Pharmacological Approaches For the Management of Patients with Moderately Elevated Triglycerides (150-499 mg/dL)

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Pharmacological Approaches For the Management of Patients with Moderately Elevated Triglycerides (150-499 mg/dL)

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Pharmacological Approaches For the Management of Patients with Moderately Elevated Triglycerides (150-499 mg/dL)

Abstract

Hypertriglyceridemia, defined as serum triglyceride (TG) levels > 150 mg/dL, now affects over one-quarter of the U.S. adult population and is associated with an increased risk of atherosclerotic cardiovascular disease. Available guidelines for managing hypertriglyceridemia vary with respect to triglyceride thresholds and severity of disease. Lifestyle modifications and management of secondary causes (e.g., diabetes) remain the first step in managing hypertriglyceridemia, with pharmacotherapy reserved to reduce the risk of pancreatitis and/or further reduce TG levels. Several classes of lipid-lowering agents are available with variable TG-lowering efficacy. While there is no consensus regarding the choice of initial TG-lowering pharmacotherapy, there is general agreement that the decision depends on the degree of hypertriglyceridemia and atherosclerotic cardiovascular disease risk. This review will discuss available and emerging lipid-lowering therapies for the management of moderately elevated TG, defined as TG 150-499 mg/dL.

Key Words: hypertriglyceridemia, guidelines, fibrates, omega-3 fatty acids, dyslipidemia
Abbreviations

ACC= American College of Cardiology
ACCORD= Action to Control Cardiovascular Risk in Diabetes
AHA= American Heart Association
AIM-HIGH= Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes
ANGPTL= angiopoietin-like protein
ApoC-III= apolipoprotein C-III
ASCVD= atherosclerotic cardiovascular disease
BAS= bile acid sequestrant
DGAT= diacylglycerol acyltransferase
ER= extended-release
FIELD= Fenofibrate Intervention and Event Lowering in Diabetes
FOURIER= Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
HDL-C= high-density lipoprotein cholesterol
HHS= Helsinki Heart Study
HPS2-THRIVE= Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events
HR= hazard ratio
LDL-C= low-density lipoprotein cholesterol
LDL-R= low-density lipoprotein receptor
Lp(a)= lipoprotein(a)
LPL= Lipoprotein Lipase
MACE= major adverse cardiovascular event
MI= myocardial infarction
NCEP ATP III= National Cholesterol Education Program Adult Treatment Panel III
Non-HDL-C= non-high-density lipoprotein cholesterol
O3FA= omega-3 fatty acid
ODYSSEY= Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab
PCSK9= Proprotein convertase subtilisin/kexin type 9
PPAR= peroxisome proliferator-activated receptor
TG = triglyceride
US = United States
VA-HIT= Veterans Affairs-High-Density Lipoprotein Cholesterol Intervention
VLDL-C= very low-density lipoprotein cholesterol
Title:
Pharmacological Approaches For the Management of Patients with Moderately Elevated Triglycerides (150-499 mg/dL)

Introduction
Targeting low-density lipoprotein cholesterol (LDL-C) with hydroxymethylglutaryl coenzymeA reductase (HMG-CoA) inhibitors, or statins, remains the primary therapy for preventing atherosclerotic cardiovascular disease (ASCVD); however, it is well established that statin-treated patients have a high-degree of residual risk.\(^1\) Possible explanations for this residual risk include inadequate reduction of LDL-C or the presence of mixed dyslipidemia. The latter is characterized by low levels of high-density lipoprotein cholesterol (HDL-C) and/or elevated triglycerides (TG); both of which are independently associated with increased ASCVD risk.\(^2\)

Elevated TG levels have long been linked to an increased risk for ASCVD, but the direct role TG play in the development and progression of atherosclerosis remains uncertain.\(^2\) While average TG levels in the United States (US) have declined, the prevalence of hypertriglyceridemia still exceeds 25% in the US.\(^3,4\) This persistent hypertriglyceridemia is likely due to the increasing prevalence of secondary factors independently associated with hypertriglyceridemia, such as diabetes, obesity, metabolic syndrome, physical inactivity, and western diet. As such, lifestyle modifications, including physical activity, weight loss, and modification of dietary patterns should be provided to all patients with elevated TG. Additionally, genetic factors contribute to hypertriglyceridemia in >95% of individuals, which may necessitate the need for pharmacotherapy.\(^4\)
The purpose of this review is to discuss current perspectives from national guidelines and the role of current and emerging lipid-lowering therapies for the management of moderately elevated TG (defined as TG values 150-499 mg/dL).

