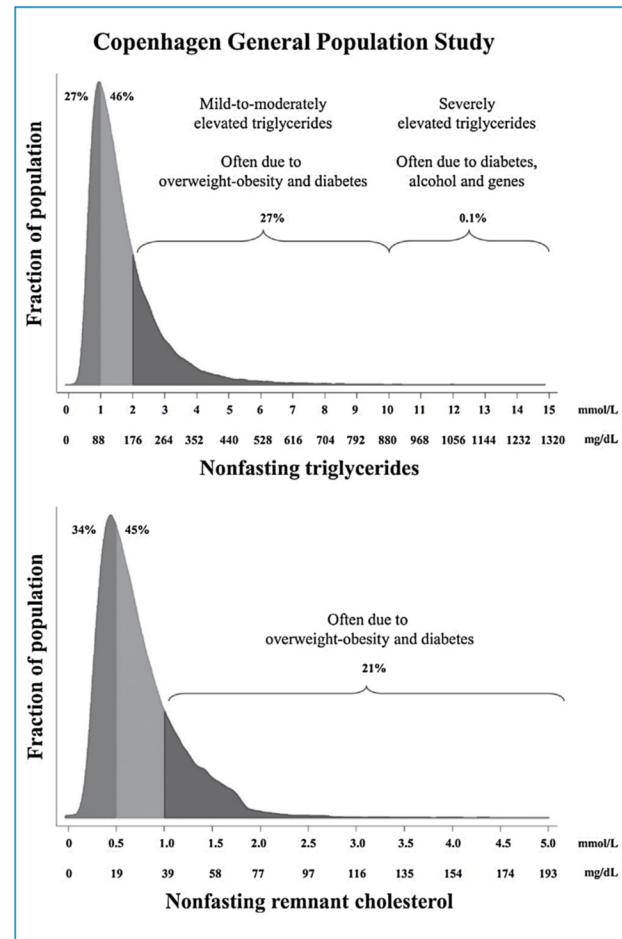


FIGURE 4
Distribution of TG levels in a general population of 84,177 individuals. Adapted with permission from [6].

elevated plasmatic TG levels do not induce ASCVD. Indeed, patients with chylomicronemia syndrome (leading to severe hyper TG) caused by lipoprotein lipase deficiency, do not present ASCVD. TG could then trigger various pathways. TG are hydrolyzed mainly by the lipoprotein lipase (LPL) and CETPs. Its lipolytic contain various molecules including large amounts of oxidized free fatty acids (ox-FFA) responsible for (1) an increase in production of reactive oxygen species (ROS), (2) a decrease in nitric oxide (NO), (3) an increase in various adherence molecules (ICAM-1, VCAM-1) and other proinflammatory ones (such as NLRP-1). This is the link with other proinflammatory actors (including interleukins TNF- α , IL-1 β).

New genetics data

Various genetics approaches provide strong evidence supporting the causal role of TG in ASCVD [20]. Genetics approaches and

Copenhagen City Heart Study and Copenhagen General Population Study

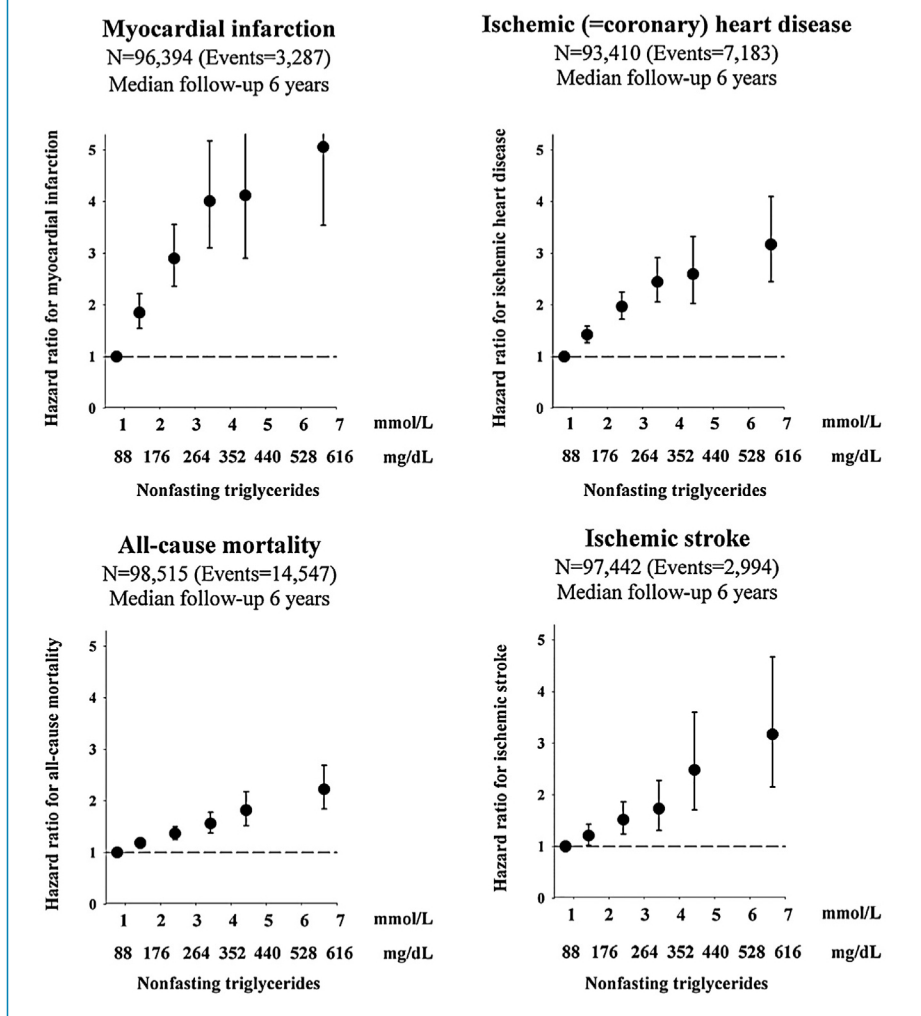


FIGURE 5
Correlations between TG and ASCVD. Adapted from [26] with permission. ASCVD: atherosclerotic cardiovascular disease.

