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Review

Recent advances in pharmacotherapy for hypertriglyceridemia

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ABSTRACT

Elevated plasma triglyceride (TG) concentrations are associated with an increased risk of atherosclerotic cardiovascular disease (CVD), hepatic steatosis and pancreatitis. Existing pharmacotherapies, such as fibrates, *n*-3 polyunsaturated fatty acids (PUFAs) and niacin, are partially efficacious in correcting elevated plasma TG. However, several new TG-lowering agents are in development that can regulate the transport of triglyceride-rich lipoproteins (TRLs) by modulating key enzymes, receptors or ligands involved in their metabolism.

Balanced dual peroxisome proliferator-activated receptor (PPAR) α/γ agonists, inhibitors of microsomal triglyceride transfer protein (MTTP) and acyl-CoA:diacylglycerol acyltransferase-1 (DGAT-1), incretin mimetics, and apolipoprotein (apo) B-targeted antisense oligonucleotides (ASOs) can all decrease the production and secretion of TRLs; inhibitors of cholesteryl ester transfer protein (CETP) and angiopoietin-like proteins (ANGPTLs) 3 and 4, monoclonal antibodies (Mabs) against proprotein convertase subtilisin/kexin type 9 (PCSK9), apoC-III-targeted ASOs, selective peroxisome proliferator-activated receptor modulators (SPPARMs), and lipoprotein lipase (LPL) gene replacement therapy (alipogene tiparvovec) enhance the catabolism and clearance of TRLs; dual PPAR-α/δ agonists and *n*-3 polyunsaturated fatty acids can lower plasma TG by regulating both TRL secretion and catabolism.

Varying degrees of TG reduction have been reported with the use of these therapies, and for some agents such as CETP inhibitors and PCSK9 Mabs findings have not been consistent. Whether they reduce CVD events has not been established. Trials investigating the effect of CETP inhibitors (anacetrapib and evacetrapib) and PCSK9 Mabs (AMG-145 and REGN727/SAR236553) on CVD outcomes are currently in progress, although these agents also regulate LDL metabolism and, in the case of CETP inhibitors, HDL metabolism. Further to CVD risk reduction, these new treatments might also have a potential role in the management of diabetes and non-alcoholic fatty liver disease owing to their insulin-sensitizing action (PPAR-α/γ agonists) and potential capacity to decrease hepatic TG accumulation (PPAR-α/δ agonists and DGAT-1 inhibitors), but this needs to be tested in future trials.

Abbreviations: AAV1, adeno-associated virus serotype 1; ACC, American College of Cardiology; ACCELERATE, A Study of Evacetrapib in High-Risk Vascular Disease; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADA, American Diabetes Association; AMP, **a**denosine monophosphate; ANGPTL, angiopoietin-like protein; ApoA-I, lipoprotein A-I; ApoB, apolipoprotein B; ApoC-III, apolipoprotein C-III; ApoE, apolipoprotein E; ASO, antisense oligonucleotide; CCS, Canadian Cardiovascular Society; CETP, cholesteryl ester transfer protein; CHD, coronary heart disease; ChREBP, carbohydrate response element binding protein; CVD, cardiovascular disease; DART, diet and reinfarction; DGAT, acyl-CoA:diacylglycerol acyltransferase; DHA, docosahexaenoic acid; DPP-4, dipeptidyl peptidase-4; EPA, eicosapentaenoic acid; EAS, European Atherosclerosis Society; ECLIPSE, Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation; ESC, European Cardiovascular Society; Examine, examination of cardiovascular outcomes with alogliptin versus standard of care; FCH, familial combined hyperlipidemia; FFA, free fatty acid; FH, familial hypercholesterolemia; FHTG, familial endogenous hypertriglyceridemia; FIELD, fenofibrate intervention and event lowering in diabetes; FOXO1, forkhead box O1; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardio—Prevenzione; GLP-1, glucagon-like peptide-1; GREACE, Greek Atorvastatin and Coronary Heart Disease Evaluation; HDL, high-density lipoprotein; HSPG, heparan sulfate proteoglycan; JELIS, Japan EPA lipid intervention study; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; LPLD, lipoprotein lipase deficiency; LRP, LDL receptor-related protein; Mab, monoclonal antibodies; miR, MicroRNA; MI, myocardial infarction; MTTP, microsomal triglyceride transfer protein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; REDUCE-IT, reduction of cardiovascular events with EPA-intervention trial; REVEAL, EValuation of the Effects of Anacetrapib through Lipid-modification; SAVOR-TIMI 53, saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus; siRNA, small interfering RNA; SMART, safely metabolized and rationally targeted; SPPARM, selective PPAR modulator; TG, triglycerides; TRL, triglyceride-rich lipoprotein; USF-1, upstream transcription factor-1; VLDL, very low-density lipoprotein; VLDLR, very low-density lipoprotein receptor.

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We summarize the clinical trial findings regarding the efficacy and safety of these novel therapies for hypertriglyceridemia.

Contents

1. Classification, etiology and clinical significance of hypertriglyceridemia

Hypertriglyceridemia refers to a fasting plasma triglyceride (TG) concentration above the 95th percentile for age and sex in a population, with most international guidelines defining it at a threshold of $\geqslant$1.7 mmol/L (Table 1). These guidelines generally recognize elevated plasma TG as being mild, moderate, severe and very severe [1–5].

Elevated plasma TG is emerging as an independent risk factor for Type 2 diabetes, metabolic syndrome and atherosclerotic cardiovascular disease (CVD) [5,6], with a prevalence of up to 30–50% in these populations. According to the recent Mendelian randomization studies, loss-of-function mutations in the gene encoding apolipoprotein C-III (*APOC3*) are associated with low plasma TG concentrations and a reduced risk of ischemic CVD in the general population; thus providing evidence on the causal role between hypertriglyceridemia and CVD [7,8]. The management of hypertriglyceridemia has been reviewed recently [1,5,9], and the following sections briefly summarize the clinical significance of hypertriglyceridemia and the mechanisms involved in its etiopathogenesis.

Hypertriglyceridemia arises from a complex interplay between several genetic susceptibility loci and environmental factors that

Table 1
Categories of hypertriglyceridemia, as defined by international guidelines [1–5].

NCEP ATPIII		Endocrine society		European atherosclerosis society		International atherosclerosis society	
Category	mmol/L[a]	Category	mmol/L	Category	mmol/L	Category	mmol/L
Normal	<1.7	Normal	<1.7	Desirable	<1.7	Normal	<1.7
Borderline high	1.7–2.3	Mild	1.7–2.3	Elevated	1.7–5.5	Elevated	1.7–5.7
High	2.3–5.6	Moderate	2.3–11.2	Very high	5.5–25.0	Severe	>5.7
Very high	>5.6	Severe	11.2–22.4	Extremely high	>25.0		
		Very severe	>22.4				

[a] ×88.5 to convert from mmol/L to mg/dL.

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