**National Guideline Recommendations**

The American Heart Association (AHA) released a Scientific Statement on Triglycerides and Cardiovascular Disease in 2011 to provide guidance on the importance of TG in assessing and managing ASCVD risk.\(^2\) While the definition for normal fasting TG remained <150 mg/dL, as recommended by the Adult Treatment Panel III of the National Cholesterol Education Program\(^5\) (NCEP ATP III), the authors suggested that *optimal* fasting TG levels should be <100 mg/dL. Significant emphasis was placed on initiation of intensive lifestyle interventions, such as eliminating trans fatty acids, reducing simple carbohydrates, implementing a Mediterranean-style diet, and weight loss of 5-10% body weight.\(^2\) Pharmacotherapy to lower TG was only recommended in individuals with TG ≥500 mg/dL, without preference toward any specific TG-lowering therapy.\(^2\)

In 2012, the Endocrine Society Task Force developed Guidelines for the Evaluation and Treatment of Hypertriglyceridemia.\(^6\) While the Task Force again recognized TG <150 mg/dL as normal, authors modified the NCEP ATP III TG classification to further differentiate between moderate, severe, and very severe hypertriglyceridemia (Table 1). The goal of this recommendation was to bring greater attention to very-high TG levels and the risk for acute pancreatitis. Non-HDL cholesterol (non-HDL-C) was identified as the treatment goal for patients with moderate hypertriglyceridemia, and maintaining TG <1000 mg/dL was the goal for patients with very severe hypertriglyceridemia. Citing a lack of conclusive evidence that TG-lowering therapies reduce ASCVD risk, pharmacotherapy was recommended only in those with severe hypertriglyceridemia.
(>1000 mg/dL), with preference for fibrates over omega-3 fatty acids (O3FA) and niacin due to subgroup analysis from clinical trials suggesting reduced ASCVD risk with fibrate therapy in patients with TG >200 mg/dL. Lastly, statin monotherapy was not recommended for individuals with severe or very severe hypertriglyceridemia.  

<table>
<thead>
<tr>
<th>NCEP ATP III</th>
<th>Normal &lt;150</th>
<th>Borderline 150-199</th>
<th>High 200-499</th>
<th>Very-high ≥500</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA 2011</td>
<td>Normal &lt;150</td>
<td>Borderline 150-199</td>
<td>High 200-499</td>
<td>Very-high ≥500</td>
</tr>
<tr>
<td>NLA 2014</td>
<td>Normal &lt;150</td>
<td>Borderline 150-199</td>
<td>High 200-499</td>
<td>Very-high ≥500</td>
</tr>
</tbody>
</table>

Table 1: Classification of fasting triglyceride concentration by guideline.  

AHA= American Heart Association; HTG= hypertriglyceridemia; NCEP ATP III= National Cholesterol Education Program Adult Treatment Panel III; NLA= National Lipid Association.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol was not intended to be a comprehensive guideline. As such, few recommendations regarding hypertriglyceridemia management were reported except that patients with TG ≥500 mg/dL receive evaluation for secondary causes. In light of limited randomized controlled trial evidence supporting the use of non-statin therapies in combination with statins, the guideline referred readers to the 2011 AHA Scientific Statement on Triglycerides.

In 2014, the National Lipid Association (NLA) released recommendations based on a broader review of available literature than the 2013 ACC/AHA Guideline, which only evaluated evidence from randomized controlled trials. As a result, the NLA expert panel embraced non-HDL-C as the primary target of therapy based on epidemiological studies.
and pooled analyses of intervention studies that suggest non-HDL-C is superior to LDL-C as a predictor of ASCVD risk.\textsuperscript{7} One explanation for the improved predictive value of non-HDL-C in patients with hypertriglyceridemia is that elevated TG levels impart greater atherogenic burden due to increased very low-density lipoprotein cholesterol (VLDL-C) levels and diminished plasma clearance of LDL-C via hepatic LDL receptors (LDL-R). In 2015, a second NLA report provided comprehensive lifestyle recommendations for managing hypertriglyceridemia, including those recommended by the 2011 AHA statement.\textsuperscript{8} Nevertheless, the variability among these expert recommendations demand continuing discussion about appropriate management of hypertriglyceridemia.

