AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Assessment and Treatment of Hypertriglyceridemia

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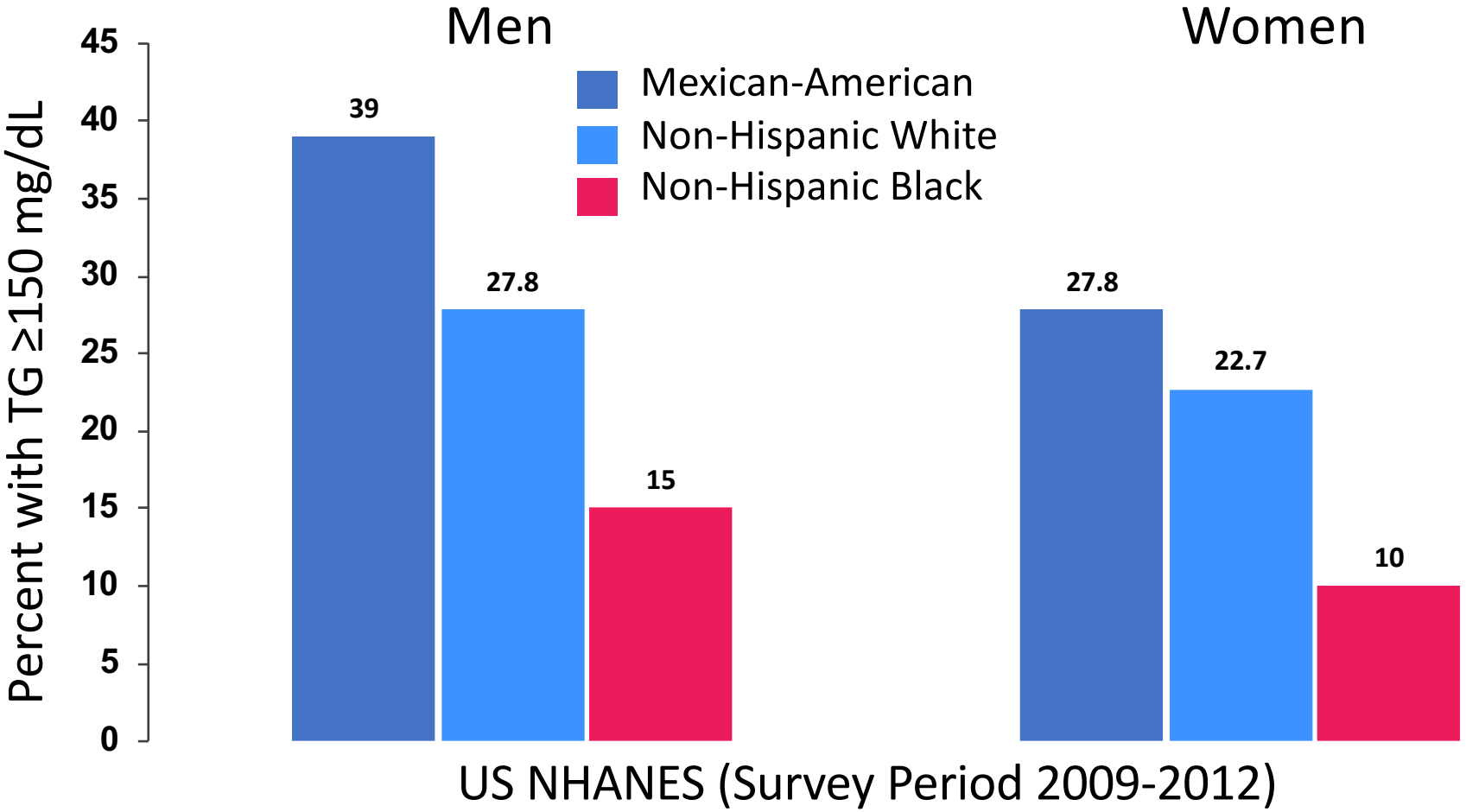
Hypertriglyceridemia

- What is the risk burden of hypertriglyceridemia?
- What is the clinical and genetic evidence for the association between elevated TG and atherosclerosis?
- What are the evidence-based guideline recommendations for managing patients with hypertriglyceridemia?
- What TG-lowering agents are available, and what are their anti-atherosclerotic and anti-inflammatory properties?

TG=triglycerides.

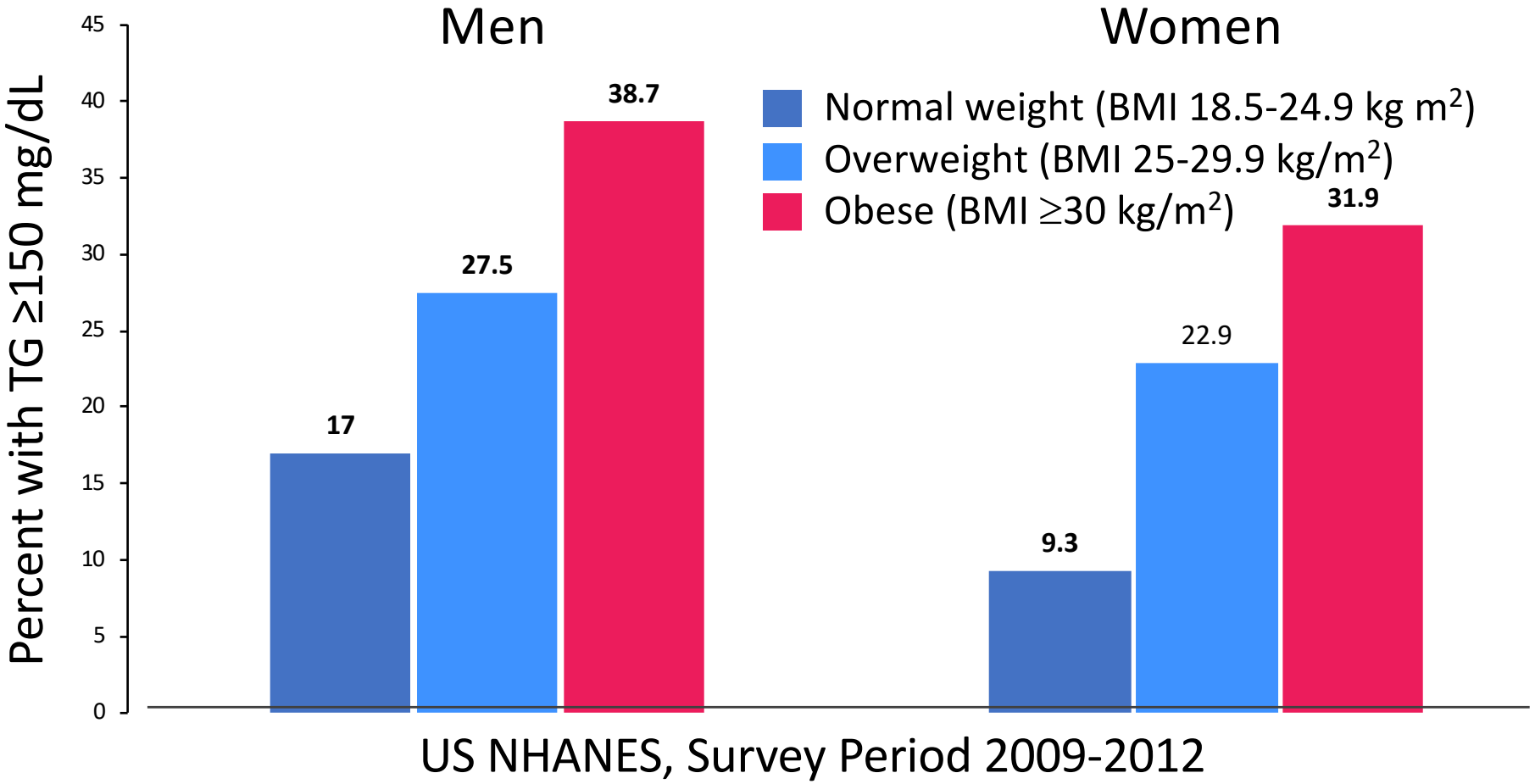
Hypertriglyceridemia: Prevalence, Risk, and Screening

Sex, Race, and Hypertriglyceridemia (Fasting TG ≥150 mg/dL)



NHANES=National Health and Nutrition Examination Surveys; TG=triglyceride; US=United States.
Carroll MD et al. NCHS Data Brief, No 198. National Center for Health Statistics. 2015.

