Management of dyslipidaemia in CKD patients: An update

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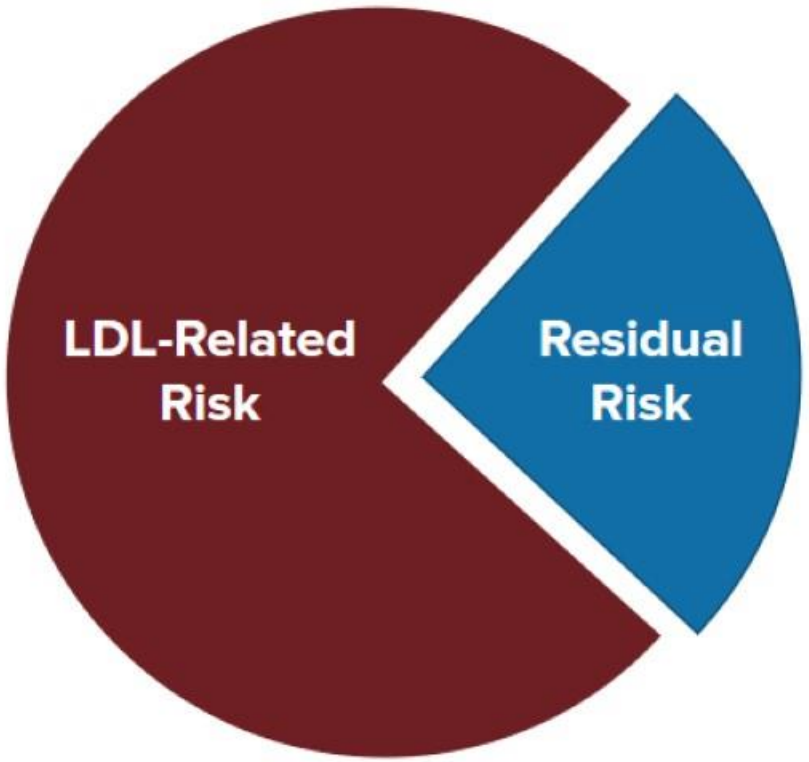
Residual Risk and unmet medical need

Residual Risk in ASCVD

Reducing LDL addresses only a fraction of the overall risk



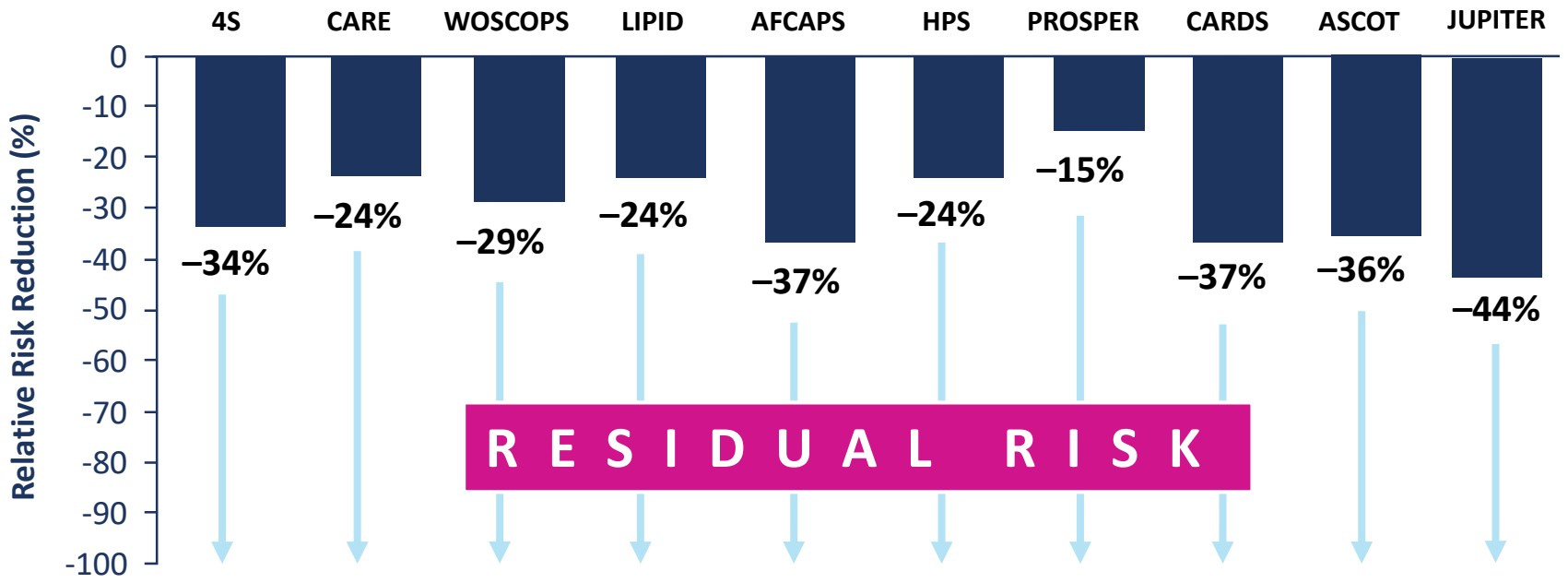
- ↑Triglycerides
- ↓HDL function
- Inflammation
- Membrane instability/oxidation
- Cholesterol crystals
- Endothelial dysfunction
- Lipoprotein oxidation

ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Mason RP. Curr Atheroscler Rep. 2019;21:2.

Patients Remain at Risk Despite Statin Monotherapy

Therapies Based on LDL-C Lowering Reduce the Risk of CAD[1-10]



Despite the benefits of LDL-C lowering, 56% to 85% residual risk remains[1-10]

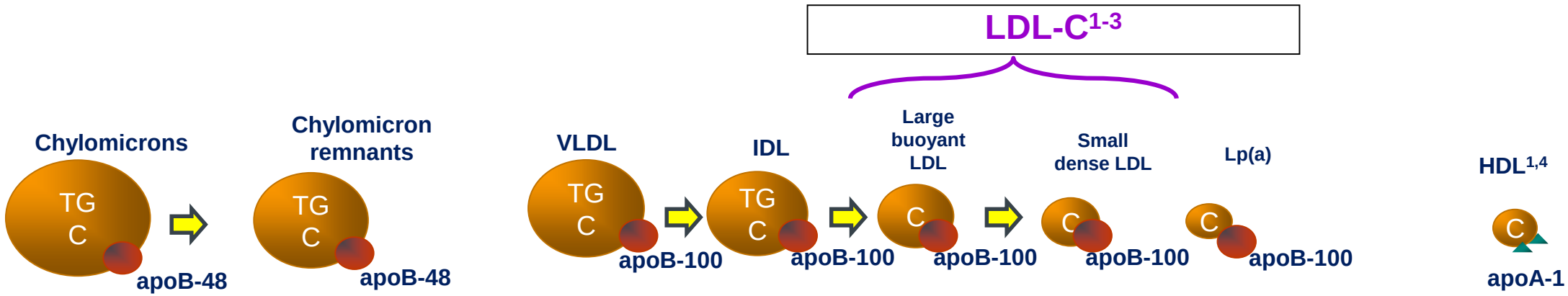
CAD=coronary artery disease.

1. Adapted from Rader DJ et al. http://www.medscape.org/viewarticle/569095. Accessed August 21, 2018; 2. Shepherd J et al. *N Engl J Med*. 1995;333(20):1301-1307; 3. Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344(8934):1383-1389; 4. Ballantyne CM. *Am J Cardiol*. 1998;82(9A):3Q-12Q; 5. Sacks FM et al. *N Engl J Med*. 1996;335(14):1001-1009; 6. Downs JR et al. *JAMA*. 1998;279(20):1615-1622; 7. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339(19):1349-1357; 8. Brown BG. *Eur Heart J Suppl*. 2005;7(suppl F):F34-F40; 9. Grundy SM et al. *Circulation*. 2004;110(2):227-239; 10. Ridker PM et al. *N Engl J Med*. 2008;359(21):2195-2207.

LDL-C vs Non-HDL-C

LDL-C Is a Risk Factor for CHD

- Multiple lines of evidence (animal studies, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled trials) indicate a strong causal association between elevated LDL-C and CHD[1]



CHD = coronary heart disease; TG = triglyceride; Apo = apolipoprotein; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein (a); C = cholesterol.

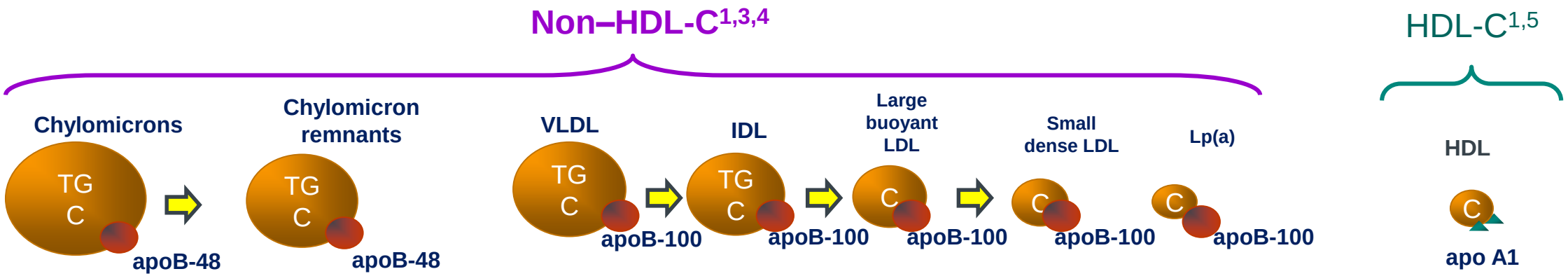
1. NCEP ATP III Expert Panel. *Circulation*. 2002;106:3143–3421. **2.** Rana JS et al. *Curr Opin Cardiol*. 2010;25:622–626. **3**. Chapman MJ et al. *Eur Heart J Suppl*. 2004;6(suppl A):A43–A48.
4. Barter P. In: Ballantyne CM. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Saunders, an imprint of Elsevier Inc; 2009:387–395. **5**. Walldius G et al. *J Intern Med*. 2004;255:188–205.

Non–HDL-C Is a Risk Factor for CHD

Non–HDL-C represents the cholesterol content of all apoB-containing lipoproteins, including VLDL, IDL, LDL, Lp(a), and chylomicrons and chylomicron remnants[1,2]

- Non–HDL-C = total cholesterol – HDL-C[1]

When TG levels are ≥200 mg/dL (~2.3 mmol/L), non–HDL-C may better represent the concentration of all atherogenic lipoproteins than does LDL-C alone[1]



Adapted with permission from Walldius G et al.[6]

Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.

CHD = coronary heart disease; ApoB = apolipoprotein B; VLDL = very low-density lipoprotein; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein (a); TG = triglyceride; CV = cardiovascular; C = cholesterol; CAD = coronary artery disease.

1. NCEP ATP III Expert Panel. *Circulation*. 2002;106:3143–3421. **2**. Rana JS et al. *Curr Opin Cardiol*. 2010;25:622–626. **3.** Hoenig MR. *Vasc Health Risk Manag*. 2008;4:143–156. **4**. Chapman M et al. *Eur Heart J Suppl*. 2004;6(suppl A):A43–A48. **5.** Barter P. In: Ballantyne CM. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Saunders, an imprint of Elsevier Inc; 2009:387–395 **6.** Walldius G et al. *J Intern Med*. 2004;255:188–205.

Non-HDL-cholesterol
Advantages as a target for treatment

Non-HDL-c = Total Cholesterol – HDL-c

- Non-HDL-c includes an **assessment of all apo B-containing lipoproteins** considered to be atherogenic (good correlation with apo B)[1]
  - VLDL, IDL, LDL, and even Lp(a)
- Non-HDL-c is an indirect **estimate of LDL particle number**, and LDL particle number relates more closely to CVD risk than LDL-c[2]

1. Aguiar C et al. *Atheroscler Suppl* **2015**;19:1.
2. Sniderman A et al. *J Clin Lipidol* **2010**;4:152. 3. Nordestgaard BG et al. *Eur Heart J* **2016**;37:1944.

Non-HDL-cholesterol
Advantages as a target for treatment

- Non-HDL-c makes no assumption about the relationship between VLDL-c and TGs
  - In T2DM, this relationship can be altered, leading to **falsely low LDL-c values** as calculated by the Friedewald formula

- **Practical advantages**
  - **Does not require fasting**[3]
  - Easily calculated (difference between 2 well standardized assays) and inexpensive (vs apo B)
  - **Can be used in patients with TG >400 mg/dL (4.5 mmol/L)**

1. Aguiar C et al. *Atheroscler Suppl* **2015**;19:1.
2. Sniderman A et al. *J Clin Lipidol* **2010**;4:152. 3. Nordestgaard BG et al. *Eur Heart J* **2016**;37:1944.