**Lipid-Lowering Pharmacotherapy and Effects on Triglycerides**

**Statins**

Statins reduce LDL-C by inhibiting HMG-CoA, which results in hepatic LDL-R up-regulation to remove LDL-C from circulation.\textsuperscript{7} Because the LDL-lowering effect of statins is dose related, the 2013 ACC/AHA guidelines recommend higher statin doses (or intensity) in patients at greater risk for ASCVD.\textsuperscript{1}

The Individual Patient Meta-analysis of Statin Therapy in at Risk Groups: Effects of Rosuvastatin, Atorvastatin and Simvastatin (VOYAGER), examined dose-related changes in lipid parameters with three statins.\textsuperscript{9} Low-intensity simvastatin 10 mg reduced TG 9.3% from baseline, while high-intensity atorvastatin 80 mg lowered baseline TG levels by 25.0%. A subgroup analysis of VOYAGER examined dose-related statin effects in patients with baseline TG levels ≥177 mg/dL.\textsuperscript{10} Simvastatin 10 mg resulted in a 15.1% TG reduction, while atorvastatin 80 mg resulted in a 31.3% reduction in TG levels. These
results suggest that the TG-lowering effect of statins is dose related, with greater TG-reductions seen in patients with higher baseline values.

The benefits of statin therapy for reducing major adverse cardiovascular events (MACE) and ASCVD risk have been extensively described elsewhere, and are beyond the scope of this article.\textsuperscript{1,7} Due to their ability to lower both ASCVD risk and TG levels, several guidelines recommend statin therapy as an initial agent for patients with moderately elevated TG and increased ASCVD risk.\textsuperscript{2,5-7}

<table>
<thead>
<tr>
<th>Lipid-lowering medication</th>
<th>Triglyceride reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>20 - 50</td>
</tr>
<tr>
<td>Niacin</td>
<td>10 - 50</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>20 - 50</td>
</tr>
<tr>
<td>Statins</td>
<td>7 - 30</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5 - 10</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>0 (may increase up to 10%)</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>0 - 17</td>
</tr>
</tbody>
</table>

Table 2: Triglyceride lowering effect by medication class.

**Fibrates**

The fibric acid derivatives (fibrates including gemfibrozil and fenofibrate) are a class of lipid-lowering agents that significantly decrease TG (Table 2). Fibrates produce lipid-lowering effects by activating the alpha subunit of peroxisome proliferator-activated receptors (PPARs).\textsuperscript{11} The PPAR-alpha belong to a superfamily of nuclear receptor proteins that act as transcription factors, leading to lipid-modifying gene expression. Activation of PPAR-alpha mediates TG reduction via three mechanisms: 1) suppressed production of lipoprotein lipase (LPL) inhibitor apolipoprotein C-III (ApoC-III); 2) reduced hepatic secretion of VLDL-C; and, 3) reduced hepatic TG production via beta-oxidation (Figure 1).\textsuperscript{11}
A meta-analysis of 53 trials reported that fibrates reduce TG levels by 36% from baseline versus placebo (p<0.00001).\textsuperscript{12} The average TG-lowering effect of gemfibrozil was 48%, whereas fenofibrate reduced TG levels by 40%. Despite large reductions in TG, the impact of fibrate therapy on ASCVD outcomes has been variable. In the pre-statin era, trials such as the Helsinki Heart Study (HHS) and Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated reduced MACE with gemfibrozil versus placebo in patients with TG \textgeq 160 mg/dL.\textsuperscript{13,14} In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, no difference in the composite primary endpoint of MACE was observed in patients randomized to fenofibrate 200 mg/day or placebo (5.9% versus 5.2%; p=0.16).\textsuperscript{15} However, a post-hoc analysis reported a trend toward reduction in the primary endpoint in patients with metabolic syndrome, including elevated TG levels (p=0.052).\textsuperscript{16} The lack of MACE reduction in the FIELD trial may be related to increased statin use in the placebo group (17%) compared with the fenofibrate (8%) group during the study period.\textsuperscript{15} In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, adding fenofibrate to statin therapy significantly reduced TG levels by 13.5% versus placebo (p<0.0001) in patients with TG >150 mg/dL at baseline, but did not reduce the composite primary endpoint of MACE.\textsuperscript{17} Again, pre-specified subgroup analysis suggested a trend toward benefit in patients with TG \textgeq 204 mg/dL and HDL-C <34 mg/dL randomized to fenofibrate versus placebo (p=0.057).\textsuperscript{17} Furthermore, a recent post-trial follow-up to ACCORD showed that after an additional five years, fenofibrate use was associated with a 27% relative risk reduction (HR, 0.73; 95% CI, 0.56-0.95) in the primary study outcome for the subgroup of patients with TG \textgeq 204 mg/dL and HDL-C <34 mg/dL.\textsuperscript{18}
Figure 1: Targets of lipid-lowering medications (prefer color for on-line only)