Obesity and Hypertriglyceridemia (Fasting TG ≥150 mg/dL)



BMI=body mass index; NHANES=National Health and Nutrition Examination Surveys; TG=triglyceride; US=United States.
Carroll MD et al. NCHS Data Brief, No 198. National Center for Health Statistics. 2015.

Secondary Causes of Hypertriglyceridemia

Cause	Clinically Useful Details
Caloric imbalance[1]	↓ Exercise, ↑ Saturated fat, ↑ Glycemic index, excess alcohol intake
↑ Carbohydrate intake[1]	↑ Simple sugars (fructose>>glucose, etc.) and ↓ Dietary fiber
Adiposity[1]	Especially ↑ visceral adiposity
Diabetes mellitus[1]	Especially if poorly controlled
Hypothyroidism[1]	If not adequately controlled
Nephrotic syndrome[1]	
Medications[1]	Antiretroviral regimens (for HIV); some phenothiazines and second-generation antipsychotics; nonselective beta-blockers; thiazide diuretics; oral estrogen; tamoxifen; glucocorticoids; Isotretinoin
Recreational drugs[2]	Marijuana (↑ Apo C-III)

Apo=apolipoprotein; HIV=human immunodeficiency virus.

1. Bays HE, et al. *J Clin Lipidol*. 2013 Jul-Aug;7(4):304-83.
2. Jayanthi S, et al. *Mol Psychiatry*. 2010 Jan;15(1):101-12.

High TG Levels Are Often Associated with Other Heart Disease Risk Factors

- Obesity/insulin resistance[1-3]
- Physical inactivity[3,4]
- Diabetes mellitus[1,3,5]
- High blood pressure[1]
- Elevated cholesterol levels[1]
- Low HDL-C levels[1]
- Elevated uric acid levels[6]

HDL-C=high-density lipoprotein cholesterol; TG=triglycerides.

1. Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87; 2. Garvey TW, et al. *Endocr Pract.* 2016 Jul;22 Suppl 3:1-203; 3. NHLBI. NIH Publication No. 02-5215. 2002; 4. Hamburg NM, et al. *Arterioscler Thromb Vasc Biol*. 2007 Dec;27(12):2650-6; 5. Handelsman Y, et al. *Endocr Pract.* 2015 Apr;21 Suppl 1:1-87; 6. Bonora E, et al. *Int J Obes Relat Metab Disord.* 1996 Nov;20(11):975-80.

Elevated TG Levels: Screening and Risk Assessment

- Fasting TG levels should be part of routine lipid screening[1]
- Classification of elevated TG should be incorporated into risk assessments to aid in treatment decisions:[1]
  - Moderately elevated TG levels (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome[2]
  - TG levels ≥200 mg/dL may indicate a substantial increase in ASCVD risk[3]

TG category[1]	Fasting TG concentration (mg/dL)	TG goal
Normal	<150	<150 mg/dL
Borderline high	150-199	
High	200-499	
Very high	≥500	
Severe[4]	1000-1999 mg/dL	
Very Severe[4]	>2,000 mg/dL	

ASCVD=atherosclerotic cardiovascular disease; TG=triglyceride.

1. Jellinger PS, et al. *Endocr Practice*. 2017;23(4):479-497; 2. Einhorn D, et al. *Endocr Pract*. 2003;9:237-252; 3. NHLBI. NIH Publication No. 02-5215. 2002. 4. Berglund L, et al. J. Clin. Endocrinol. Metab. 2012;97:2969–2989.

Elevated TG Levels: Screening and Risk Assessment

- TG levels increase with age, and the importance of HTG as an ASCVD risk factor also appears to increase with age[1]
- High serum TG levels may act synergistically with other lipid abnormalities to increase ASCVD risk[1]
- Serum TG levels may also predict coronary risk when they are associated with a high LDL-C to HDL-C ratio (>5), or when HDL-C levels are low[1]
- Several studies indicate that postprandial, or nonfasting, TG may be an equally or more potent ASCVD risk factor than fasting TG[1]
  - Two major prospective studies:
    - The Women's Health Study[2] (N=26,509, 11.4-year follow-up) and the Copenhagen City Heart Study[3] (N=13,981, 26-year follow-up), found that non-fasting TGs were independently associated with MI and ischemic heart disease

ASCVD=atherosclerotic cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; HTG=hypertriglyceridemia; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; TG=triglycerides.

1. Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87; 2. Bansal S, et al. *JAMA.* 2007 Jul 18;298(3):309-16; 3. Nordestgaard BG, et al. *JAMA*. 2007;298:299-308.

Plasma TG Independently Predicts CVD Death and Total Mortality, Meta-Analysis of >1 Million Patients

33 studies evaluating CVD mortality (17,018 CVD deaths among 726,030 patients) and 38 studies evaluating all-cause mortality (58,419 all-cause deaths among 330,566 patients).

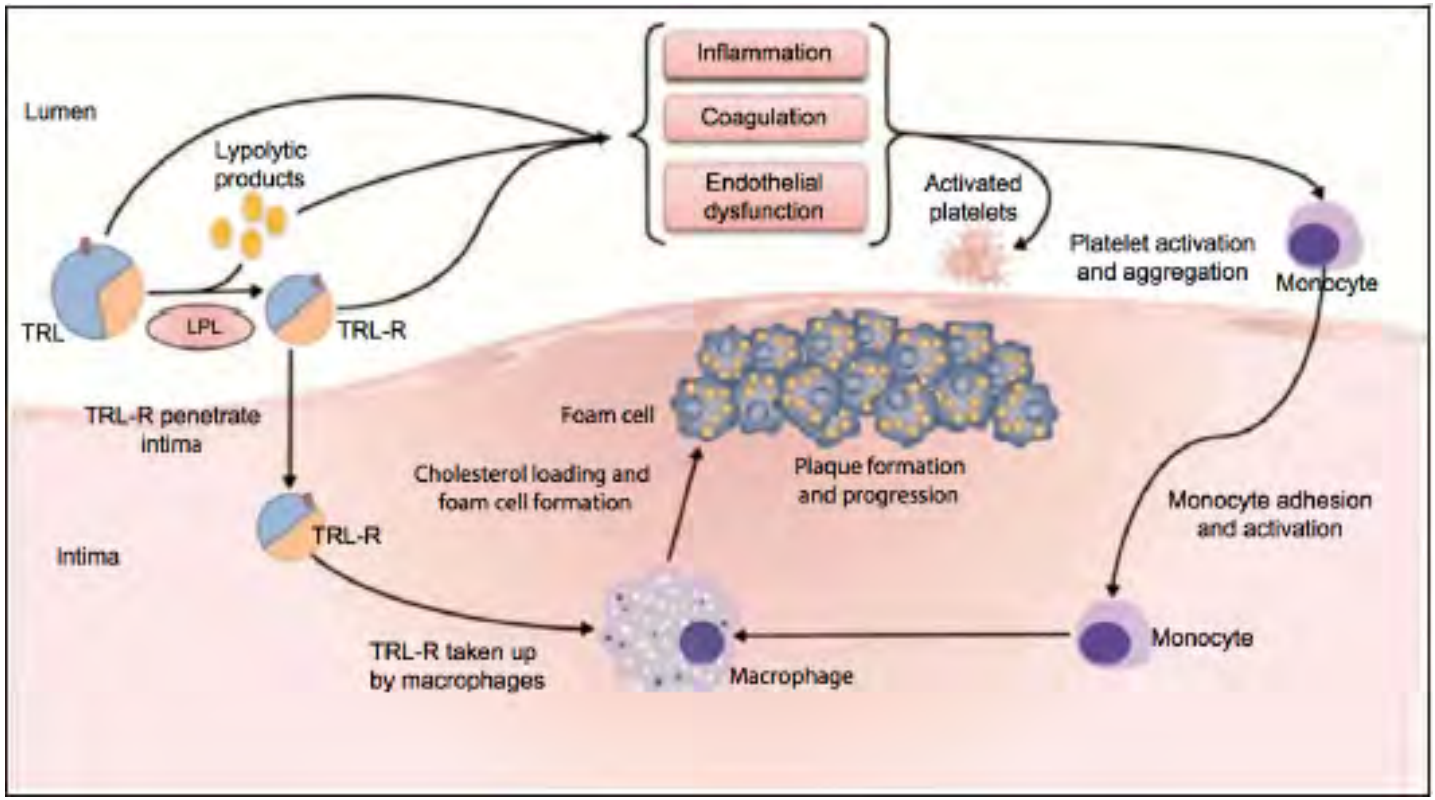
Median duration of follow-up was 12.0 years; patients with diabetes, CVD, or cancer were excluded.