Disadvantage of using LDL-c is the methodologic limitation of its calculations using Friedewald´s equation, which cannot be used in the setting of hypertriglyceridemia

LDL* = (TC) - (HDL-C) - (TG/5)

*Valid only when concentrations of triglycerides are less than 4.5 mmol/L (400 mg/dL)

Friedewald equation

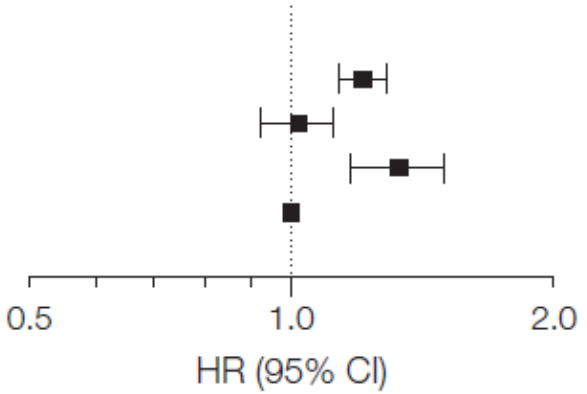
- This method is valid only for values obtained during the **fasting state** and becomes increasingly **inaccurate** when TG ≥ 200 mg/dl and **invalid** when TG ≥ 400 mg/dl, respectively (Grade C)

Patients reaching the LDL-C but not the Non-HD-C target have a 32% significant higher cardiovascular risk

A meta-analysis of statins RCTs. Individual patient data were requested and obtained for **62,154 patients** enrolled **in 8 trials**, published between 1994 and 2008 to study the association of LDL-C, Non-HDL-C and Apo-B with risk of cardiovascular events among patients treated with statins

Risk of Major Cardiovascular Events by LDL and non-HDL Cholesterol Categories

Target Level		No. of Major Cardiovascular Events	Total No. of Participants	HR (95% CI)
LDL-C	Non–HDL-C			
≥100 mg/dL	≥130 mg/dL	1877	10419	1.21 (1.13-1.29)
≥100 mg/dL	<130 mg/dL	467	2873	1.02 (0.92-1.12)
<100 mg/dL	≥130 mg/dL	283	1435	1.32 (1.17-1.50)
<100 mg/dL	<130 mg/dL	2760	23426	1.00 [Reference]

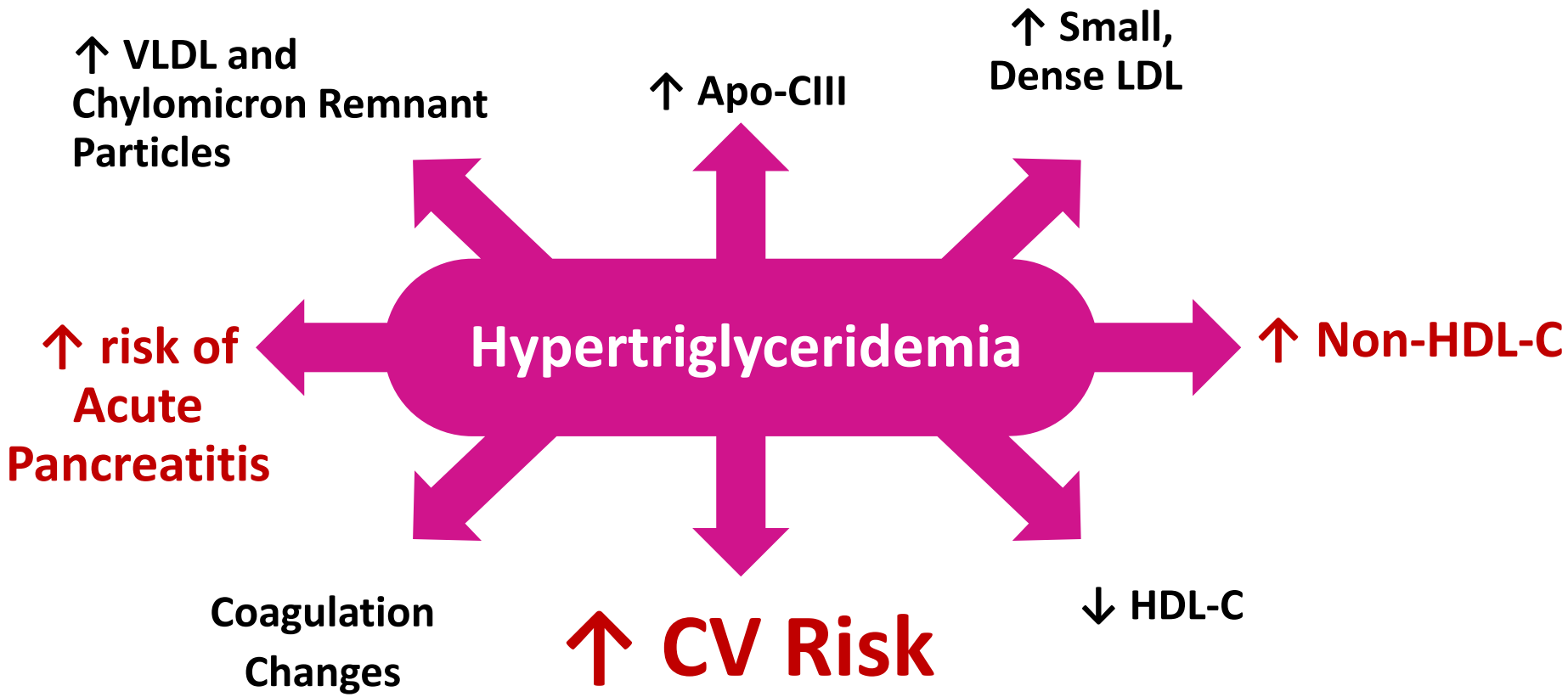


Among statin-treated patients, on-treatment levels of LDL-C, Non– HDL-C, and Apo-B were each associated with risk of future major cardiovascular events, but **the strength of this association was greater for non–HDL-C than for LDL-C and Apo-B**

Boekholdt et al. Association of LDL Cholesterol, Non–HDL Cholesterol, and Apolipoprotein B Levels With Risk of Cardiovascular Events Among Patients Treated With Statins A Meta-analysis, JAMA, March 28, 2012—Vol 307, No. 12

DOES High Triglyceride Have Deleterious Effects?

High Triglycerides Have Many Deleterious Effects

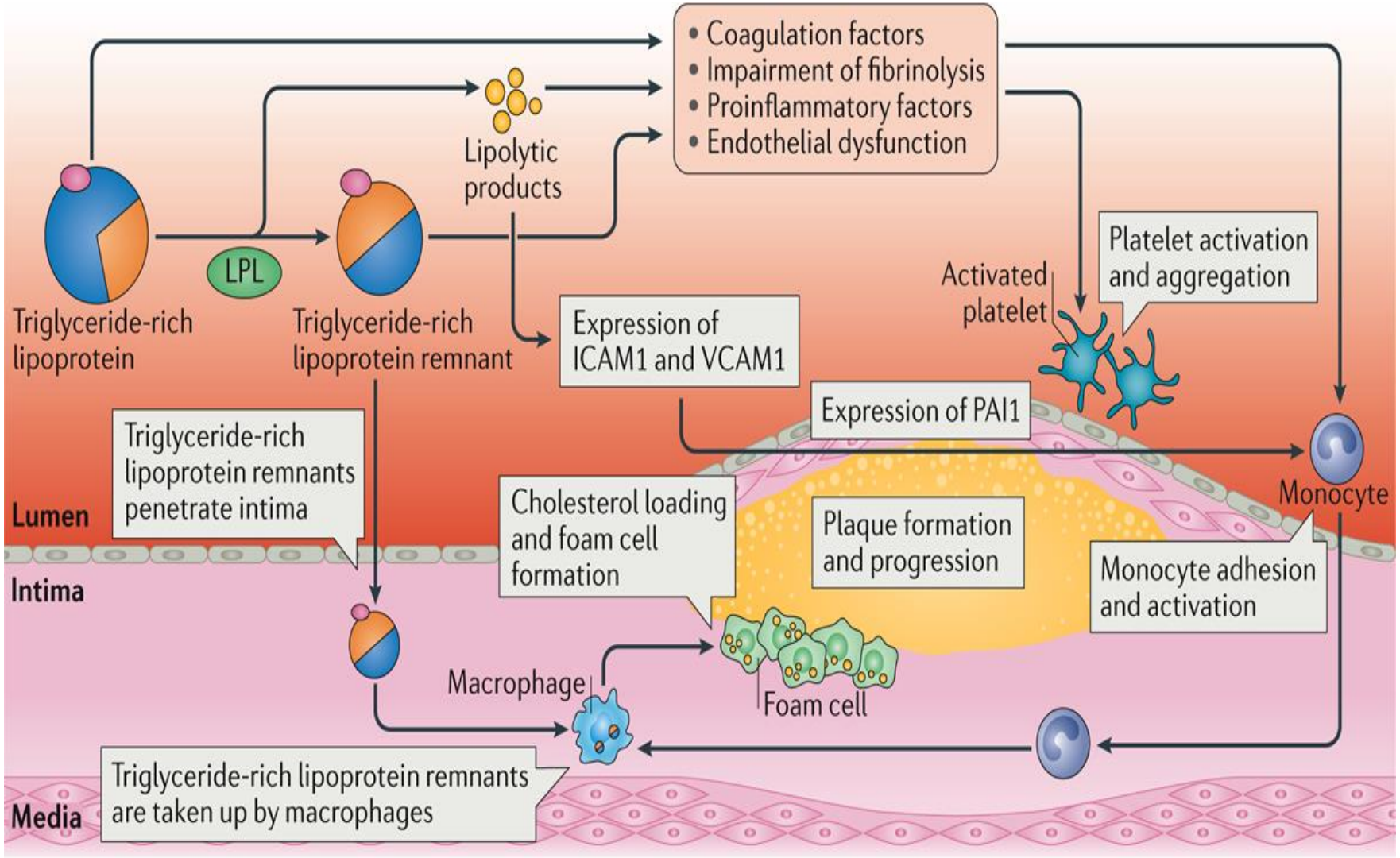


1. Bays H, et al. *Expert Rev Cardiovasc Ther*. 2008;6:391-409. 2. Stevens T, et al. *Acute Pancreatitis*. Available at: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/acute-pancreatitis/. Accessed December 30, 2013.

TG-rich Lipoproteins (TRLs): Postulated Mechanisms in Atherogenesis

Direct Toxic Effects

Remnant Cholesterol Entrapment



Nature Reviews | Cardiology

Reiner,Z
Nature Rev Cardiology
2017, 7: 401-411

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Classification of Elevated Triglyceride Levels

TG levels that are even moderately elevated (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome. TG levels ≥200 mg/dL may indicate a substantial increase in ASCVD risk. Hypertriglyceridemia is also commonly associated with a procoagulant state and hypertension.

TG category	TG concentration (mg/dL)	TG goal
Normal	<150 (1.7 mmol/L)	<150 mg/dL (<1.7 mmol/L)
Borderline high	150-199 (1.7-2.2 mmol/L)	
High	200-499 (2.3-5.5mol/L)	
Very high	≥500	

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; TG, triglycerides.

Einhorn D, et al. *Endocr Pract*. 2003;9:237-252; Frick MH, et al. *NEJM*. 1987;317:1237-1245; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Keech A, et al. *Lancet*. 2005;366:1849-1861; NHLBI. NIH Publication No. 02-5215. 2002; Tenaknen L, et al. *Arch Intern Med*. 2006;166:743-748.

Secondary Causes HTG

Table 1. Clinical Conditions and Drugs Associated With HTG

Clinical conditions
Overweight or obesity*
Insulin resistance or metabolic syndrome*
Diabetes mellitus, especially with poor glycemic control*
Alcohol consumption, especially if in excess*
Excess sugar intake, especially if added in food processing
High saturated fat intake
Hypothyroidism†
Chronic kidney disease
Nephrotic syndrome*
Sedentary lifestyle
Pregnancy (especially third trimester)*
Lipodystrophy*
Systemic inflammatory diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, many infections)

Drugs
Oral estrogen* (contraceptives or postmenopausal replacement)
Tamoxifen*
Systemic glucocorticoids*
Retinoic acid derivatives*
Nonselective β-blockers
Thiazide and loop diuretics
Antiretroviral protease inhibitors*
Atypical antipsychotics (eg, clozapine, olanzapine, risperidone)
Sirolimus,* cyclosporine A,† and tacrolimus
Cyclophosphamide

HTG indicates high triglyceride.
*May cause a major increase in triglycerides.
†More commonly causes increased low-density lipoprotein cholesterol with little impact on triglycerides.
Data derived from Miller et al,[1] Yuan et al,[14] and Herink and Ito.[15]

Circulation. 2019;140:e673–e691
September 17, 2019

Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease

Question: Which screening tests should be used?