ApoB = apolipoprotein B; ApoC-III = apolipoprotein CIII; BA = bile acids; BAS = bile acid sequestrants; CE = cholesterol esters; CETP = cholesteryl ester transfer protein; DGAT = diglyceride acyltransferase; FFA = free fatty acids; IDL = intermediate-density lipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LDL-R = low-density lipoprotein receptor; LPL = lipoprotein lipase; NPC1L1 = Niemann-Pick C1-Like1; O3FA = omega-3 fatty acids; PCSK9 = proprotein convertase subtilisin/kexin type 9; TG = triglycerides; VLDL = very-low-density lipoprotein.

Niacin

Niacin, also known as nicotinic acid or vitamin B3, is a water-soluble vitamin which at high doses demonstrates the ability to lower total cholesterol, TG, VLDL-C, LDL-C, lipoprotein(a) [Lp(a)], while increasing HDL-C.\textsuperscript{19} Niacin decreases TG by inhibiting diacylglycerol acyltransferase (DGAT) 2, an enzyme that catalyzes the formation of TG from diacylglycerol and acyl-CoA.\textsuperscript{20} Niacin also inhibits lipolysis and subsequent release of TG into the circulation.\textsuperscript{20}

The Coronary Drug Project (CDP) was among the first clinical trials demonstrating niacin’s ability to reduce TG. The CDP randomized male patients to one of six treatment
arms, including niacin 3.0 g/day, with a primary aim to evaluate the efficacy of these therapies on long-term ASCVD risk. After a 5-year follow-up period, niacin reduced TG 26.1% from baseline versus placebo. Additionally, a meta-analysis of 30 trials reported an average TG reduction of 20% from baseline. Furthermore, the TG-lowering effect was consistent for both intermediate-release and extended-release (ER) niacin, with reported 26% and 20% reduction, respectively.

Reduction in ASCVD events has been reported with niacin monotherapy, although before the discovery of statins. In the CDP trial, niacin did not significantly reduce the risk of death due to coronary artery disease, but did reduce risk of non-fatal myocardial infarction (MI) by 27% (8.9% in niacin and 12.2% in placebo). At 15 years of follow-up, nearly 9 years after trial end, mortality in the niacin group was 11% lower than placebo (52.0% versus 58.2%, p=0.0004). Recently, two trials have evaluated the benefit of niacin/statin combination therapy to reduce residual risk in patients with a history of ASCVD. In both the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) studies, adding ER niacin to statin therapy failed to reduce the primary endpoint of composite MACE in patients at LDL-C goal. However, higher rates of select adverse effects (glucose intolerance, gastrointestinal symptoms) were reported in the niacin treatment groups.

**Omega-3 Fatty Acids (O3FA)**

Omega-3 fatty acids (O3FA) are polyunsaturated fatty acids with the first double bond occurring in the omega-3 position of the carbon backbone. Currently there are three formulations of O3FA: eicosapentaenoic acid (EPA) ethyl ester, combination EPA and
docosahexaenoic acid (DHA) ethyl esters, and EPA/DHA carboxylic acids; however, insurance formularies will likely dictate which, if any, O3FA product is covered. There are a variety of over-the-counter O3FA supplements, but due to lack of regulation, may contain varying amounts and types of long-chain fatty acids. Although the exact mechanism is unknown, O3FAs may exert their TG-lowering effects similar to fibrates, including: increased hepatic beta-oxidation of fatty acids; increased LPL hydrolysis through activation of PPAR-alpha; and inhibition of ApoC-III.