evidences are extensively presented elsewhere [21]. Indeed, large-scale meta-analyses of cohorts and population-based sequencing studies have investigated if some variants in genes could be determinants of plasma TG levels and associated with ASCVD. Some candidates are clearly identified, including: lipoprotein lipase and proteins that interact with it, such as apolipoprotein (apo) A-V, apo C-III and angiopoietin-like proteins 3 and 4. For instance, loss-of-function mutations in APOC3 were associated with low levels of triglycerides and with reduced risk of ischemic cardiovascular disease [22]. More importantly, strong associations with clinical outcomes were established, corroborating the causal link. As a bias, a second lipid

disturbance, especially decreased HDL cholesterol was often associated, suggesting a synergic action.

Clinical trials

Until now, there are no strong data from clinical trials supporting the interest to treat TG for controlling the CVD. The main reason is that no trial evaluated the strategy of reducing TG-rich lipoproteins on ASCVD and all-cause mortality, in patients with elevated TG, except one [23]. Above all, the efficacy of statins in various trials overshadowed the potential interest of strategies targeting TG. Trials with fibrates could provide promising information when subgroups are considered. Nevertheless, they are only old

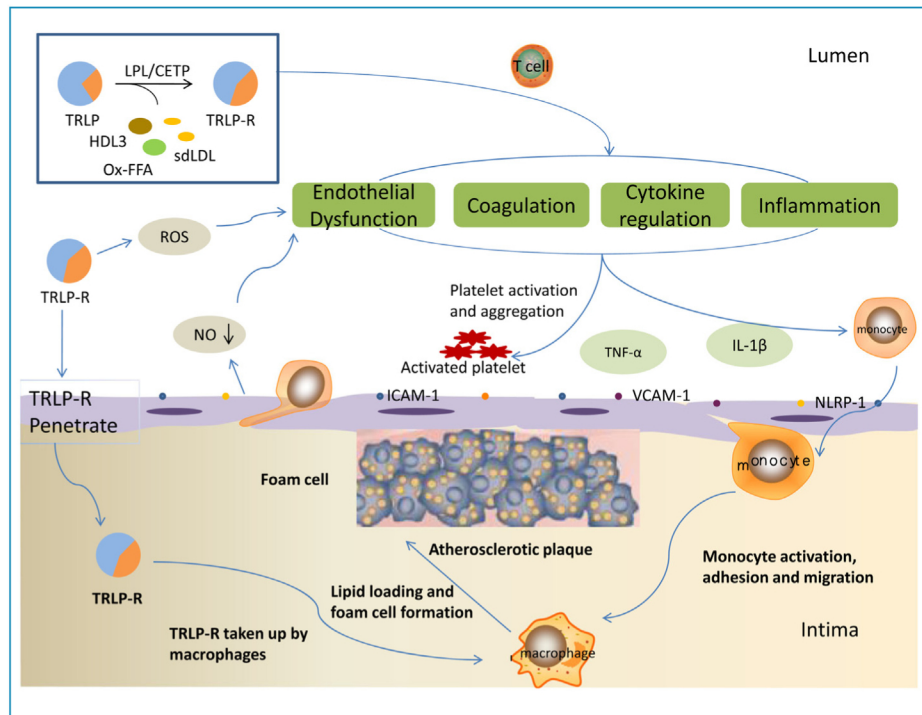


FIGURE 6
Involvement of TG in pathophysiology of atherosclerosis, adapted from [27], open access.

TABLE I
Currently ongoing trials aiming clinical endpoints

	NCT		Number of patients	Endpoint	Date
Reduce-it	01492361	TG lowering n-3 fatty acid: AMR101	8000	MACES Y4-6	2018: end of recruitment
Strength	02104817	Epanova: omega-3 carboxylic acids	13,000	MACE	2019: end of recruitment
Prominent	03071692	PPAR-α Pemafibrate	10,000	MACE, Y4	2022

Clinicaltrials.org, Jan 2017: Phase III, primary endpoint: MACES

studies and management of patients totally changed, urging to tailor new studies in the contemporaneous context. All the new data briefly presented there taken into consideration, new approaches are currently evaluating the TG hypothesis. For instance, targeting ApoC-III to reduce ASCVD could be obtained through different approaches [24]. Among these, some small clinical trials have shown that innovative options could offer TG reduction in patients. For instance, through selective antisense inhibition of APOC3 synthesis [25], lowering TG levels, among patients with a broad range of baseline levels has been shown possible. Importantly, many trials are currently investigating the interest of this strategy as presented briefly in *table I*. These studies are

large PROBE-designed studies and should help to answer the question in the following years.

Conclusions

TG are of importance for the management of patients. The cardiologist has to keep in mind that LDL alone cannot be the Holy Grail for ASCVD management (both in primary and secondary prevention). New data from biology and basic research but also from epidemiology, genetics and preliminary clinical trials are consistent to support the hypothesis that TG-rich lipoproteins could be causal factors for ASCVD. Here, we briefly presented these data and presently growing interest leading to large trials in the field. However, we should keep

in mind that actually current recommendations focused on LDL cholesterol target and treatment by statins in term of ASCVD reduction.

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