Recommendations associated with this question:

Non-HDL-C

- **R24. Non-HDL-C (total cholesterol minus HDL-C) should be calculated to assist risk stratification in individuals with moderately elevated TG (200 to 500 mg/dL), diabetes, and/or established ASCVD (Grade B; BEL 2).**
- **R25.** If insulin resistance is suspected, non-HDL-C should be evaluated to gain useful information regarding the individual's total atherogenic lipoprotein burden **(Grade D)**.

Triglycerides

- **R26. TG levels should be part of routine lipid screening: moderate elevations (≥150 mg/dL) may identify individuals at risk for insulin resistance syndrome and levels ≥200 mg/dL may identify individuals at substantially increased ASCVD risk (Grade B; BEL 2).**

200 mg/dl=2.3mol/L

Apolipoproteins

- **R27.** Apo B and/or an apo B/apo A1 ratio calculation and evaluation may be useful in at-risk individuals (TG ≥150, HDL-C <40, prior ASCVD event, T2DM, and/or insulin resistance syndrome [even at target LDL-C levels]) to assess residual risk and guide decision-making **(Grade A; BEL 1)**.
- **R28.** Apo B measurements (reflecting the particle concentration of LDL and all other atherogenic lipoproteins) may be useful to assess the success of LDL-C–lowering therapy **(Grade A; BEL 1)**.

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Evidence for TG Levels ≥200 mg/dL(2.3mol/L) may identify individuals at substantially increased ASCVD risk ?

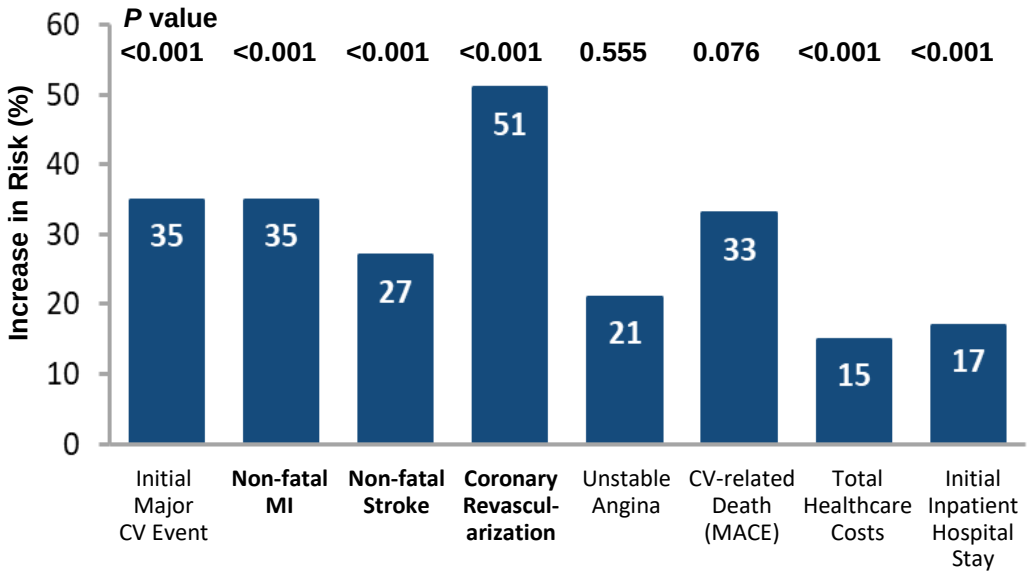
Plethora of Genetic Data Support Causative Role of TGs in ASCVD

Genetic data supporting causative role of TGs in ASCVD: mutational analyses				
Reference	**N**	**Variable**	**Effect on TGs**	**Effect on CV Outcomes**
Jorgensen 2014	75,725	ApoC-III null mutations	-44% (P<0.001)	IVD: HR=0.59 (95% CI: 0.41-0.86; P=0.007) IHD: HR=0.64 (95% CI: 0.41-0.99; P=0.04)
Crosby 2014	3,734	ApoC-III null mutations	-39% (P=6 x 10^{-9})	CHD: OR=0.60 (95% CI: 0.47-0.75; P=4 x 10^{-6})
Natarajan 2015	6,699	ApoC-III null mutations	-43.7% (P=1.83 x 10^{-21})	CAC: -27.9 U (95% CI: -51.1 to -4.7; P=0.019)
Dewey 2016	42,930	ANGPTL4 variants	-13% (P=2 x 10^{-23})	CAD: OR=0.81 (95% CI: 0.70-0.92; P=0.002)
Stitziel 2016	120,575	ANGPTL4 variants	-0.3 SD per allele	CAD: OR=0.86 (P=4.0 x 10^{-8})
Do 2015	13,432	ApoA-V mutations	+61% (P=0.007)	MI/CAD: OR=2.2 (P=5 x 10^{-7})
Genetic data supporting causative role of TGs in ASCVD: genome-wide association analyses				
Reference	**N**	**Study Type**	**Key Results**	
Willer 2013	188,578	Linear regression of 149 lipid SNPs	TG effect size correlated with CAD (Pearson r=0.46; P= -0.02)	
Varbo 2013	188,577	Multivariate analysis of 185 lipid SNPs	TG effect size correlated with CHD after adjusting for LDL-C and HDL-C effect sizes (P=1 x 10^{-9})	

Budoff M. *Am J Cardiol*. 2016;118(1):138-145.

Real-World Data (Optum): Patients With Elevated TG Have Higher CV Risk and Costs

Outcomes, Costs, and Hospitalization in Statin-Treated Patients With TG 200–499 mg/dL*,†



Compared with lower-TG patients, high-TG patients:

+35%
⬆ in Major CV Event Rate

+15%
⬆ in Total Healthcare Costs

+17%
⬆ in Inpatient Hospital Stays

ASCVD=atherosclerotic cardiovascular disease; MI=myocardial infarction.

Data from retrospective administrative claims analysis of adults ≥45 years with diabetes and/or ASCVD on a statin, with TG 200–499 mg/dL (n=13,411) compared with those of comparator control (TG <150 mg/dL and HDL-C >40 mg/dL, n=32,506). Baseline LDL-C was 106 mg/dL and 101 mg/dL, respectively (*P*<0.001) for propensity scored matched cohorts.

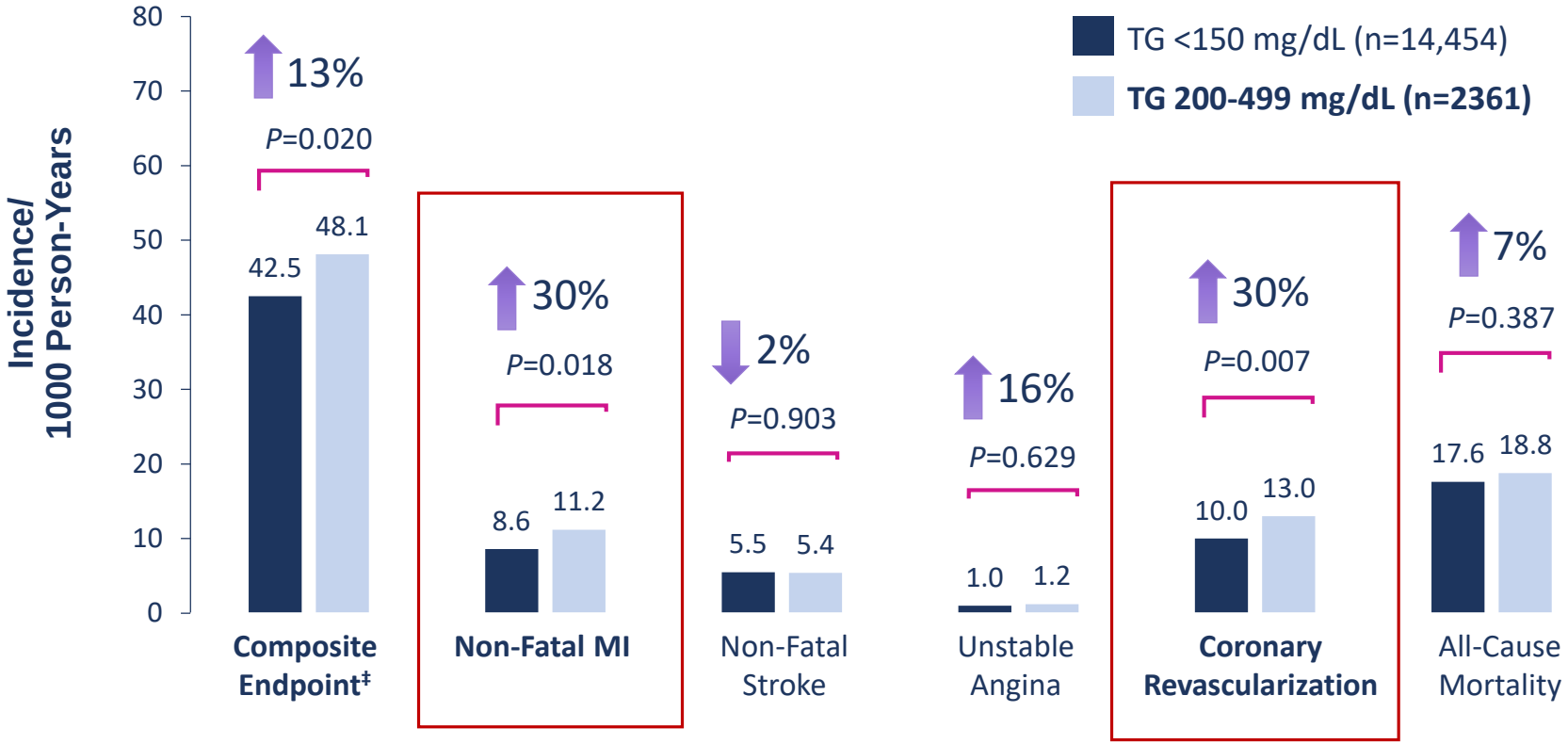
*Separate multivariate analyses of major CV events, total healthcare costs, and initial inpatient stay were performed. Covariates included TG cohort, age, gender, insurance coverage type, geographic region of enrollment, baseline clinical characteristics, and baseline medication use; †Cox proportional hazards model was used for all multivariate analyses except "Total Healthcare Costs," which used a generalized linear model.

Toth PP et al. *J Am Heart Assoc*. 2018;7(15):e008740.

GLF2342907

NEW: Real-World Data (Kaiser) Reported Increased CV Risk in Patients With HTG Despite Statin Therapy*

Adjusted Incidence Rates and Rate Ratios† in Patients With ASCVD on Statin Therapy With LDL-C 40–100 mg/dL



ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index. LDL-C=low-density lipoprotein cholesterol.

*Mean follow-up of 4.2 years.

†Controlled for age, sex, non-white race, BMI, smoking, systolic blood pressure, creatinine, and use of insulin or sulfonylureas.

‡Composite endpoint includes non-fatal MI, non-fatal stroke, unstable angina, revascularization, and all-cause mortality.

Nichols GA et al. *Circulation*. 2017;136(suppl 1):A14161.

GLF2342907

Management of HTG

What Should Clinicians Do in Patients With ASCVD and High TGs?

Diet and lifestyle modifications

- Very effective at lowering TGs

Fibrates

- Can lower TGs but inconsistent RCT-based evidence in CV risk reduction

Omega-3 fatty acids

Kim NH, et al. Diabetes Metab J. 2020;44: 213-221.

Impact of Specific Lifestyle Changes on TG Levels
2019 ESC/EAS Guidelines

Lifestyle Interventions to Reduce TG-Rich Lipoprotein Levels	Magnitude of the Effect	Level
Reduce excessive body weight	+	A
Reduce alcohol intake	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrates	++	A
Use supplements of n-3 polyunsaturated fats	++	A
Reduce intake of mono- and disaccharides	++	B
Replace saturated fats with mono- or polyunsaturated fats	+	B

+++, > 10%; ++, 5% to 10%; +, < 5%.

Mach F, et al. Eur Heart J. 2020;41:111-188.

Fenofibrate: Optimizing CVD outcomes in T2DM

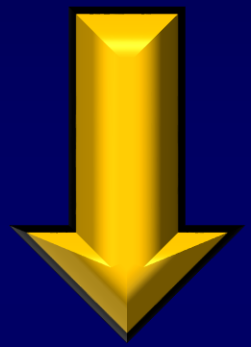
Trial	Patient population		Outcomes	
FIELD[1,2]	9795 patients with T2DM • **22% patients with CVD**	**All patients** Baseline median TG levels of 1.7 mmol/L **Non-fatal MI + CHD death** **RRR 11% (p=0.16)**	**Patients with TG ≥2.30 mmol/L and HDL <1.30/1.29 mmol/L men/women**[a] **Total CV events (CV deaths, MI, stroke, revascularisation)** **RRR 27% (p=0.005)**	NNT_5=23
ACCORD Lipid[3,4]	5518 patients with T2DM • **37% patients with CVD**	**All patients** Baseline median TG levels of 1.8 mmol/L **CVD death, non-fatal MI + non-fatal stroke** **RRR 8% (p=0.32)**	**Patients with TG ≥2.3 mmol/L and HDL-c ≤0.9 mmol/L**[b] **CVD death, non-fatal MI + non-fatal stroke** **RRR 31% (p=0.032)**	NNT_5=20

[a]Post-hoc analysis of data from the FIELD trial[2]; [b]Pre-specified subgroup analysis for ACCORD Lipid trial

C, cholesterol. CHD, coronary heart disease. CVD, cardiovascular disease. HDL, high density lipoprotein.
MI, myocardial infarction. NNT_5, number needed to treat for 5 years. T2DM, type 2 diabetes mellitus. TG, triglycerides.