	CVD Mortality		All-Cause Mortality	
TG quartile/mg/dL	**RR**	***P*-value**	**RR**	***P*-value**
I. <90	0.83	0.001	0.94	0.150
II. 90-149 (referent)	1.00		1.00	
III. 150-199	1.15	0.015	1.09	0.011
IV. ≥200	1.25	0.013	1.20	0.011

CVD=cardiovascular disease; RR=relative risk; TG=triglyceride.
Liu J, et al. *Lipids Health Dis*. 2013;12:159.

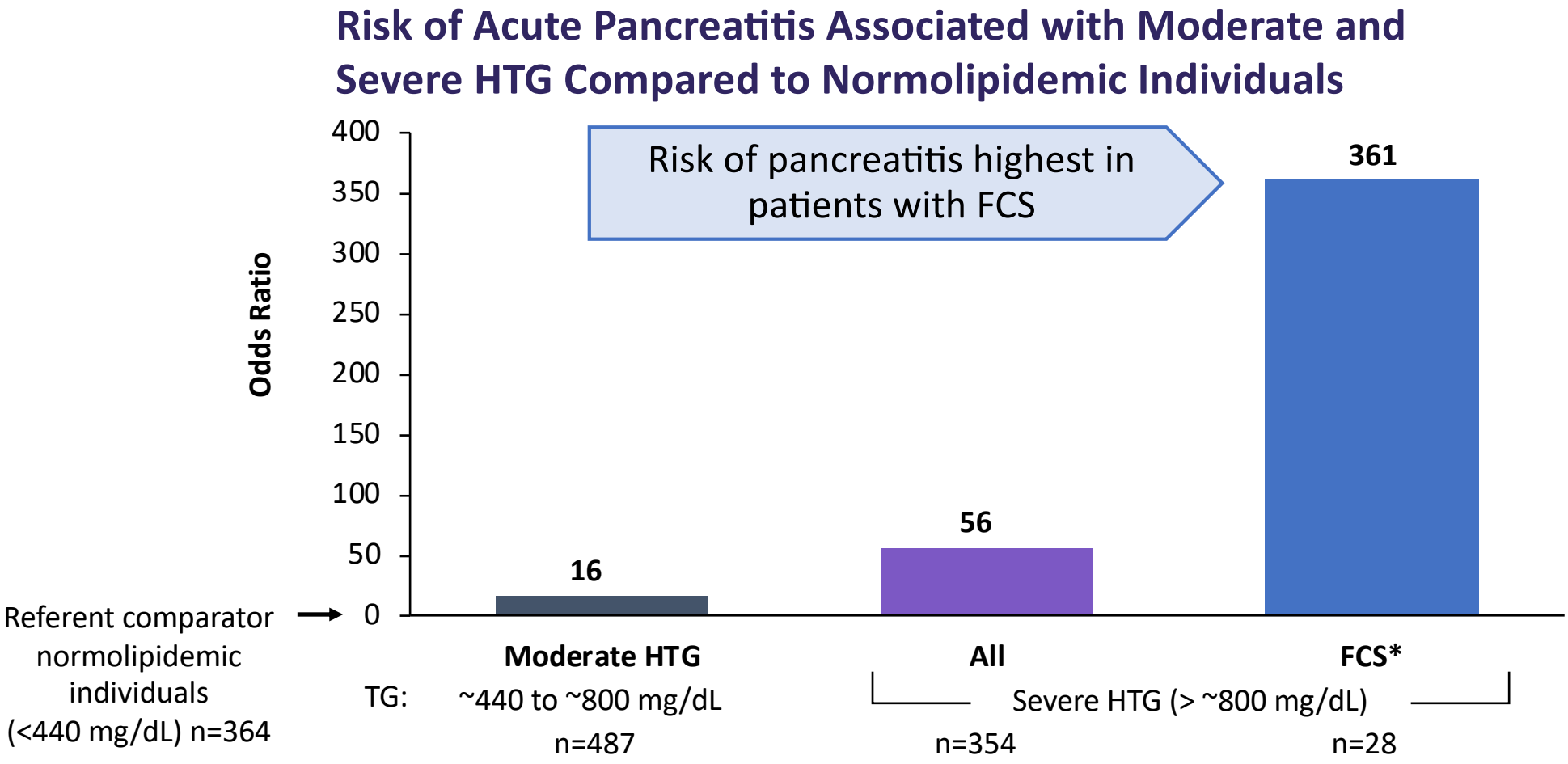
Proposed Mechanisms of Triglyceride-rich Lipoproteins in Atherosclerosis

Inflammation, coagulation, and endothelial dysfunction in the vessel lumen also cross the endothelium, leading to foam cell formation and plaque formation and progression



LPL=lipoprotein lipase; TRL=triglyceride-rich lipoprotein; TRL-R=triglyceride-rich lipoprotein remnants.
Watts GF, et al. *Nat Rev Cardiol.* 2013;10:648-661.

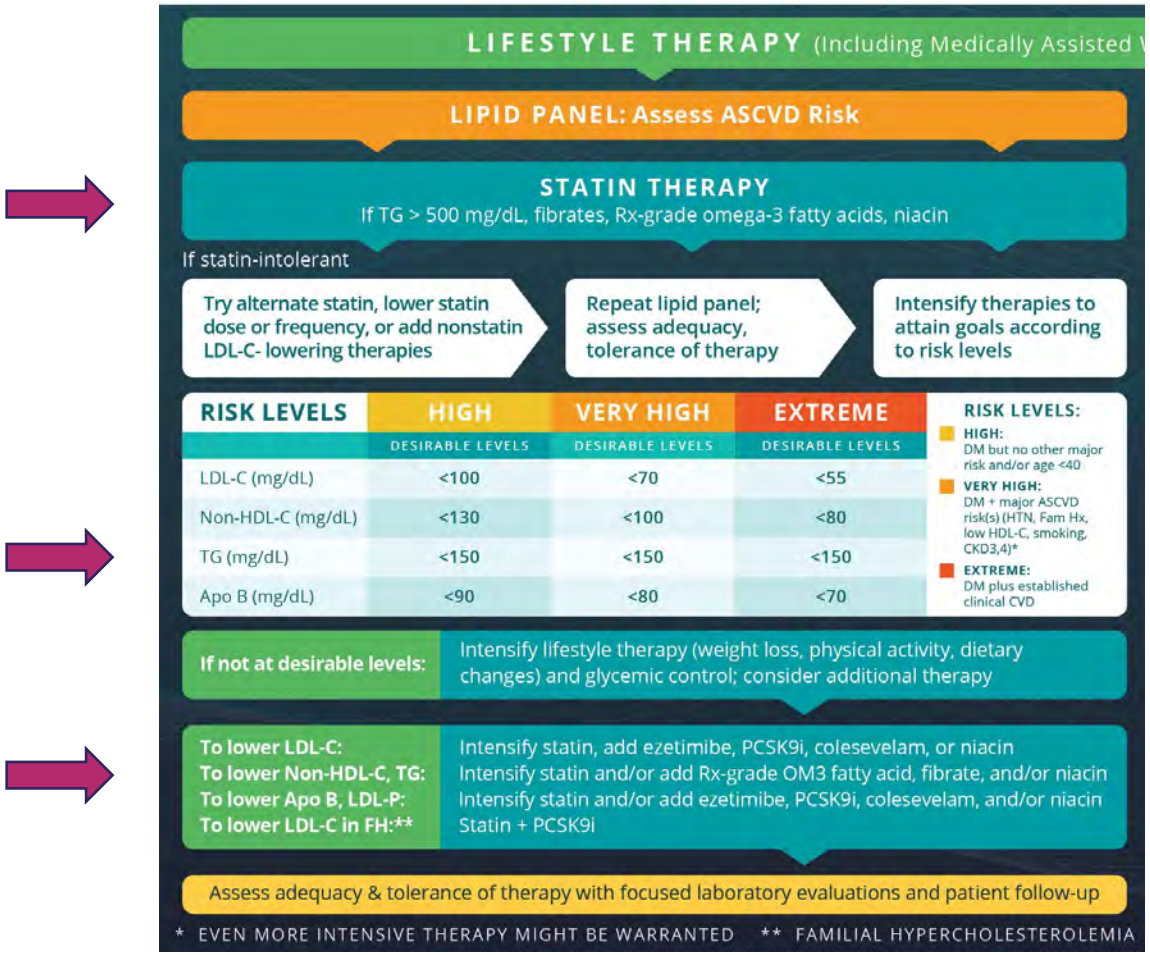
Among Patients with Severe HTG, Patients with FCS Have the Highest Risk of Pancreatitis