In placebo-controlled trials including patients with TG levels 200-500 mg/dL, O3FA reduced TG by 22% from baseline compared to placebo. In a meta-analysis of placebo-controlled trials, O3FA demonstrated a 25-36% reduction in TG levels, with greater reductions observed in patients with baseline values ≥177 mg/dL versus <177 mg/dL (34% versus 25%).

Multiple trials evaluating O3FA (at daily doses 1 to 2 g/day) to reduce cardiovascular risk in patients with ASCVD have produced conflicting results. In a trial of recent MI patients, 95% of whom were not receiving lipid-lowering therapy post-MI, O3FA lead to a 10% reduction in the primary endpoint of death, non-fatal MI, and stroke versus placebo (p=0.048). However, several other studies in patients with ASCVD or at high risk were unable to demonstrate significant MACE benefit of O3FAs versus placebo. A recent AHA advisory statement suggests that O3FA supplementation is reasonable for secondary prevention of cardiovascular events in patients with prevalent ASCVD, and to reduce mortality and hospitalizations in patients with reduced ejection-fraction heart failure.
Bile Acid Sequestrants (BAS)

The BAS are non-soluble resins that bind bile acids in the intestines, removing bile acids from enterohepatic circulation, and ultimately leading to an up-regulation of LDL-R to remove serum cholesterol.\textsuperscript{31} Use of BAS is associated with 15-30\% LDL-C reduction, and up to a 10\% increase in TG values.\textsuperscript{7}

In one of the earliest primary-prevention trials, male patients with baseline LDL-C $\geq 190$ mg/dL and TG of 154 mg/dL were randomized to BAS (cholestyramine) or placebo for an average of 7.4 years.\textsuperscript{32} Treatment with cholestyramine significantly lowered both total cholesterol and LDL-C, and reduced the primary endpoint of MACE by 19\% (p<0.05). Patients who received BAS had a greater increase in TG at 1-year (10.2\%) compared to the placebo group (5.74\%). By year seven, TG had increased by 17\% to 182.9 mg/dL in the BAS group compared to an increase of 13.3\% in the placebo group (significance not reported).\textsuperscript{32} Given the risk of increased TG, the 2013 ACC/AHA guideline recommends against use of BAS in patients with TG $\geq 300$ mg/dL.\textsuperscript{1}

Ezetimibe

Ezetimibe inhibits the Niemann-Pick C1-Like 1 transporter, thereby inhibiting absorption of cholesterol at the intestinal border.\textsuperscript{33} As anticipated from this mechanism of action, ezetimibe has little effect on TG. A meta-analysis of ezetimibe’s lipid-lowering effects found ezetimibe 10 mg daily to be associated with a mean 8\% reduction in TG versus placebo (p<0.00001).\textsuperscript{34} Ezetimibe is indicated for use in combination with statin therapy for primary hyperlipidemia (to reduce total-C, LDL-C, Apo B, and non-HDL-C) and in combination with fenofibrate for patients with mixed dyslipidemia. Despite minimal TG-
lowering effects, ezetimibe may be used in combination with other lipid-lowering agents to further reduce LDL-C, without increasing TG.

Clinical ASCVD trials have primarily evaluated ezetimibe/statin combination versus statin monotherapy or placebo. The Improved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) trial found that combination ezetimibe/simvastatin significantly reduced the composite MACE endpoint in patients with recent acute coronary syndrome compared to simvastatin monotherapy (32.7% vs. 34.7%, respectively, p=0.016). Whether ezetimibe monotherapy reduces ASCVD risk in patients with hypertriglyceridemia has not been evaluated by clinical trials.