1. Keech A et al. *Lancet* **2005**;366:1849.
2. Scott R et al. *Diabetes Care* **2009**;32:493. 3. Ginsberg HN et al. *N Engl J Med* **2010**;362:1563.
4. FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting. 19 May 2011.

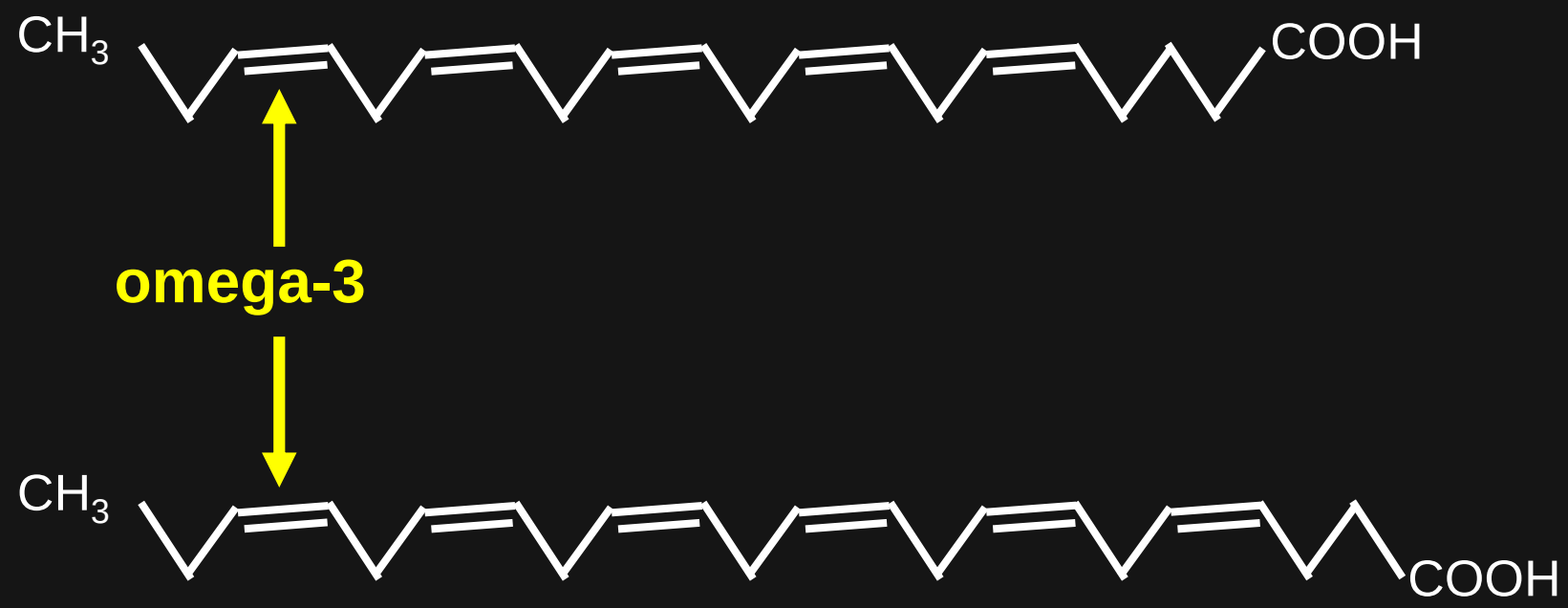
Management of HTG



Omega n-3 Fatty Acids

Active Ingredients of Omega-3

Eicosapentaenoic acid (EPA) *c20:5* (omega-3) 46%



Docosahexaenoic acid (DHA) *c22:6* (omega-3) 38%

Mechanism of Action

The use of Omega-3 (EPA +DHA) in Hypertriglyceridemia, ESC 2019

ESC
European Society of Cardiology

8.8 n-3 fatty acids

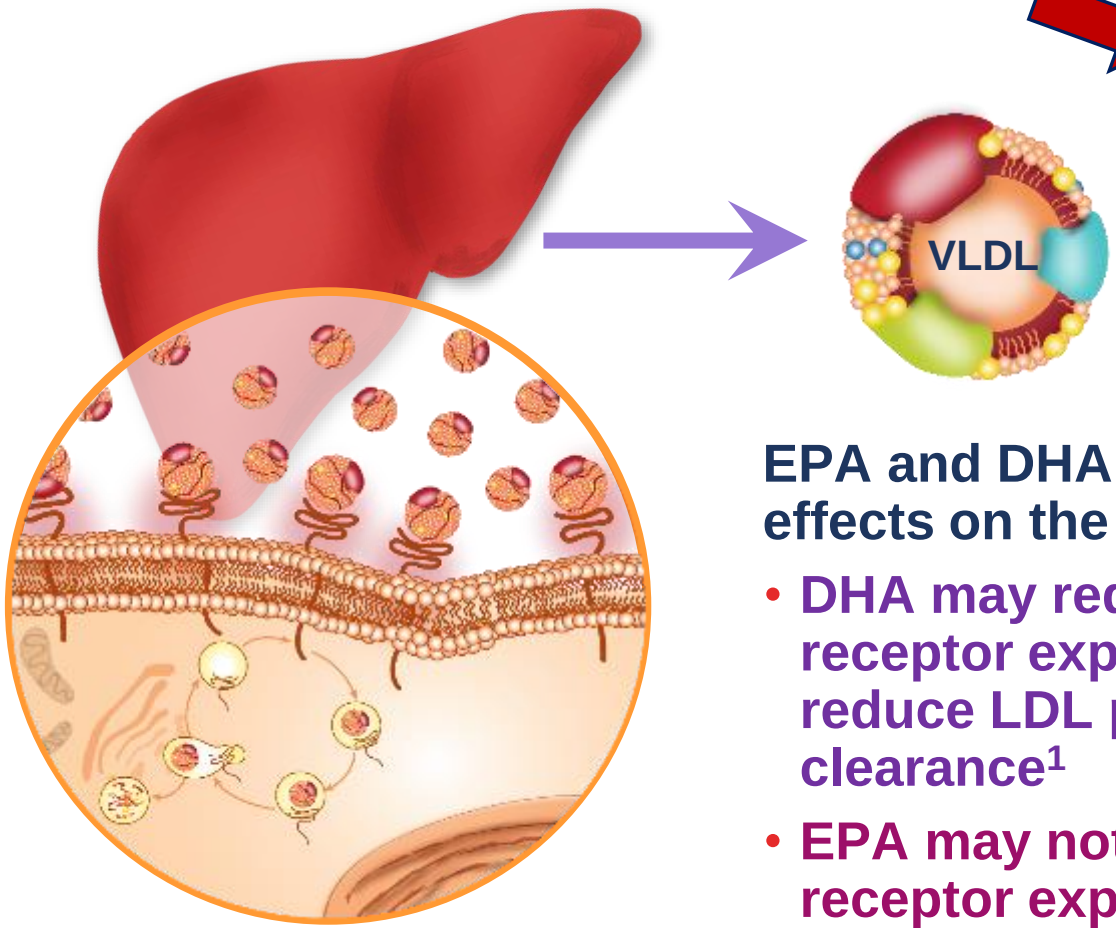
8.8.1 Mechanism of action

The n-3 (or omega-3) fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] can be used at pharmacological doses to lower TGs. n-3 fatty acids (2–4 g/day) affect serum lipids and lipoproteins, in particular VLDL concentrations. The underlying mechanism is poorly understood, although it may be related, at least in part, to their ability to interact with PPARs and to decreased secretion of ApoB.

Omega -3 appears to reduce production of triglycerides in the liver, and to enhance clearance of triglycerides from circulating (VLDL) particles

mechanisms include increased breakdown of fatty acids; inhibition of diglyceride acyltransferase which is involved in biosynthesis of triglycerides in the liver; and increased activity of lipoprotein lipase in blood

EPA and DHA Are Distinct Omega-3 Fatty Acids With Different Effects[1,2]



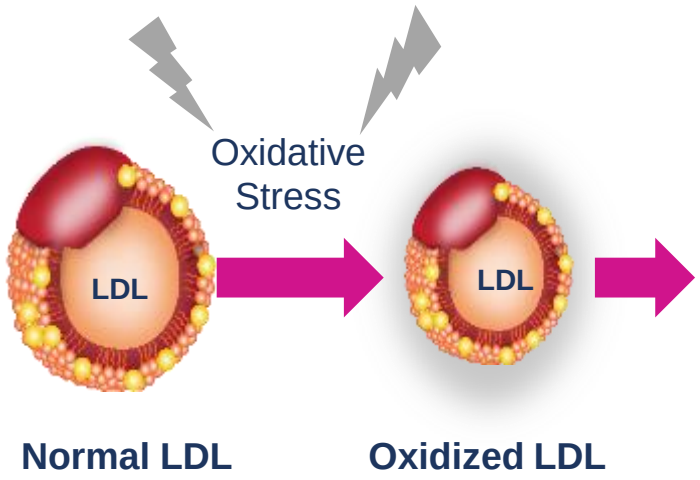
Both EPA and DHA may reduce VLDL secretions and induce Apo B degradation, as demonstrated in an animal model

EPA and DHA have different effects on the LDL receptor

- **DHA may reduce LDL receptor expression and reduce LDL particle clearance[1]**
- **EPA may not impact LDL receptor expression and may increase LDL particle clearance**

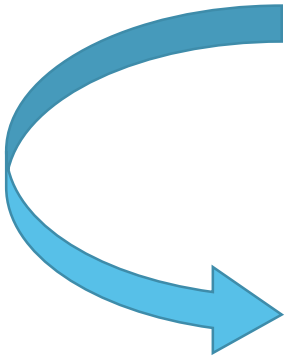
1. Ishida T et al. *Prostaglandins Leukot Essent Fatty Acids*. 2013;88(4):281-288; 2. Wei MY, Jacobson TA. *Curr Atheroscler Rep*. 2011;13(6):474-483.

HTG Leads to Dysfunctional sdLDL: ↑LDL Oxidation, ↓LDL Clearance, and ↑Atherogenicity [1,2]

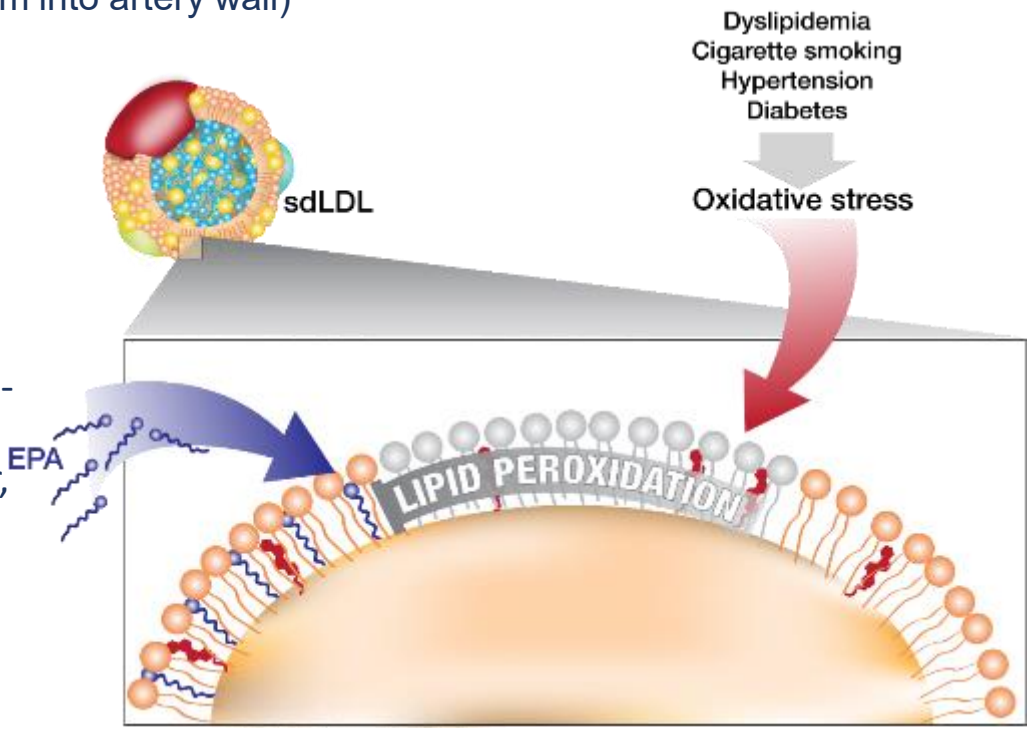


Abnormal LDL & Macrophage Metabolism

- ↑LDL oxidation
- ↓LDL receptor binding (↓LDL clearance)
- ↑Monocyte chemoattraction
- ↑Monocyte adhesion to endothelial cells
- ↑Monocyte chemotaxis (through endothelium into artery wall)
- ↑Monocyte→ macrophage conversion
- ↑LDL uptake by macrophages
- ↑Foam cell formation