*Only includes patients with LPL mutation and <5% LPL functionality
FCS=familial chylomicronemia syndrome; HTG=hypertriglyceridemia; LPL=lipoprotein lipase gene; TG=triglyceride.
Adapted from Gaudet D, et al. *Atheroscler Suppl* 2010;11:55-60.

Hypertriglyceridemia: Recommendations for Management

AACE ACSVD Risk Factor Modifications



Apo B=apolipoprotein B; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; CVD=cardiovascular disease; DM=diabetes mellitus; FH=familial hypercholesterolemia; HDL-C=high-density lipoprotein cholesterol; HTN=hypertension; Hx=history; LDL-C=low-density lipoprotein cholesterol; LDL-P=low-density lipoprotein particle; OM3=omega-3; PCSK9i=proprotein convertase subtilisin/kexin type 9 inhibitor; Rx=prescription; TG=triglyceride Garber AJ, et al. *Endocr Pract*. 2018 Jan;24(1):91-120.

Algorithm for Pharmacologic Management of Dyslipidemia in Patients with Cardiometabolic Risk and Diabetes

Treatment Objectives for Elevated TGs

Triglyceride Level	Rationale (Primary Goal) for Therapy
"Very High" TGs ≥500 mg/dL	Prevention of Pancreatitis*
"High" or "Moderate Hypertriglyceridemia" 200-499 mg/dL	Prevention of CVD*

* To date, no large clinical outcome trials have been completed to provide support

CVD=cardiovascular disease; TG=triglyceride.

Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; NHLBI. NIH Publication No. 02-5215. 2002; Berglund L, et al. *J Clin Endocrinol Metab.* 2012; 97:2969.

Hypertriglyceridemia Treatment Summary: Part 2

- After addressing secondary risk factors and implementing lifestyle therapy, treat with pharmacotherapy (combination therapy usually required):
  - TG ≥500 mg/dL to prevent pancreatitis and atherosclerosis
    - Prescription-grade omega-3 fatty acids and/or
    - Fibrates and/or
    - Nicotinic acid (lowers VLDL-C and VLDL-triglycerides)
  - TG 200-499 mg/dL to achieve LDL-C and non-HDL-C goal
    - Statins (lowers LDL-C and VLDL-C)
    - Omega-3 Fatty acids and/or
    - Fibrates and/or
    - Nicotinic acid

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride; VLDL=very low-density lipoprotein; VLDL-C=very low-density lipoprotein cholesterol.

NHLBI. NIH Publication No. 02-5215. 2002. Brahm A, Hegele RA. Hypertriglyceridemia. *Nutrients.* 2013 5(3):981–1001.

Pharmacotherapy for Hypertriglyceridemia: Options, Considerations, and Evidence

Drug Classes Used to Treat HTG

Drug Class	% TG Lowering
Statins	6% to 30%
Fibrates	20% to 35%
Omega-3 Fatty Acids	27% to 45%
Niacin	20% to 30%
MTP Inhibitor*	~45%

*Lomitapide; Data from small trial limited to patients with heterozygous familial hypercholesterolemia

- Niacin or fibrates in combination with statins may be appropriate options for many individuals with hypertriglyceridemia and associated low HDL-C.
- Omega-3 fatty acid (fish oil) supplementation (2 to 4 g/day) is supported for individuals with TG levels >500 mg/L.

HDL-C=high-density lipoprotein cholesterol; HTG=hypertriglyceridemia; MTP=Microsomal triglyceride transfer protein; TG=triglyceride.
Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87

Statins: Starting Dosages, Dose Ranges, and Metabolic Effects

Statin	Recommended Starting Daily Dose	Dosage Range
Lovastatin[1]	20 mg	10-80 mg
Pravastatin[2]	40 mg	10-80 mg
Simvastatin[3]	20-40 mg	5-80 mg[a]
Fluvastatin[4]	40 mg	20-80 mg
Atorvastatin[5]	10-20 mg	10-80 mg
Rosuvastatin[6]	10 mg	5-40 mg
Pitavastatin[7]	2 mg	2-4 mg

Metabolic Effects:[8]

- Inhibits HMG-CoA reductase, a key rate-limiting enzyme in hepatic cholesterol synthesis
  - Triggers increased expression of hepatic LDL receptors and increased LDL-C clearance
- Decreases plasma LDL-C in a dose-dependent fashion by 20%-55%
- Exerts modest lowering effects on VLDL-C, IDL-C, and TG (10%-30%)
- Raises HDL-C by 2%-10%
- Improves LDL subfraction profiles (atorvastatin and rosuvastatin)
  - Larger clinical trials may be necessary to confirm effect of statins on LDL particle size and density

[a] Simvastatin, 80 mg, not approved for therapy unless individual has been on treatment for more than 1 year without myopathy. ASCVD=atherosclerotic cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; HMG-CoA=3-hydroxy-3-methyl-glutaryl-coenzyme A; IDL=intermediate-density lipoprotein cholesterol; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides; VLDL-C=very low-density lipoprotein cholesterol. See notes for references.

Main Considerations

- Liver function test prior to therapy and as clinically indicated thereafter
- Myalgias and muscle weakness may present in some individuals
- Potential for drug-drug interaction between some statins and CYP450 3A4 inhibitors, such as cyclosporine, warfarin, and protease inhibitors, and multiple other medications
- Myopathy/rhabdomyolysis in rare cases; increased risk with coadministration of some drugs (see product labeling)
- Simvastatin dosages should not exceed 40 mg in most individuals; dosages of 80 mg are no longer recommended except in those who have tolerated 80 mg for 12 months or more without muscle toxicity
- Do not exceed 20 mg simvastatin daily with amlodipine or ranolazine
- Plasma elevations of rosuvastatin may be higher among Asian persons than other ethnic groups
- New-onset diabetes is increased in individuals treated with statins; however, it is dose-related, occurs primarily in individuals with MetS, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in ASCVD

ASCVD=atherosclerotic cardiovascular disease; MetS=metabolic syndrome.

Jellinger PS, et al. *Endocr Pract.* 2017 Apr;23(Suppl 2):1-87.

