Diabetes, cardiovascular risk, hypertriglyceridemia

49 y/o woman.

Personal history :

- Type 2 Diabetes Mellitus diagnosed 7 years ago. Treated with Metformin and Sitagliptin. Fasting glucose levels between 120-140 mg/dl. HbA1c: Average 7.2%
- HBP on treatment with Perindopril + Indapamide maintaining BP around 130/80 mmHg.
- A carotid sonography showed an IMT above 75 percentile for her age and gender.
- No smoker. Sedentary. No menopausal.
- She was overweight (BMI: 29).

Blood tests:

Fasting Glucose 118 mg/dl. HbA1c 6.9%.
TCh: 187 mg/dl; HDL: 44 mg/dl; LDL: 89 mg/dl; TG: 270 mg/dl

What is the cardiovascular risk of this patient?

1) She is at low cardiovascular risk
2) Moderate CV risk
3) High CV risk
4) Very high CV risk

ESC/EAS 2019 guidelines: Cardiovascular risk categories

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

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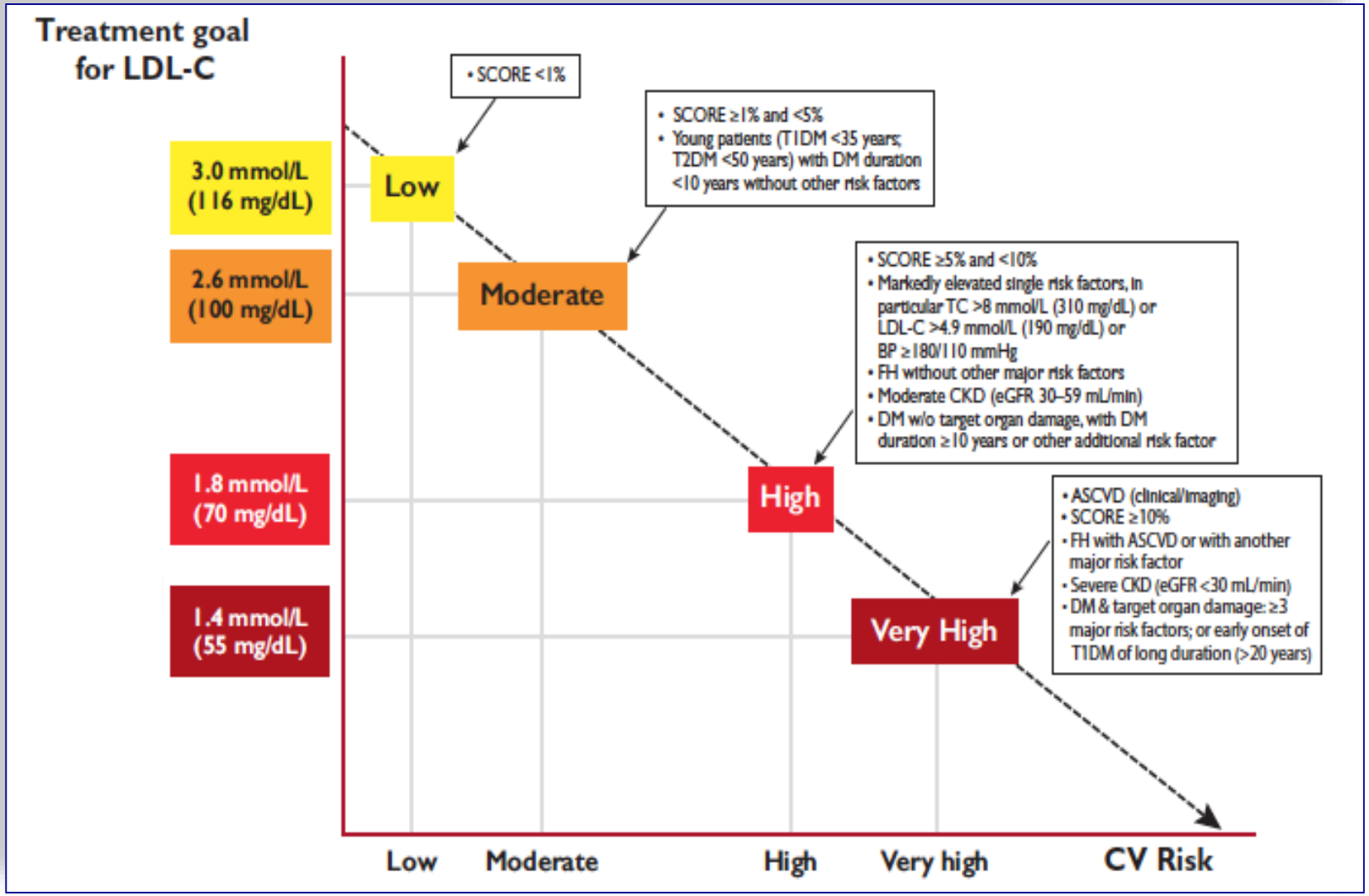
According the new ESC / EAS guidelines this patient is at HIGH CARDIOVASCULAR RISK

Which are the lipid targets recommended to reduce her cardiovascular risk?