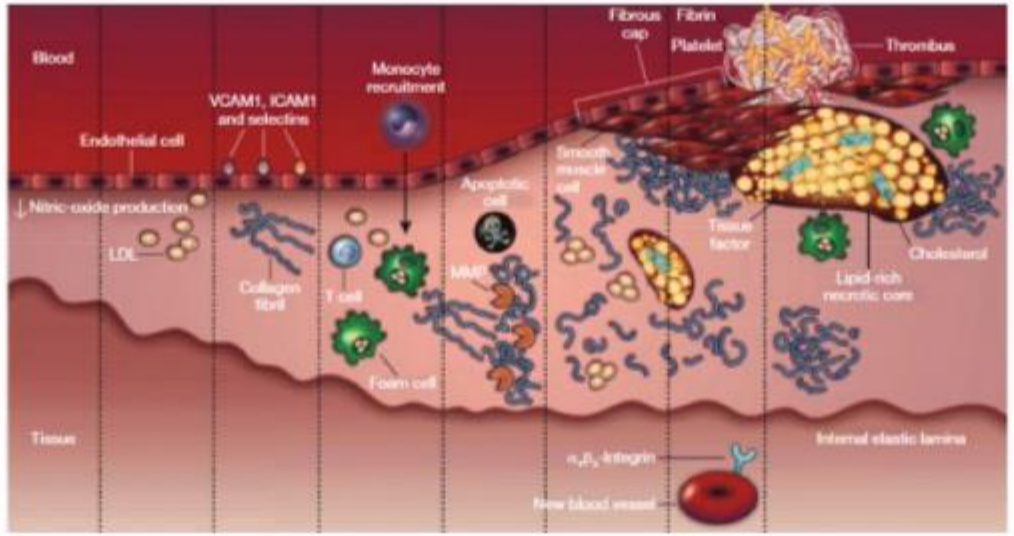
EPA is believed to block free-radical propagation through the phospholipid monolayer, **preventing lipid oxidation and deleterious changes** in lipid structural organization



1. Maiolino G et al. *Mediators Inflamm*. 2013;2013:714653; 2. Niki E. *J Clin Biochem Nutr*. 2011;48(1):3-7.

Potential Effects of Omega-3 on Plaque Development

Pathological Parameters and Processes in Atherosclerosis				
Circulating parameters	Endothelial cell dysfunction & activation	Inflammation, monocyte recruitment, & proteolysis	Lipid core and fibrous cap formation with ongoing inflammation	Plaque formation, progression, & thrombosis
Beneficial Effects of EPA				
↓TG ↓Non-HDL-C ↓ApoB ↓VLDL-C	↑Antioxidant effects ↑Endothelial function ↓Cholesterol crystalline domains ↓RLP-C	↑EPA/AA ratio ↑Resolvins, protectins & IL-10 ↓Inflammation: Ox-LDL, IL-6, hsCRP, $LpPLA_2$, & ICAM-1 ↓Monocyte adhesion ↓MMPs	↑Fibrous cap thickness ↑Lumen diameter ↓Macrophages ↓Foam cell formation ↓Ongoing inflammation	↑Plaque stability ↓Plaque formation & progression ↓Plaque volume & vulnerability ↓Arterial stiffness ↓Platelet response ↓Thrombosis



Nemiroff RL. *Contemp OB/GYN*. 2016:61.

Table 2. Triglyceride-Lowering Efficacy of Non–n-3 FA Agents

Drug	Approximate Efficacy, % Triglyceride Lowering
Fibrates	30–50
Immediate-release niacin	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

PCSK9-I 16

n-3 FA indicates omega-3 fatty acid.

September 17, 2019

Circulation. 2019;140:e673–e691

AHA Science Advisory

Table 5. Summary Statements About the Effects of n-3 FA in Managing HTG

	Summary Statements
Triglycerides 200–499 mg/dL	≈20%–30% reduction in triglycerides and no LDL-C increase with 4 g/d prescription n-3 FA
Triglycerides ≥500 mg/dL	≥30% reduction in triglycerides with 4 g/d prescription n-3 FA, LDL-C increase with DHA-containing agents
Use with other lipid therapy	Safe and apparently additive triglyceride reduction with statin therapy; apparently safe with fibrates or niacin but more research needed to evaluate efficacy
Prescription n-3 FA agent	On the basis of available data, all prescription agents appear comparably effective, but head-to-head comparisons are lacking

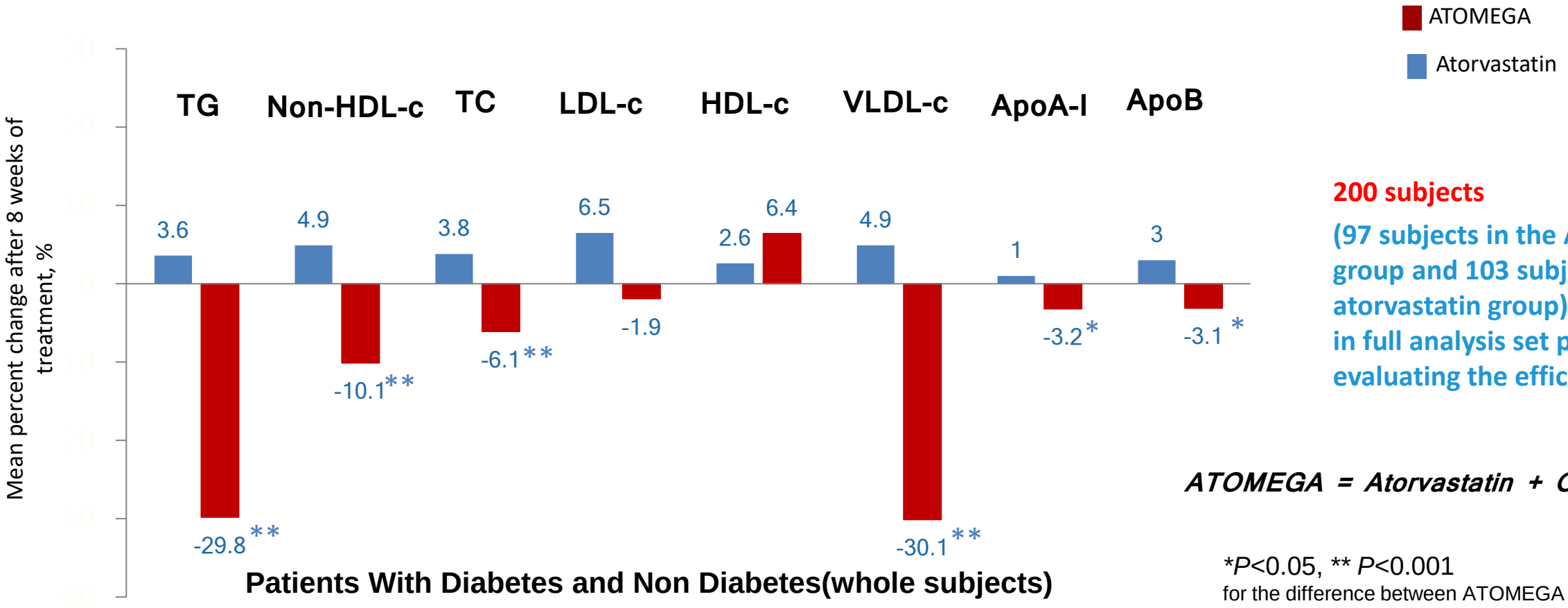
DHA indicates docosahexaenoic acid; HTG, high triglycerides; LDL-C, low-density lipoprotein cholesterol; and n-3 FA, omega-3 fatty acid.

Skulas-Ray AC et al. *Circulation* **2019** Aug 19

A favorable effect of the combination on the lipid profile

The combination has greater effect in reducing TG and Non-HDL-c

Change in lipid and lipoprotein levels after 8 weeks of treatment



Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), Very Low Density Lipoprotein Cholesterol (VLDL), Apolipoprotein A-1 and Apo-B, Triglycerides (TG)

200 subjects

(97 subjects in the ATOMEGA group and 103 subjects in the atorvastatin group) were included in full analysis set population for evaluating the efficacy endpoints.

ATOMEGA = Atorvastatin + Omega-3 group

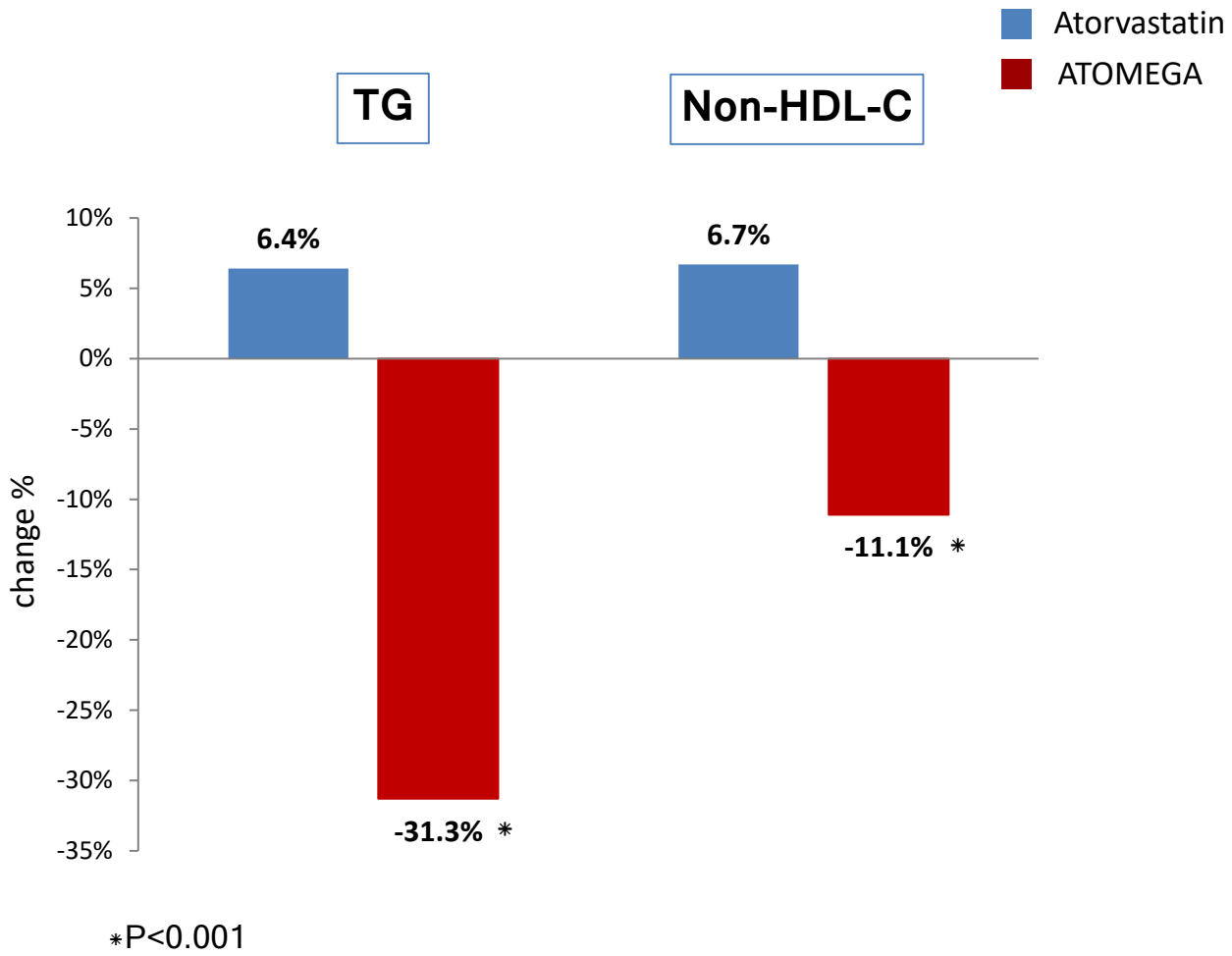
*$P<0.05$, ** $P<0.001$
for the difference between ATOMEGA and atorvastatin group.