Statins Reduce CVD Events in Patients with HTG (HTG Subgroup Data; Median follow-up: ≥5 years)

Trial (Subgroup, mg/dL) (drug)	Risk difference vs placebo (P-value)	
	All subjects	HTG subgroup
WOSCOPS (TG ≥148) (Pravastatin)	–31% (<0.001)	–32% (0.003)
CARE (TG ≥144) (Pravastatin)	–24% (0.003)	–15% (0.07)
PPP Project (TG ≥200) (Pravastatin)	–23% (<0.001)	–15% (0.029)
4S (TG >159, HDL-C <39) (Simvastatin)	–34% (<0.001)	–52% (<0.001)
JUPITER (TG ≥150) (Rosuvastatin)	–44% (<0.001)	–21% (NS)
CTT (TG >177) (Various)	–21% (<0.001)	–24% (<0.001)

CARE=Cholesterol and Recurrent Events Trial; CTT=Cholesterol Treatment Trialists; HTG=hypertriglyceridemia; JUPITER=Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; NS=not significant; PPP=Prospective Pravastatin Pooling; 4S=Scandinavian Simvastatin Survival Study; WOSCOPS=West of Scotland Coronary Prevention Study; yrs=years.

Maki KC et al. *J Clin Lipidol*. 2012;6:413-26.

Fibrates: Starting Dosages, Dose Ranges, and Metabolic Effects

Agent	Usual recommended starting daily dosage	Dose range	Method of administration
Fibrates			
Fenofibrate	48-145 mg	48-145 mg	Oral
Gemfibrozil	1,200 mg	1,200 mg	Oral
Fenofibric acid	45-135 mg	45-135 mg	Oral

Metabolic Effects:

- Primarily ↓ TG 20%-35%, ↑ HDL-C 6%-18% by stimulating lipoprotein lipase activity
- Fenofibrate may ↓ TC and LDL-C 20%-25%
- Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size
- Fenofibrate ↓ fibrinogen level

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; VLDL-C=very low-density lipoprotein cholesterol.

Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87

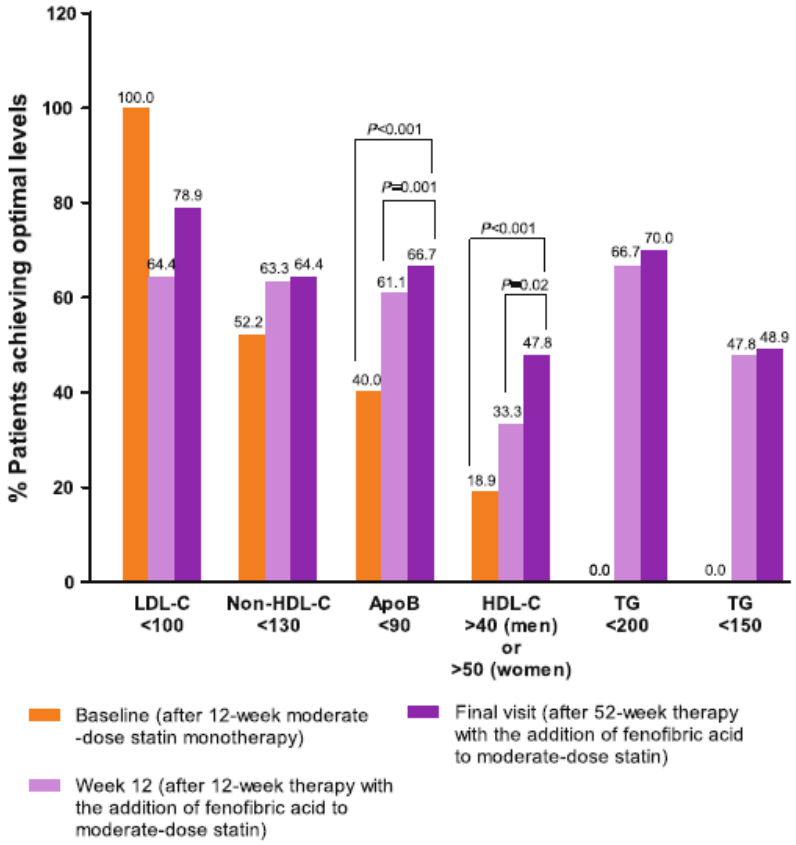
Fibrates: Main Considerations

- Gemfibrozil may ↑ LDL-C 10%-15%[1]
- GI symptoms, possible cholelithiasis[1]
- May potentiate effects of orally administered anticoagulants[1]
- Gemfibrozil may ↑ fibrinogen level[1]
- Gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations[1]
- Myopathy/rhabdomyolysis when used with statin[1]
- Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction[1]
- Fenofibrate dose should be cut by two-thirds and gemofibrozil by one-half when eGFR is 30-59, and fibrates should be avoided when eGFR is <30[2]
- May cause muscle disorders[1]
- Can improve diabetic retinopathy[1]

eGFR=estimated glomerular filtration rate; GI=gastrointestinal; LDL-C=low-density lipoprotein cholesterol.

1. Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87; 2. Tricor (fenofibrate) [PI]; 2018.

Long-Term Efficacy of Adding Fenofibric Acid to Moderate-Dose Statin Therapy in Patients with Persistent Elevated Triglycerides



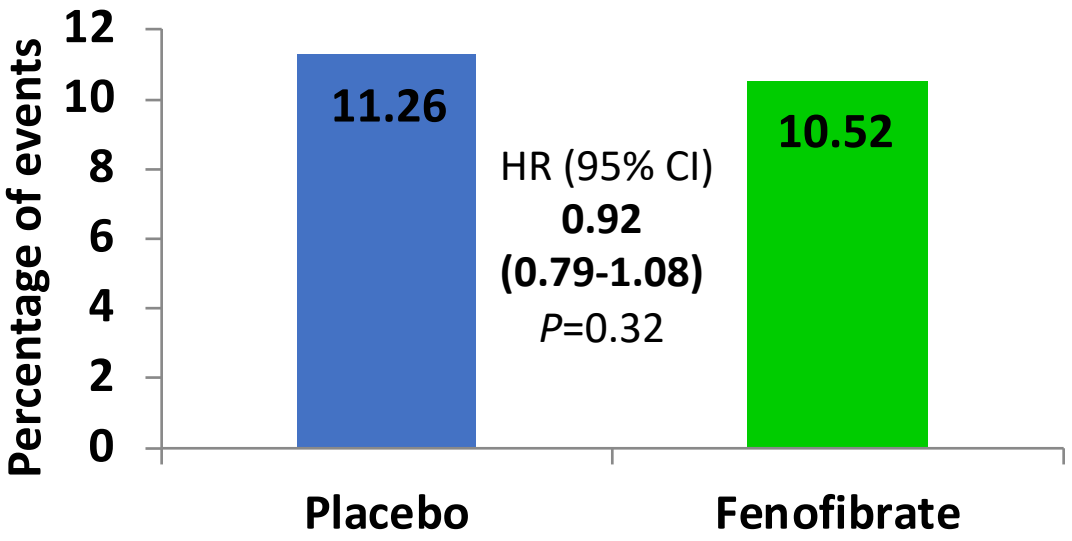
- Proportion of patients with optimal levels of lipids at baseline (after 12 weeks of treatment with moderate-dose statin) and at week 12 and final visit (week 52) after addition of fenofibric acid to moderate-dose statin therapy

ApoB=apoliporotein B; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides. Ballantyne CM, et al. *Cardiovasc Drugs Ther.* 2011 Feb;25(1):59-67.