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-I)

Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) prevents degradation of LDL-R, resulting in prolonged clearance of LDL-C from the plasma. Two humanized monoclonal antibodies (evolocumab, alirocumab) that inhibit PCSK9 are approved for LDL-C lowering in in patients with heterozygous familial hypercholesterolemia or clinical ASCVD, in addition to maximally tolerated statin therapy. Additionally, evolocumab is approved for homozygous familial hypercholesterolemia patients who require additional LDL-C lowering despite lipid-lowering therapy.

A phase III study investigated the safety and efficacy of evolocumab in patients without current lipid-lowering therapy or previous statin intolerance. Patients received evolocumab subcutaneously, biweekly (140 mg) or monthly (420 mg), ezetimibe 10 mg plus placebo injection, or placebo for 12 weeks. Biweekly and monthly evolocumab treatment reduced TG 8.1% and 15.6% from baseline, respectively. Compared to placebo, monthly evolocumab significantly reduced TG 17.7% from baseline (p<0.001).
More recently, a meta-analysis of 20 trials found that PCSK9-I treatment was associated with a significant 12.2% TG reduction (p<0.00001).\textsuperscript{37}

Recently, the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial found that evolocumab significantly reduced the primary composite MACE endpoint compared to placebo (9.8% vs. 11.3%; p<0.001) over a median follow up period of 2.2 years.\textsuperscript{38} Results of a second ASCVD outcome trial, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES), are expected in 2018.

**TG-Lowering Therapies in Development**

Volanesorsen (ISIS 304801) is an antisense oligonucleotide that targets ApoC-III mRNA in the liver, which regulates TG production via inhibition of LPL. Two Phase II trials have been completed in subjects with elevated TG 350-2000 mg/dL and familial chylomicronemia syndrome, an autosomal recessive disorder characterized by LPL deficiency.\textsuperscript{39,40} In both studies, volanesorsen reduced TG by as much as 80%. Given that individuals with ApoC-III loss-of-function variants are at lower ASCVD risk, there is potential for such therapies to translate to improved clinical outcomes.
Pemafibrate (K-877) is a highly-potent and selective antagonist of PPAR-alpha, which promotes macrophage cholesterol efflux to HDL, and reduces inflammatory markers.\textsuperscript{41} In a phase II study, pemafibrate reduced TG by 43% and increased HDL-C 21%.\textsuperscript{42} As such, an international, multi-centered cardiovascular outcomes trial, PROMINENT, is in development with plans to randomize 10,000 high-risk patients with diabetes, with or without ASCVD, to pemafibrate or placebo, in addition to background high-intensity statin therapy.\textsuperscript{43}

Angiopoietin-like proteins (ANGTL) 3 and 4 are highly expressed in the liver and potent inhibitors of LPL, leading to decreased TG clearance. Importantly, individuals with an ANGPTL loss-of-function mutation have lower TG levels and are at lower risk of CVD. As such, there is great interest in developing inhibitors of ANGPTL proteins and early human clinical trials are ongoing.\textsuperscript{43–45}

**Discussion**

Current guidelines addressing hypertriglyceridemia differ in their pharmacotherapy recommendations and choice of therapy seems to remain largely provider-dependent. Additionally, definitions of hypertriglyceridemia and TG thresholds for initiating pharmacotherapy to reduce the risk of ASCVD and acute pancreatitis vary. The 2012 Endocrine Society's recommendation to initiate TG-lowering pharmacotherapy for TG >1000 mg/dL was a departure from previous guidelines, which recommended TG-lowering medications for TG >500 mg/dL to prevent pancreatitis.\textsuperscript{2,5} A recent cohort study reported that hypertriglyceridemia was associated with increased risks of acute pancreatitis and MI, with the highest event rates occurring in patients with TG ≥443 mg/dL.\textsuperscript{46} Therefore, in accordance with previous guidelines, TG-lowering
pharmacotherapy should be initiated in patients with TG $\geq 500$ mg/L to reduce risk of pancreatitis.