GLF2342907

Patients with Diabetes benefited from the combination in terms of TG and Non-HDL reduction

Patients With Diabetes

Only the ATOMEGA combination significantly reduced TG and Non-HDL-C levels in subjects with DM after 8 weeks of treatment, while atorvastatin slightly increased TG and Non-HDL-C levels compared to baseline



*P<0.001

Triglycerides (TG), Non-High Density Lipoprotein Cholesterol (Non-HDL-C)
ATOMEGA = Atorvastatin + Omega-3 group, Diabetes Mellitus (DM)

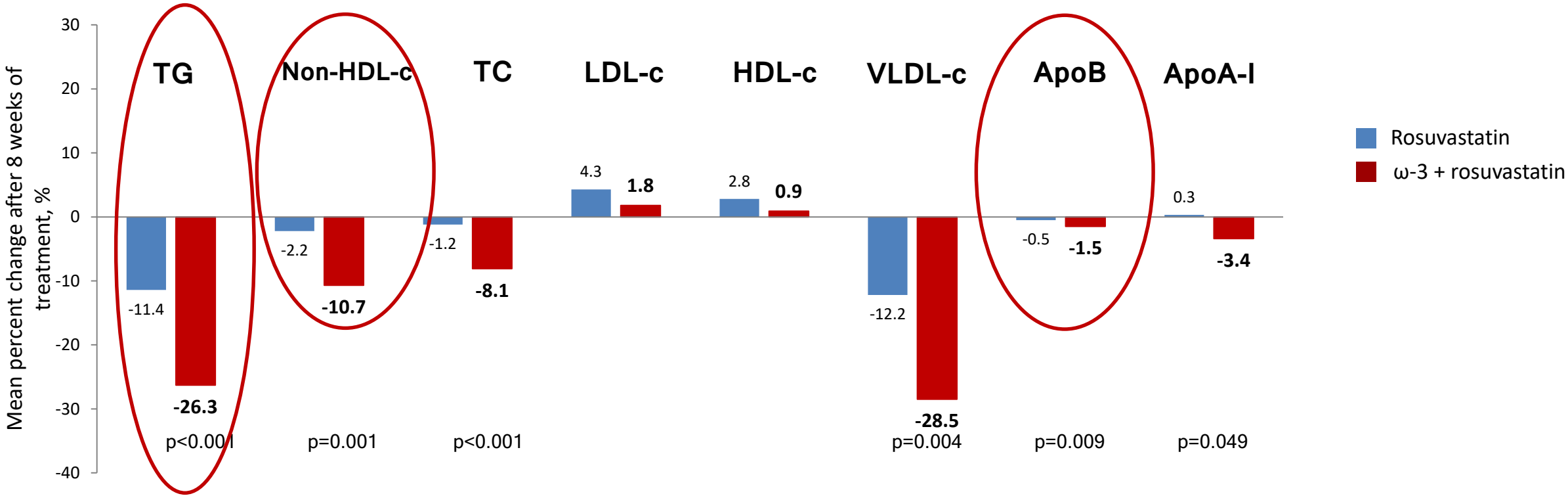
ATOMEGA = Atorvastatin + Omega-3 group

ROMANTIC

Omega-3 – Rosuvastatin combination

Combination has greater effect in reducing TG and non-

Change in lipid and lipoprotein levels after 8 weeks of treatment[1]



ROMANTIC: **201 patients** at high Cardiovascular Disease risk with TG 200-499 mg/dL (2.3-5.6 mmol/L) despite rosuvastatin 20 mg od were randomized to rosuvastatin 20 mg od **+ 4 g ω-3 od or rosuvastatin 20 mg** od (double-blind)

1. Kim CH et al. Clin Ther **2018**;40:83

VLDL -c = Very Low Density Lipoprotein - Cholesterol, ω-3 = Omega-3, LDL-C = Low Density Lipoprotein Cholesterol
HDL-c = High Density Lipoprotein-Cholesterol , TG = Triglycerides, Apo-B (A-I) = Apolipoprotein B (A-I)

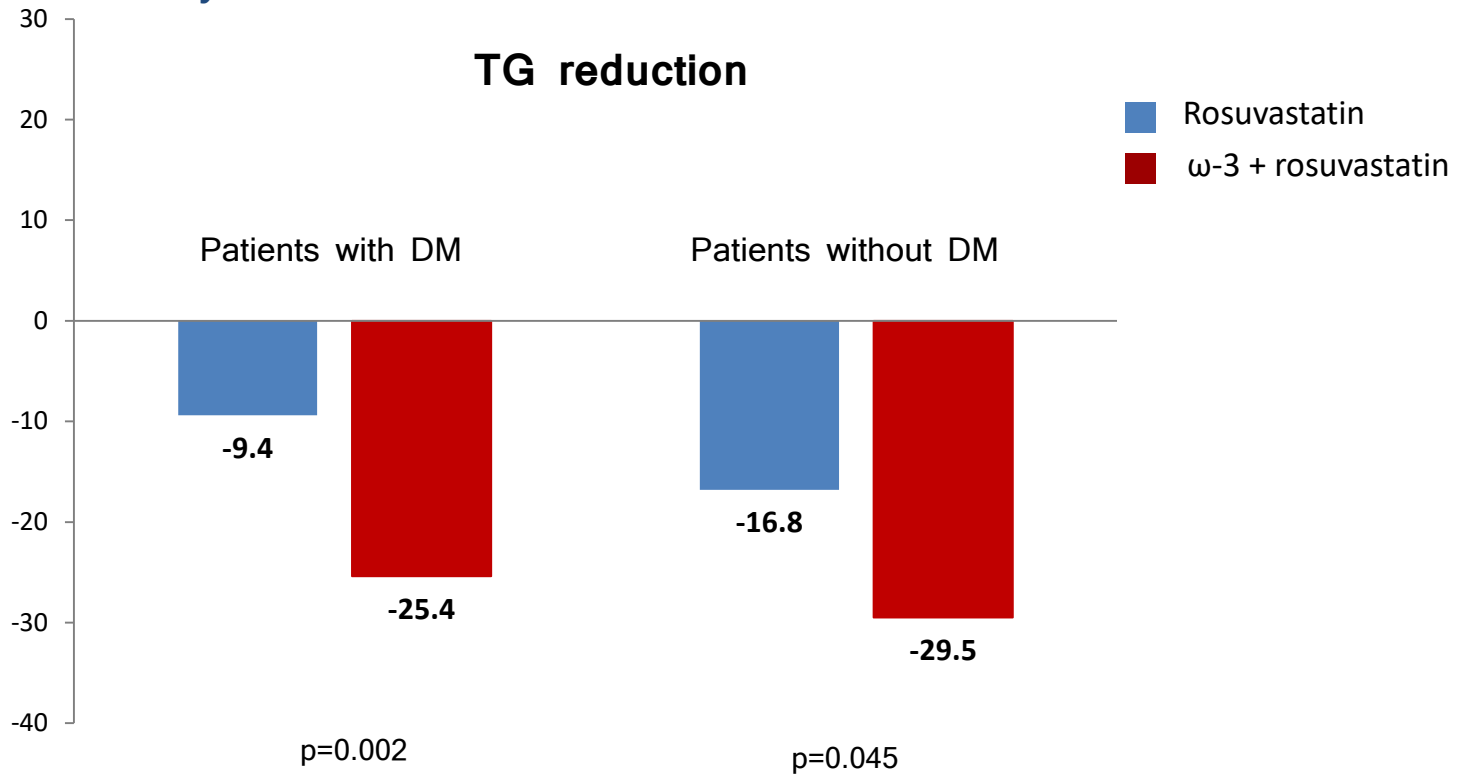
GLF2342907

Omega-3 – Rosuvastatin combination

The most important treatment in patients with dyslipidemia is **statins,** which mainly **lowers LDL-C**

However, statins do not control TG levels effectively

The ROSUMEGA group had a greater reduction in TG levels after 8 weeks compared with the rosuvastatin group regardless of the presence of DM



Hypertriglyceridemia is known as an independent risk factor associated with cardiovascular event [1-3]

1- Freiberg JJ,et al. JAMA. 2008;300:2142–2152.
2- Labreuche J et alAtherosclerosis. 2009;203:331–345.
3- Sarwar N et al. Circulation. 2007;115:450–458.

*1. Kim CH et al. Clin Ther **2018**;40:83*

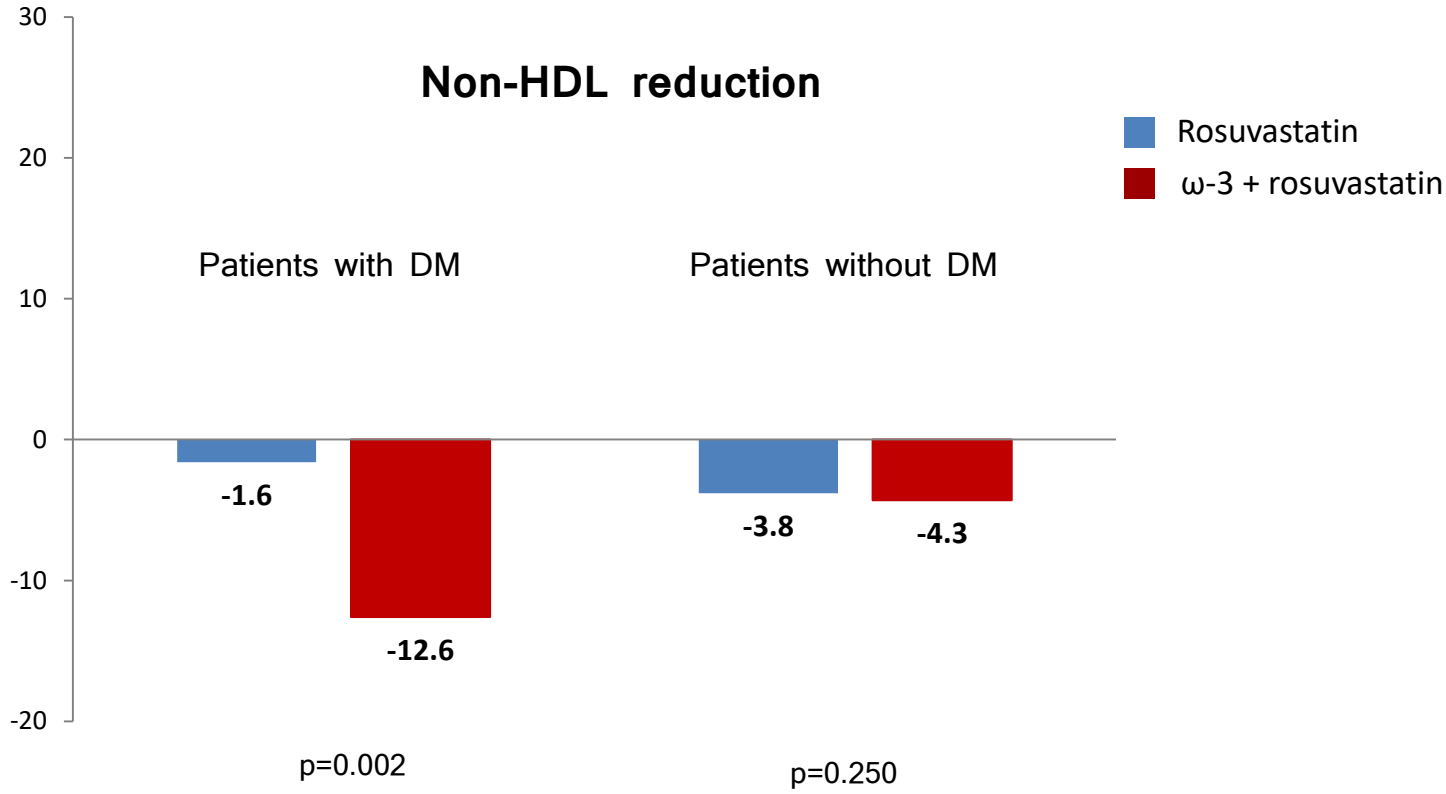
DM= Diabetes Mellitus, ω-3 = Omega-3, LDL-C = Low Density Lipoprotein Cholesterol, TG = Triglycerides

Omega-3 - Rosuvastatin combination

Non-HDL-C is a more inclusive measure of all **atherogenic Apo B** containing lipoproteins :VLDL-C, IDL-C, chylomicron remnants, lipoprotein A and LDL-C.

It serves as a strong predictor of cardiovascular disease in patients with DM*

In patients with DM, ROSUMEGA had a greater lowering effect on non-HDL-C than rosuvastatin but in patients without DM, ROSUMEGA had similar effects on non-HDL-C as rosuvastatin



*Lu W et al. Diabetes Care. 2003;26:16–23.

1. Kim CH et al. Clin Ther **2018**;40:83

VLDL -c = Very Low Density Lipoprotein - Cholesterol, ω-3 = Omega-3, LDL-C = Low Density Lipoprotein Cholesterol, DM = Diabetes Mellitus
HDL-c = High Density Lipoprotein-Cholesterol, IDL= Intermediate Density Lipoprotein, Apo-B = Apolipoprotein B

GLF2342907

GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell´Infarto miocardico

GISSI-P
172 Cardiology centres

n= 11,324 patients

GISSI-Prevenzione Investigators. *Lancet* 1999;354:447-455.