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study

- Does a statin plus a fibrate reduce CVD* compared to statin monotherapy in T2D patients at high risk for CVD disease?
- All patients (N=5,518) on simvastatin (mean dose: 22.3 mg/day) randomized to fenofibrate (54 mg or 160 mg) or placebo
- Mean follow-up 4.7 years

Baseline cholesterol (all patients)	Mean (mg/dL)
TC	175
LDL-C	100
HDL-C	38
Non-HDL-C	137
TG (median)	162

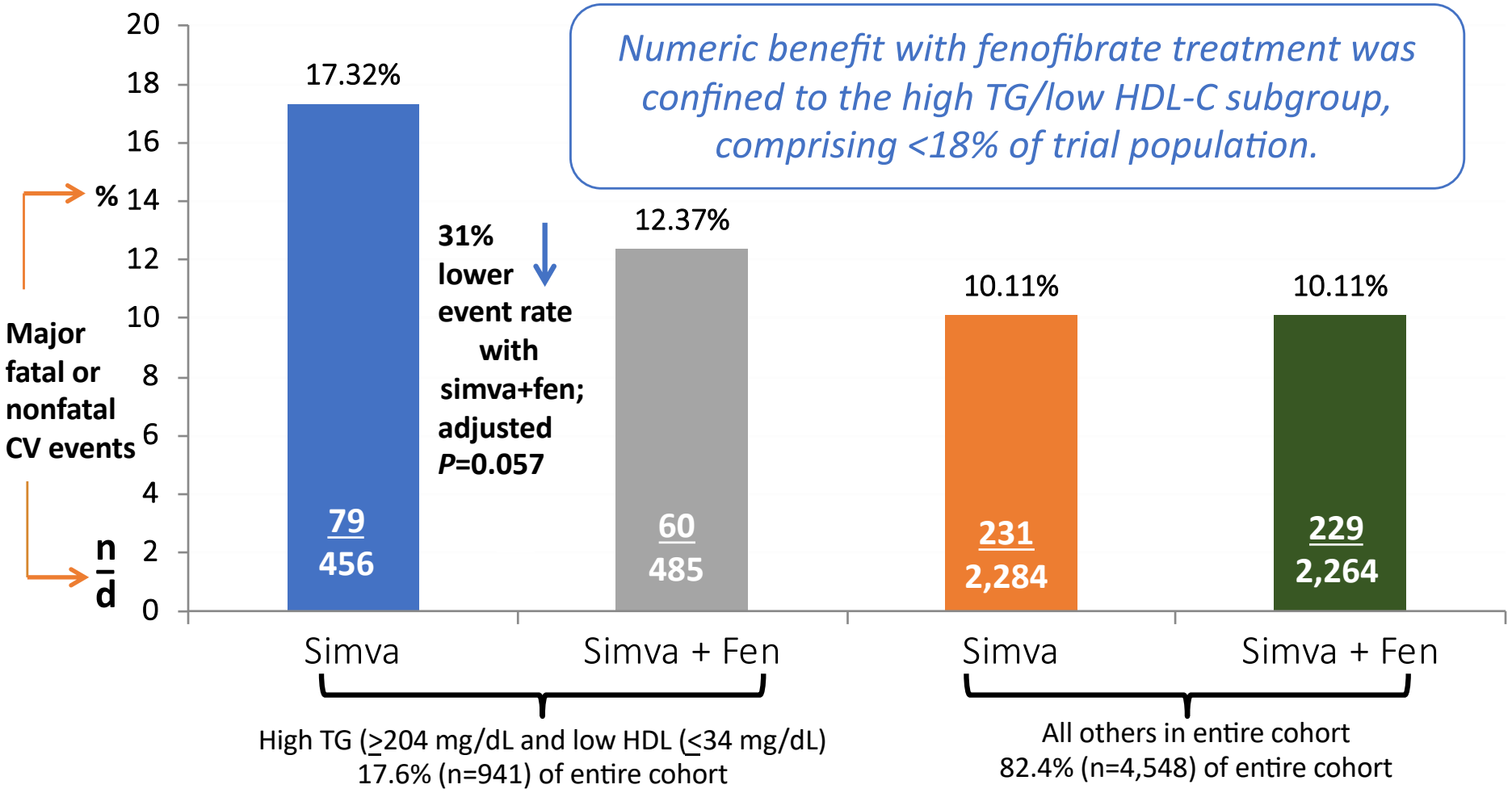


*Primary outcome: first nonfatal MI, nonfatal stroke, or death from CVD

CI=confidence interval; CVD=cardiovascular disease; f/u=follow-up; HDL-C=high-density lipoprotein cholesterol; HR=hazard ratio; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; T2D=type 2 diabetes; TC=total cholesterol; TG=triglycerides.

The ACCORD Study Group. *NEJM.* 2010; 362:1563-1574.

ACCORD-Lipid: Primary Outcomes High TG/Low HDL-C vs All Others in Full Cohort

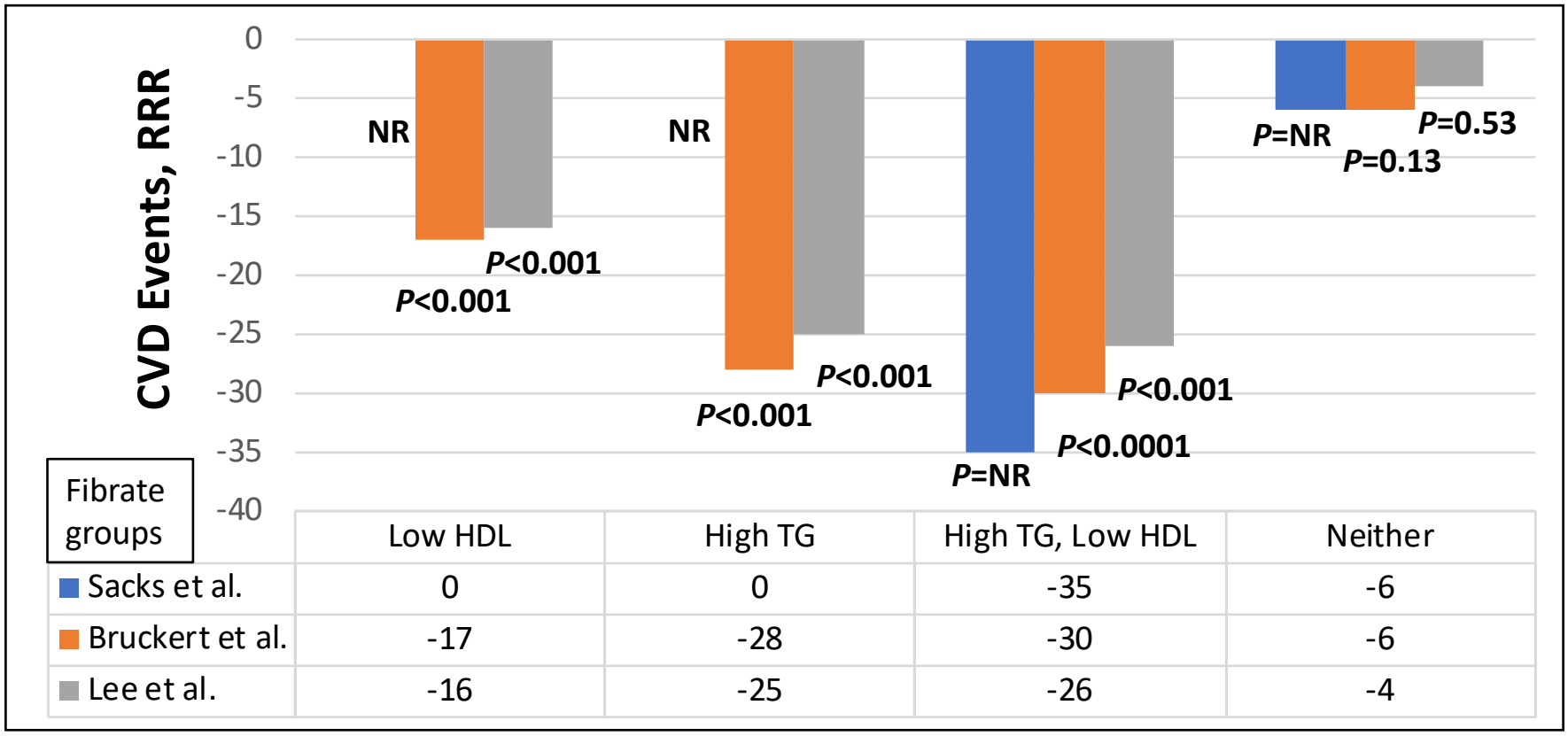


ACCORD=Action to Control Cardiovascular Risk in Diabetes; CV=cerebrovascular; HDL=high-density lipoprotein; HDL-C=high-density lipoprotein cholesterol; TG=triglycerides.