When treating TG $< 500$ mg/dL, most guidelines recommend using non-HDL-C as the primary treatment goal.$^{5,7}$ In patients with moderately elevated TG (150-499 mg/dL), multiple lipid-lowering agents (fibrates, niacin, O3FA, and high-intensity statins) have proven ability to reduce TG by $\geq 30\%$; however, evidence supporting ASCVD risk reduction among non-statin therapies remains uncertain. Several guidelines recommend statin therapy as an initial agent for TG 150-499 mg/dL because of proven ASCVD risk reduction and respectable TG-lowering efficacy.$^{2,5-7}$ The TG-lowering effect of statins appears dose-related, thus high-intensity statin should be initiated in most scenarios. Subgroup analysis suggests that statins exhibit greater TG-lowering effects in patients with higher baseline TGs ($\geq 177$ mg/dL) compared to patients with baseline TGs $< 177$ mg/dL.$^{10}$

A practical approach to treating moderately elevated TG may be to initiate high-intensity statin, followed by additional lipid-lowering agents as necessary to reach non-HDL-C goal. Additional agents to consider include fibrates, niacin, and O3FA because of larger TG-lowering efficacy than other non-statin agents. Fibrates have substantial TG-lowering ability and may be a preferred agent to add to statin therapy due to once-daily administration, favorable adverse effect profile, and generic product availability for most formulations. Preference should be given to fenofibrate products over gemfibrozil due to potential drug-drug interactions with several statins.$^{47}$ While available clinical trials have not demonstrated additional ASCVD risk reduction with fenofibrate/statin combination, sub-group analysis suggests a benefit in patients with elevated TG.$^{17,18}$
In patients with TG 200-500 mg/dL, addition of O3FA to statin therapy further reduces TG 20-30% from baseline. Because O3FA are available as a dietary supplement, some patients may prefer this “natural” approach over prescription TG-lowering agents. Potential limitations of O3FA include multiple capsules required to achieve TG-lowering effects, and modest LDL-C increases with select O3FA products due to a shift toward larger, more buoyant LDL particles. Furthermore, no randomized trials to date have investigated ASCVD risk reduction when adding prescription strength O3FA to statin therapy, but two active clinical trials (REDUCE-IT and STRENGTH) are examining ASCVD outcomes in high-risk ASCVD patients with hypertriglyceridemia. These trials are expected to be completed in 2017 and 2019, respectively, and will shed more light on the impact of these agents in the context of modern treatment.

The support for niacin in combination with statins has diminished, likely due to increased risk of adverse effects and lack of ASCVD risk reduction reported by recent clinical trials. The American Diabetes Association (ADA) 2017 Standards of Care recommend against routine combination of niacin with statins, but that fibrate therapy may be considered in addition to statin therapy in men with TG ≥204 mg/dL and reduced HDL-C. The 2016 ACC Consensus Decision Pathway for non-statin therapies also recommend against combination of niacin with statin therapy; however, this update primarily focused on non-statin agents to further lower LDL-C and did not specifically address management of hypertriglyceridemia. Other lipid-lowering agents (BAS, ezetimibe, PCSK9-inhibitors) demonstrate greater efficacy in lowering LDL-C than TG, thus are preferred for patients receiving statin therapy who require further LDL-C reduction. Newer agents are currently being investigated in Phase 2 and 3 trials.
Conclusion

While much progress has been made in reducing TG values among US adults, hypertriglyceridemia remains prevalent and contributes to increased risk of ASCVD and acute pancreatitis. Lifestyle interventions should be recommended in all patients with elevated TG levels, while selection of initial drug therapy depends on degree of hypertriglyceridemia. For moderately elevated TG (150-499 mg/dL), high-dose statin therapy should be preferred because of significant TG-lowering ability and ASCVD risk reduction benefits. If necessary, additional lipid-lowering agents may be added to reach non-HDL-C goals in effort to lower ASCVD risk. For individuals with TG levels ≥500 mg/dL, non-statin therapies that significantly reduce TG are preferred initial agents to achieve TG <500 mg/dL and reduce the risk of acute pancreatitis. Ongoing trials evaluating the use of combination statin and TG-lowering therapies compared to statin monotherapy will shed light on the ongoing dilemma surrounding the treatment of moderately elevated TG to reduce ASCVD risk.

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• Elevated triglycerides (150-499 mg/dL) are associated with increased risk of ASCVD
• Pharmacologic treatment for elevated triglycerides varies by guideline
• High-intensity statin therapy can significantly lower triglycerides and ASCVD risk
• Additional non-statin agents may be necessary to reach non-HDL-C goals