Aim of the study:

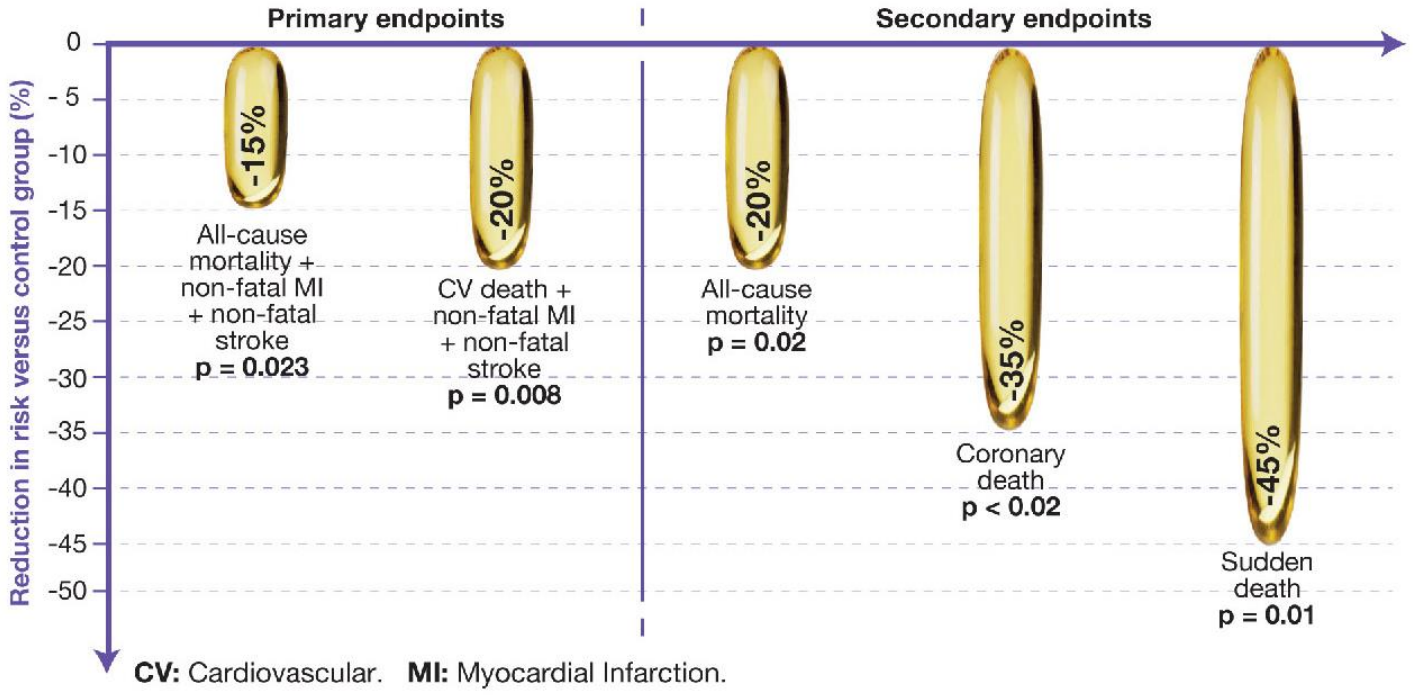
- **The GISSI-P trial investigated for the first time, the independent and combined effect of EPA + DHA EE (1 g), and vitamin E (300 mg) on mortality and morbidity in patients surviving a myocardial infarction (MI)**

GISSI-Prevenzione Investigators. *Lancet* 1999;354:447-455.

Improved patient prognosis post-MI

In GISSI-Prevenzione a multicenter randomized double blind placebo controlled trial,

Omega-3 (EPA +DHA) was given as an adjuvant treatment in **secondary prevention after MI** (within 90 days) in **addition to standard therapy** (**1g per day, n= 11,324 patients**)



Total mortality and sudden death supports the hypothesis of an anti-arrhythmic effect of this drug

Benefits on cardiovascular outcomes compared with control (% risk reduction)

GISSI-Prevenzione Investigators. Lancet 1999;354:447-455.

Prescription Omega 3 Preparations

Supplement fish oil vs Prescription Omega-3

Not regulated by FDA

Fish oil supplements
Contain up to 30% EPA +DHA
EPA & DHA as Triacylglycerols
Rapidly degraded in the duodenum
Short acting
May contain toxins such as lead or mercury
Oxidation products exceed maximum levels for international standards of quality

FDA approved

Prescription Omega-3
1 capsule contains 90% EPA +DHA
EPA & DHA as Ethyl Esters
Sustained release absorbed more slowly
Covering 24 hours
Highly purified
Highly regulated to meet international standards of quality

AACE 2020 : Over-the-counter fish oil dietary supplements are not FDA-approved for lowering triglycerides and are not recommended for this purpose because they contain very low amounts of polyunsaturated omega-3 fatty acids as well as trans fatty acids and saturated fat.

Jellinger P, Handelsman Y, Rosenblit P, et al. Endocr Practice. 2020

Supplement fish oil vs Prescription Omega-3

Omega-3 supplements

- ≥10 capsules of these products are required to achieve ≥3 g/d EPA+DHA[3]
- Contain cholesterol, oxidized fatty acids, saturated fatty acids, or other contaminants[3]
- 37% saturated fat content[3]
- not initially reviewed or approved, nor are they subsequently monitored or assured by the FDA[3]
- Only to be used as a supplement [3]

FDA approved prescription Omega-3

- 1 capsule Contains 90% EPA & DHA[1]
- EPA & DHA as Ethyl esters[1]
- Sustained release, Absorbed more slowly[1]
- Efficacy, as demonstrated in clinical trials, is mandatory[3]
- Indicated for secondary prevention for Post-MI patients[1]

American Heart Association.

AACE

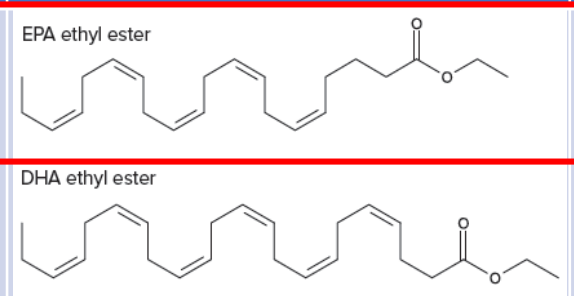
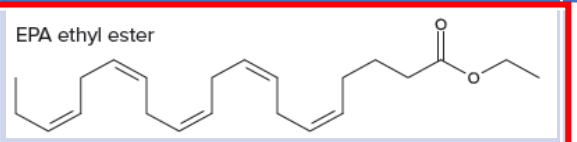
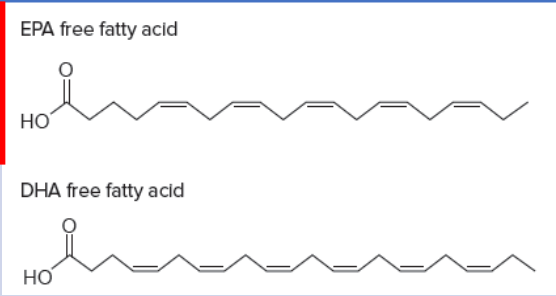
The potency, quality, and efficacy of dietary supplements are not initially reviewed or approved, nor are they subsequently monitored or assured by the FDA; thus, they are not indicated for the treatment of disease[3]

Over-the-counter fish oil supplements are not approved by the FDA for hypertriglyceridemia[2].

1- Omega-3 EPA/DHA Ethyl Easters Leaflet – UAE; 2- Susan L. Samson, Priyathama Vellanki et al. AACE Consensus Statement American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm -2023 Update; Endocrine Practice 29 (2023) 305e340; 3- Ann C. Skulas-Ray, PhD, Peter W.F. Wilson et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association- Circulation. 2019;140:e673–e691. DOI: 10.1161/CIR.0000000000000709

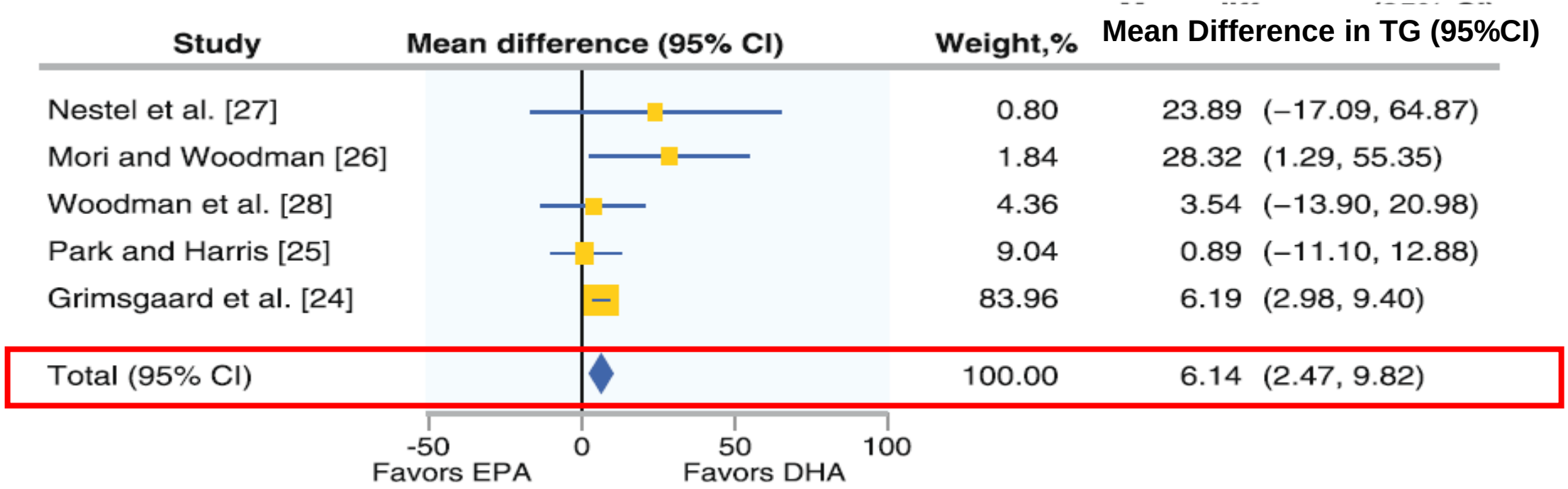
Prescription Omega 3 Preparations

FDA Approved Products

Product	(EPA / DHA Ethyl Ester)	RX EPA (EPA Ethyl Ester)	(Omega-3-Carboxylic Acids)
Content			
FDA Approved?	Yes (2004)	Yes (2012)	Yes (2014)
Positive Outcome Data?	- GISSI-P (1 Capsule) - GISSI-HF (1 Capsule)	REDUCE IT (4 capsules)	None Only STRENGTH, -ve
Indications & Dose?	- Hypertriglyceridemia (>200 mg/dL), (2 – 4 capsules/d) - Post Myocardial infarction (1 capsule)	- Reduction high TG (above 150), (4 capsules)	- Severe Hypertriglyceridemia (above 500 mg/dl) (2 - 4 capsules)
Cost Effectiveness (Monthly cost, AED)	AED 285 (2 capsules) to AED 570 (4 Capsules)	AED 936 (4 Capsules)	Not Available in UAE

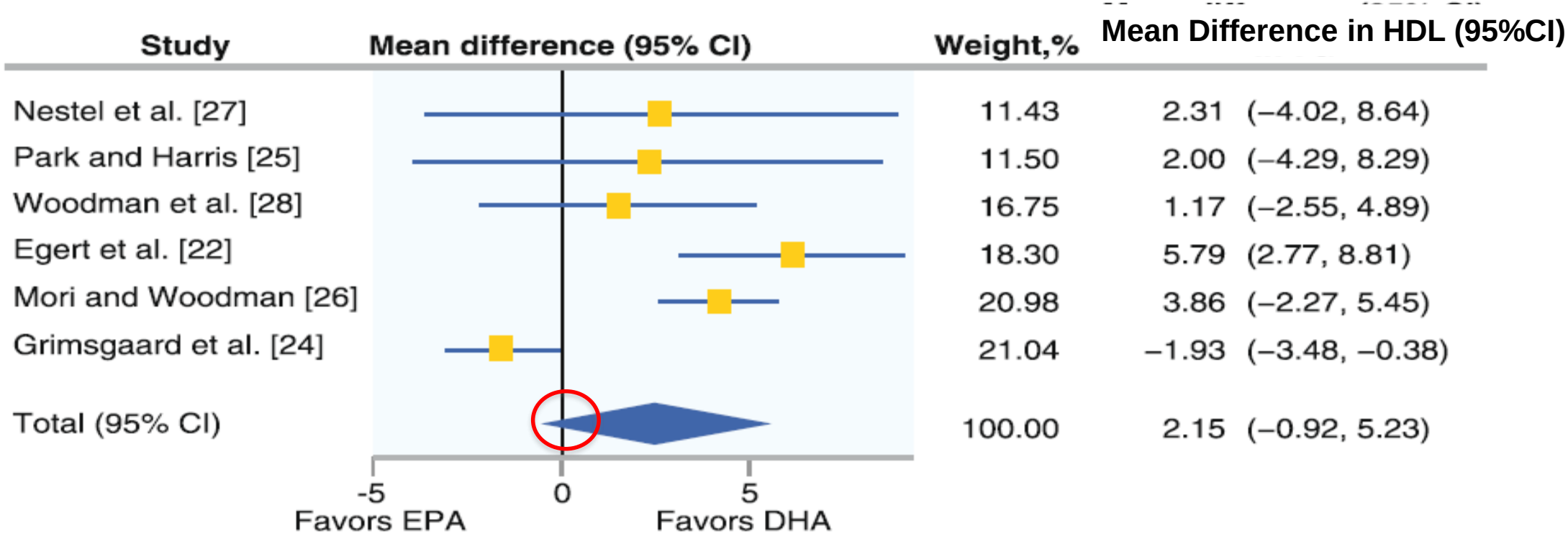
K. Ito, M., 2015. A Comparative Overview of Prescription Omega-3 Fatty Acid Products. *Pharmaceutical & Therapeutics Journal*, Vol. 40 No. 12, 826 - 828.