Elam, et al, *Clin Lipidol*. 2011(6):9-20; Ginsberg, et al., The ACCORD Study Group. NEJM. 2010; 362:1563-1574.

Baseline 'Moderate Dyslipidemia' (TG>200, HDL-C<35-40 mg/dL) Predicts 26%-35% Significant CVD Risk Reduction from PPAR-a Agonists (Fibrates = Gemfibrozil, Bezafibrate, Fenofibrate)

HHS, BIP, VA-HIT, FIELD, ACCORD-Lipid



	Low HDL	High TG	High TG, Low HDL	Neither
Sacks et al.	0	0	-35	-6
Bruckert et al.	-17	-28	-30	-6
Lee et al.	-16	-25	-26	-4

ACCORD=Action to Control Cardiovascular Risk in Diabetes; BIP=Bezafibrate Infarction Prevention; CVD=cardiovascular disease; FIELD=Fenofibrate Intervention and Event Lowering in Diabetes; HDL=high-density lipoprotein; HHS=Helsinki Heart Study; NR=not reported; PPAR-a=peroxisome proliferator-activated receptor alpha; TG=triglyceride; VA-HIT=Veterans Affairs High-Density Lipoprotein Intervention Trial.

Bruckert E, et al. *J Cardiovasc Pharmacol* 2011; 57:267–272; Lee M, et al. *Atherosclerosis* 2011;217:492-298; Sacks FM, et al. *N Engl J Med* 2010;363:692–694; Rosenblit PD. *Curr Cardiol Rep*. 2012;14(1):112-124.

Omega-3 Fatty Acids: Starting Dosages, Dose Ranges, and Metabolic Effects

Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
Omega-3 fatty acids			
Omega-3-acid ethyl esters (Lovaza)[1]	4 g per day	4 g per day	Oral
Icosapent ethyl (Vascepa)[2]	4 g per day	4 g per day	Oral

Metabolic Effects:[3]

- ↓ **TG 27%-45%**, TC 7%-10%, VLDL-C 20%-42%, apo B 4%, and non-HDL-C 8%-14% in individuals with severe HTG most likely by reducing hepatic VLDL-TG synthesis and/or secretion and enhancing TG clearance from circulating VLDL particles. Other potential mechanisms of action include: increased ß-oxidation; inhibition of acyl-CoA; 1,2-diacylglyceral acyltransferase; decreased hepatic lipogenesis; and increased plasma lipoprotein activity.
- Icosapent ethyl ↓ LDL-C 5%, whereas, omega-3-acid ethyl esters ↑ LDL-C 45%

Apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; HTG=hypertriglyceridemia; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; VLDL=very low-density lipoprotein. 1. Lovaza (omega-3-acid ethyl esters) [PI]; 2015; 2. Vascepa (icosapent ethyl) [PI]; 2016; 3. Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87.

Omega-3 Fatty Acids: Main Considerations

Main Considerations[1-3]

- Assess TG levels prior to initiating and periodically during therapy.
- Omega-3-acid ethyl esters can increase LDL-C levels. Monitor LDL-C levels during treatment.
- May prolong bleeding time. Monitor coagulation status periodically in patients receiving treatment with omega-3 fatty acids and other drugs affecting coagulation.
- Monitor ALT and AST levels periodically during treatment in patients with hepatic impairment. Some patients may experience increases in ALT levels only.
- Exercise caution when treating patients with a known hypersensitivity to fish and/or shellfish.
- The effect of omega-3 fatty acids on cardiovascular morbidity and mortality and the risk of pancreatitis has not been determined in patients with severe hypertriglyceridemia.
- In patients with paroxysmal or persistent atrial fibrillation, therapy with omega-3-acid ethyl esters may be associated with increased frequency of symptomatic AF or flutter, especially within the first 2 to 3 months after initiation.
- Most common adverse events include arthralgia (2.3%), eructation (4%), dyspepsia (3%), and taste perversion (4%). May also experience constipation, gastrointestinal disorders, vomiting, rash, or pruritus.
- Pharmaceutical doses should be used with caution in nursing mothers and only be used in pregnant women if the benefits of treatment outweigh the potential risk of fetal harm.

AF=atrial fibrillation; ALT=Alanine transaminase; AST=aspartate aminotransferase; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides.

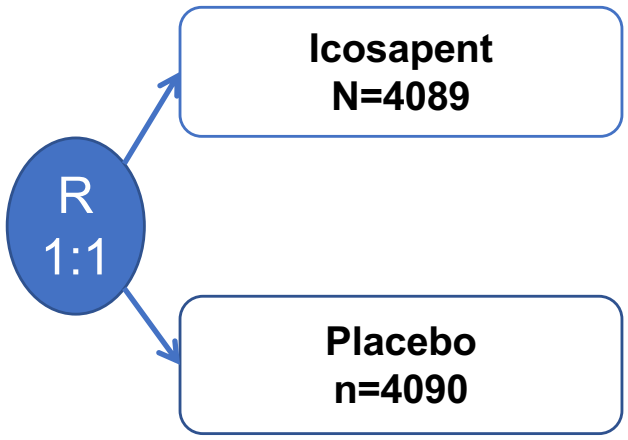
1. Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87; 2. Lovaza (omega-3-acid ethyl esters) [PI]; 2015; 3. Vascepa (icosapent ethyl) [PI]; 2016.

REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial)

REDUCE-IT Study Design and Objectives

Eligibility criteria:

- Age ≥45 years with CVD, or ≥50 years with diabetes with ≥1 additional risk factor for CVD
- Fasting TG levels ≥150mg/dL* and <500 mg/dL
- LDL-C >40mg/dL and ≤100mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to randomization



Primary outcome:
Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

Key secondary outcome:
Composite of CV death, nonfatal MI, or nonfatal stroke

- **Study design:** Phase 3B**,** multi-center, randomized, double-blind, placebo-controlled trial with long-term follow-up at 470 centers, worldwide
- **Primary objective:** To assess whether treatment with icosapent ethyl reduces ischemic events in statin-treated patients with high TG at elevated CV risk

*Due to the variability of TGs, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying TG ≥135 mg/dL. CV, cardiovascular; CVD, cardiovascular disease, LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides. Bhatt DL, et al. *Clin Cardiol*. 2017;40(3)138-148. (Epub prior to print).

Niacin: Starting Dosages, Dose Ranges, Metabolic Effects, and Main Considerations

	Usual recommended starting daily dosage	Dose range	Method of administration
Niacin (nicotinic acid)			
Immediate release[1]	250 mg	250-3,000 mg	Oral
Extended release[2]	500 mg	500-2,000 mg	Oral

Metabolic Effects:[1]

- ↓ ApoB, VLDL, TG 20%-30%
- ↓ LDL-C 10%-25%
- ↑ HDL-C 10%-35% by decreasing hepatic synthesis of VLDL-C-TG and ultimately LDL-C
- ↓ Lipoprotein (a)
- Lowering TG and raising HDL-C is associated with less-atherogenic LDL phenotype B, increased average LDL-P size, decreased LDL-P concentration, and reduced highly atherogenic TG-rich remnant cholesterol

Main Considerations:[1]

- Potential for frequent skin flushing, pruritus, GI symptoms (including abdominal discomfort), hepatoxicity (rare but may be severe), nausea, peptic ulcer, atrial fibrillation
- Increased bleeding may occur, especially when aspirin is utilized to reduce flushing symptoms
- Deleterious effect on serum glucose levels at higher dosages
- Increases uric acid levels, may lead to gout

Apo=apolipoprotein; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; LDL-P=low-density lipoprotein particle; TG=triglyceride; VLDL-C=very low-density lipoprotein cholesterol.