EPA vs DHA Monotherapy and Triglycerides: DHA reduces TG significantly more than EPA



Wei MY and Jacobson TA. Curr Athero Reports 2011 (online10/6/11)

EPA vs DHA Monotherapy and HDL-C:
DHA "Trends" to raise HDL-C more than EPA



Wei MY and Jacobson TA. Curr Athero Reports 2011 (online10/6/11)

Guidelines Recommendations and Managing Dyslipidaemia in Chronic Kidney Disease

Drugs used for Dyslipidemia Management

Fibrates

- R61. Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL) (Grade A; BEL 1).
- R62. Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL (Grade A; BEL 1).

Omega-3 Fish Oil

- R63. Prescription omega-3 oil, 2 to 4 g daily, should be used to treat severe hypertriglyceridemia (TG >500 mg/dL).
- Dietary supplements are not FDA-approved for treatment of hypertriglyceridemia and generally are not recommended for this purpose (Grade A, BEL 1).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides, BEL: Best Evidence Level.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

ESC 2021 recommendations for drug treatments of patients with hypertriglyceridemia

4.6.4. Important groups
Recommendations for drug treatments of patients with hypertriglyceridaemia.

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].[533]	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.[534–536]	IIb	B
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) may be considered in combination with a statin.[84]	IIb	B

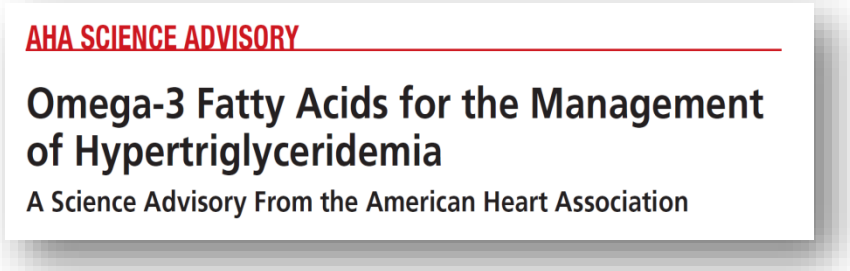
CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acid.
[a]Class of recommendation.
[b]Level of evidence.
Adapted from [3]

4.6.3.2 Strategies to control plasma triglycerides

Although CVD risk is increased when fasting triglycerides are >1.7 mmol/L (150 mg/dL),[531] the use of drugs to lower triglyceride levels may only be considered in high-risk patients when triglycerides are >2.3 mmol/L (200 mg/dL) and triglycerides cannot be lowered by lifestyle measures. The available pharmacological interventions include statins, fibrates, PCSK9 inhibitors, and n-3 PUFAs (in particular icosapent ethyl in doses of 2–4 g/day; see *section 4.3.2.4.4*).

Frank Visseren, Francois Mach, Yvo Smulders et al. European Heart Journal (2021) 42, 3227-3337, doi:10.1093/eurheartj/ehab484

AHA Science Advisory



Prescription n-3 FAs (EPA+DHA or EPA-only) at a dose of **4 g/d (>3 g/d total EPA+DHA)** are an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents.

All prescription agents appear **comparably effective,** but head-to-head comparisons are lacking

In patients with **very high TG** treated with prescription EPA +DHA products LDL-C increased by 15 to 36 %.

However there was no increase in Apo-B suggesting that **the increase in LDL-C may reflect an increase in the average size of LDL particles** rather than an increase in LDL particle concentration

Skulas-Ray AC et al. *Circulation* **2019** Aug 19

The cardioprotective role of DHA

DHA is known to have cardioprotective activity:

- In a series of electrophysiological experiments, it was shown that EPA and **DHA inhibit Na+ channel activity** and that the effect of DHA was more pronounced;[32,33]

- **Serum DHA, and not EPA,** was associated with **lower inducibility of atrial fibrillation** in patients without atrial fibrillation and without structural heart disease;[34]

32. Leaf A, Kang JX, Xiao Y-F, et al. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation* 2003;107(21):2646–2652.
33. Pignier C, Revenaz C, Rauly-Lestienne I, et al., Direct protective effects of poly-unsaturated fatty acids, DHA and EPA, against activation of cardiac late sodium current: a mechanism for ischemia selectivity. *Basic Res Cardiol* 2007;102(6):553–564.

Table 3 Mechanisms of Dyslipidemia in Chronic Kidney Disease

Protein	Change	Effect on Plasma Lipids or LP
ApoA-1	2	2 HDL
LCAT	2	2 HDL-C, HDL-2/HDL-3
CETP	1	2 HDL-C
ACAT	1	1 VLDL-C, 2 HDL-C
LPL	2	1 Trig (1 delipidation of VLDL and CM)
VLDL receptor	2	1 VLDL, Trig
Hepatic lipase	2	1 IDL, CM remnants, HDL-TG, Trig, LDL-TG
LRP	2	1 IDL, CM remnants
ApoCII/CIII ratio	2	1 Trig (1 LPL activity)
Pre-b HDL	1	1 Trig (1 LPL activity)

JACC Vol. 51, No. 25, 2008 June 24, 2008:2375– 84

2 = decreases ; 1 = increases

Dosing Modifications for Lipid-Lowering Drugs in CKD

Table 7 Dosing Modifications for Lipid-Lowering Drugs in CKD

Agent	GFR 60–90 ml/min/1.73 m²	GFR 15–59 ml/min/1.73 m²	GFR <15 ml/min/1.73 m²	Notes
Statins				
Atorvastatin	No	No	No	
Fluvastatin	No	Not defined	Not defined	↓ dose to one-half at GFR <30 ml/min/1.73 m²
Lovastatin	No	↓ to 50%	↓ to 50%	↓ dose to one-half at GFR <30 ml/min/1.73 m²
Pravastatin	No	No	No	Start at 10 mg/day for GFR <60 ml/min/1.73 m²
Rosuvastatin	No	5–10 mg	5–10 mg	Start at 5 mg/day for GFR <30 ml/min/1.73 m², max dose 10 mg/day
Simvastatin	No	No	5 mg	Start at 5 mg if GFR <10 ml/min/1.73 m²
Nonstatins				
Nicotinic acid	No	No	↓ to 50%	34% kidney excretion
Cholestyramine	No	No	No	Not absorbed
Colesevelam	No	No	No	Not absorbed
Ezetimibe	No	No	No	
Fenofibrate	↓ to 50%	↓ to 25%	Avoid	May ↑ serum creatinine
Gemfibrozil	No	No	No	NLA recommends a dose of 600 mg/day for GFR 15–59 ml/min/1.73 m² and avoiding use for GFR <15 ml/min/1.73 m²
Omega-3 FAs	No	No	No	

Adapted from the K/DOQI clinical practice guidelines (29).

↓ = decrease; ↑ = increase; CKD = chronic kidney disease; FA = fatty acid; GFR = glomerular filtration rate; NLA = National Lipid Association.

JACC Vol. 51, No. 25, 2008 June 24, 2008:2375– 84

GLF2342907

Proposed Treatment Algorithm for Lipid Management in Patients With CKD (Stage 3 to 5)

Table 8 **Proposed Treatment Algorithm for Lipid Management in Patients With CKD (Stage 3 to 5)**

Lipid Disorder	Therapeutic Option (See Table 7 for Dose Adjustments)
Moderate to severe CKD, stages 3 to 4 (GFR 15–59 ml/min/1.73 m²)	
Elevated LDL-C	1) Atorvastatin, add ezetimibe if not at LDL-C goal 2) Fluvastatin, add ezetimibe if not at LDL-C goal
Mixed dyslipidemia* (not at non-HDL† goal)	1) Atorvastatin or fluvastatin + ezetimibe 2) Fluvastatin + gemfibrozil 600 mg/day + ezetimibe if not at non-HDL goal 3) Statin + omega-3 fatty acids, add ezetimibe if not at non-HDL goal 4) Statin + fenofibrate 48 mg/day, add ezetimibe if not at non-HDL goal
Very high triglycerides (triglyceride >500 mg/dl)	1) Gemfibrozil 600 mg/day 2) Omega-3 fatty acids 3–4 g/day 3) Fenofibrate 48 mg/day
CKD stage 5 (hemodialysis or GFR <15 ml/min/1.73 m²)	
Elevated LDL-C	Atorvastatin (10–80 mg/day) or fluvastatin 40 mg/day, add ezetimibe if not at LDL-C goal
Mixed dyslipidemia	Atorvastatin or fluvastatin 40 mg/day, add ezetimibe 10 mg/day or omega-3 fatty acids 3–4 g/day if not at non-HDL goal
Very high triglycerides	Omega-3 fatty acids 3–4 g/day or gemfibrozil 600 mg/day

*Mixed dyslipidemia = elevated triglycerides and low HDL with or without elevated LDL. †Non-HDL = total cholesterol − HDL cholesterol.
CKD = chronic kidney disease; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol.

JACC Vol. 51, No. 25, 2008 June 24, 2008:2375– 84

KDOQI
KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE
National Kidney Foundation

eat right® Academy of Nutrition and Dietetics

KDOQI CLINICAL PRACTICE GUIDELINE FOR NUTRITION IN CKD: 2020 UPDATE

T. Alp Ikizler, Jerrilynn D. Burrowes, Laura D. Byham-Gray, Katrina L. Campbell, Juan-Jesus Carrero, Winnie Chan, Denis Fouque, Allon N. Friedman, Sana Ghaddar, D. Jordi Goldstein-Fuchs, George A. Kaysen, Joel D. Kopple, Daniel Teta, Angela Yee-Moon Wang, and Lilian Cuppari

LC n-3 PUFA Nutritional Supplements for Lipid Profile

4.3.3 In adults with CKD 5D on MHD, we suggest that 1.3-4 g/d LC n-3 PUFA may be prescribed to reduce triglycerides and LDL cholesterol (2C) and raise HDL levels (2D).

4.3.4 In adults with CKD 5D on PD, it is reasonable to consider prescribing 1.3-4 g/d LC n-3 PUFA to improve the lipid profile (OPINION).

4.3.5 In adults with CKD 3-5, we suggest prescribing ~ 2g/d LC n-3 PUFA to lower serum triglyceride levels (2C).

Harper and Jacobson Treatment of Dyslipidemia in CKD

The omega-3 fatty acids may also be used in combination with a statin. Although published data on this combination in patients with CKD is limited, omega-3 fatty acids do not have significant interactions with statins and do not require dose reductions for impaired renal function (53).

Although fibrates can be used to treat mixed dyslipidemia, they need to be used carefully, because they are predominantly metabolized by the kidneys.

Another option for very high triglycerides is to treat with omega-3 fatty acids derived from fish oil. The main active ingredients in fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic (DHA). Four grams of omega-3 fatty acids per day, in the form of fish oil capsules, have been shown to reduce triglycerides 35% to 45% (54). The omega-3 fatty acids are safe in patients with CKD and have minimal drug interactions. Until recently, a major limitation was that over-the-counter preparations had only 200 to 300 mg omega-3 fatty acids per capsule, requiring the consumption of 12 to 16 capsules/day. The only available prescription-brand omega-3 fatty acid contains almost 900 mg omega-3 fatty acids, requiring only 4 capsules/day (54).

Ikizler TA, Burrowes JD, Byham-Gray LD, et al; KDOQI Nutrition in CKD Guideline Work Group. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis. 2020;76(3)(suppl 1):S1-S107. Charles R. Harper, MD, FACP,* Terry A. Jacobson, MD, FACP*† Managing Dyslipidemia in Chronic Kidney Disease, Journal of the American College of Cardiology, doi:10.1016/j.jacc.2008.03.025

THANK YOU