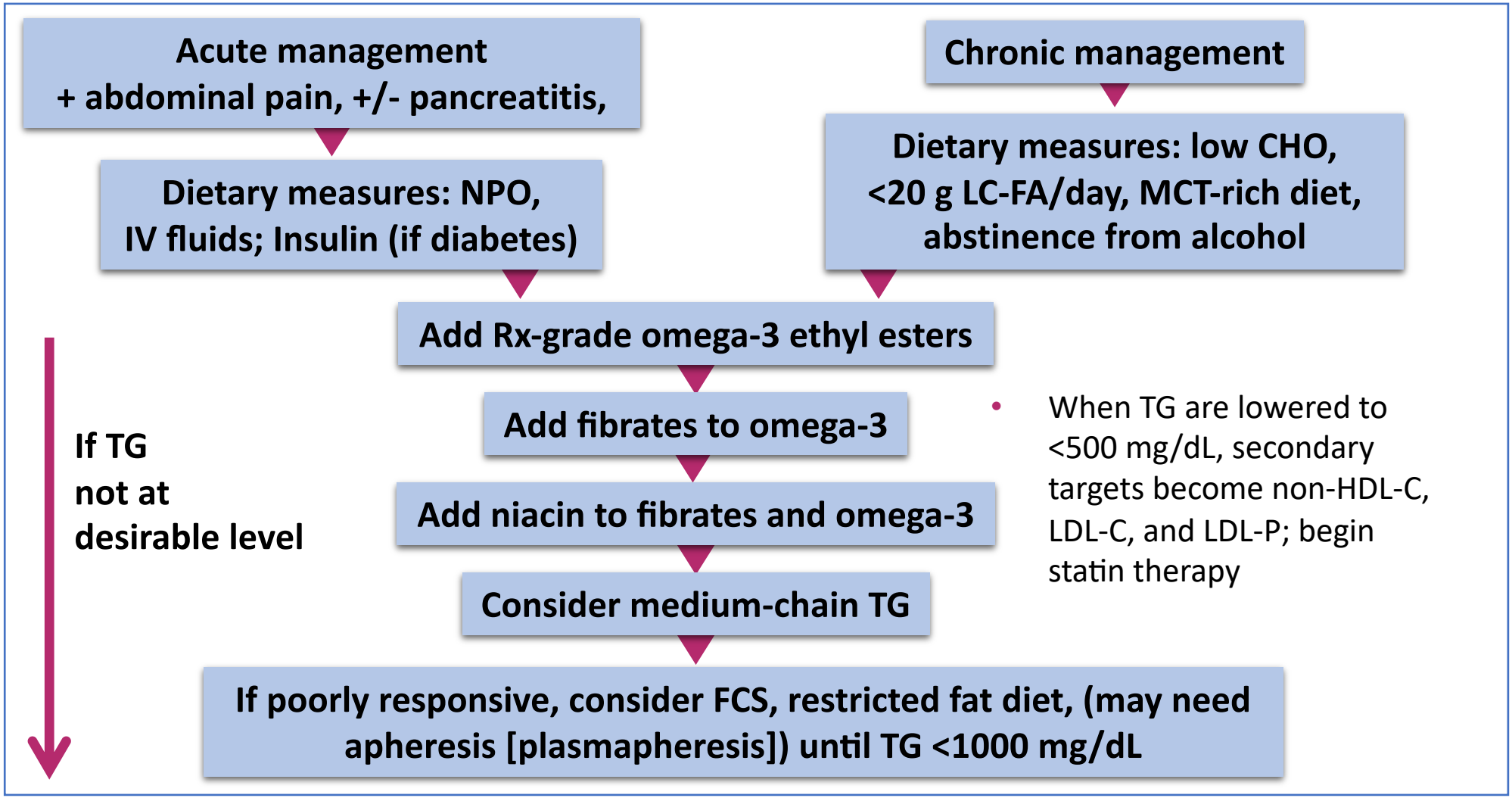
1. Jellinger PS, et al. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87; 2. Niaspan (niacin extended-release) [PI] 2015.

FDA Withdraws Approval of Niaspan ER and Fenofibric Acid DR in Combination with Statins

On April 18th 2016, the FDA announced retraction of prior approvals related to combinations of statins with niacin extended release (ER) and statins with fenofibric acid delayed release (DR).[1] The decision to remove these indications was prompted by evidence from three large published trials, which failed to show reductions in important cardiovascular events when either niacin ER or fenofibric acid DR was added to statin therapy in the populations studied.[2-4] The FDA has concluded that existing evidence does not support

DR=delayed release; ER=extended release; FDA=Food and Drug Administration.
https://www.pbm.va.gov/PBM/linksotherresources/ezminutes/docs/Statins_Niacin_or_Fibrates_EZ_Minutes_submission_5_2016.pdf

Algorithm for Managing Severe Hypertriglyceridemia (TG>1000 mg/dL)



CHO=carbohydrate; FCS=familial chylomicronemia syndrome; HDL-C=high-density lipoprotein cholesterol; IV=intravenous; LC-FA=long-chain fatty acid; IV=intravenous; LDL-C=low-density lipoprotein cholesterol; LDL-P=low-density lipoprotein particle; MCT=medium-chain triglycerides; NPO=nothing by mouth; Rx=prescription; SHTG= severe hypertriglyceridemia; TG=triglyceride.

Ewald N, et al. *Clin Res Cardiol Suppl.* 2012;7:31-35; Bays HE, et al. *J Clin Lipidol*. 2016 Jan-Feb;10(1 Suppl):S1-43.

Ongoing and Planned CV Outcomes Trials Dedicated to Patients with Hypertriglyceridemia

	STRENGTH (Ongoing)	PROMINENT (Planned)
Agent **Dose**	EPA+DHA (FFA) 4 g/d	SPPARMα – Pemafibrate 0.2 mg bid
Population	International	International
N	Estimated 13,000	Estimated 10,000
Age	≥18 years	≥18 years
Risk Profile	CVD (50%) or ↑CVD risk (50%)	T2D only CVD (2/3) or ↑CVD risk (1/3)
Follow-up	3–5 years (planned)	5 years (planned)
Statin Use	100% (at LDL-C goal)	Moderate-/high-intensity or LDL <70 mg/dL
1° EP	Expanded MACE	Expanded MACE
Result	Powered for 15% RRR	Powered for 18% RRR
Entry TG **Entry HDL**	200 to 499 mg/dL <40 mg/dL M, <45 mg/dL W	200 to 499 mg/dL ≤40 mg/dL

CVD=cardiovascular disease; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; HDL=high-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; MACE=major adverse cardiovascular event; PROMINENT=Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes; REDUCE-IT=Reduction of Cardiovascular Events With EPA - Intervention Trial; STRENGTH=STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia; T2D=type 2 diabetes; TG=triglyceride.
http://www.clinicaltrials.gov. PROMINENT: NCT03071692; STRENGTH: NCT02104817.

Summary

- As a component of the insulin resistance (metabolic) syndrome, HTG predicts incident T2D and ASCVD.
- Severe HTG/chylomicronemia predicts high risk for acute pancreatitis.
- Elevated small, dense LDL particle numbers and TG-rich lipoprotein remnants contribute to increased atherogenicity, relative to LDL-C, associated with HTG.
- The TG in TG-rich remnant particles may have independent inflammatory properties.
- AACE recommends screening for and management of HTG as a standard part of a lipid management.
- Recommended TG-lowering therapeutic options for TG>500 mg/dL, to reduce pancreatitis risk include:
  - Fibrates, omega-3 fatty acids, and niacin, usually in combination
  - For TG >180 to 499 mg/dL, maximal-tolerated statins followed by specific TG-lowering agents as needed

AACE=American Association of Clinical Endocrinologists; ASCVD=atherosclerotic cardiovascular disease; HTG=hypertriglyceridemia; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; T2D=type 2 diabetes; TG=triglyceride.