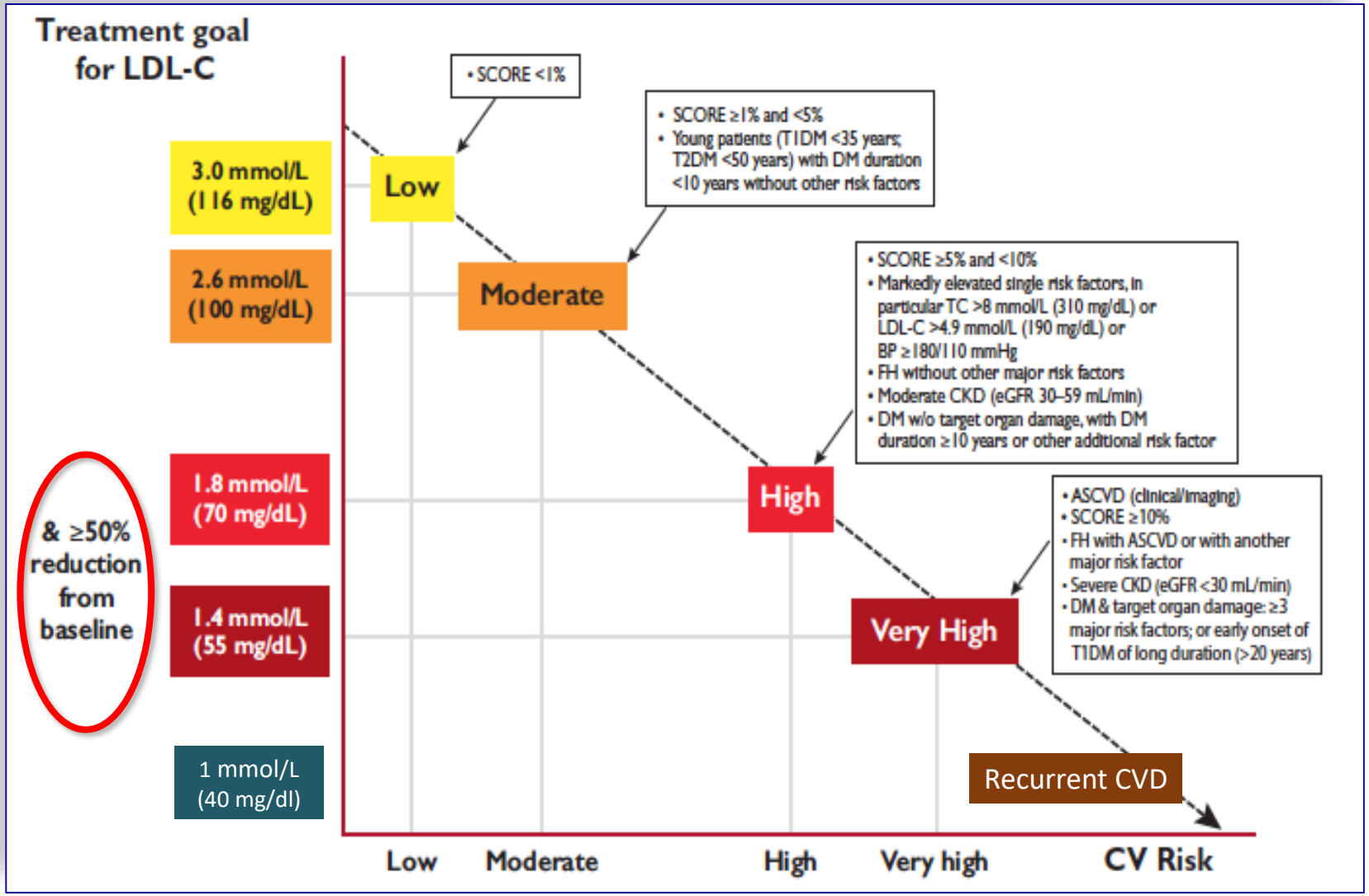
1) Less than 116 mg/dl
2) Less than 100 mg/dl
3) Less than 70 mg/dl
4) Less than 55 mg/dl
5) Less than 40 mg/dl

ESC/EAS 2019 guidelines: Treatment goals for LDL-C across cardiovascular risk categories



Mach F et al. European Heart Journal (2019) 00, 178

ESC/EAS 2019 guidelines: Treatment goals for LDL-C across cardiovascular risk categories



Mach F et al. European Heart Journal (2019) 00, 178

ESC/EAS 2019 guidelines: Treatment targets beyond LDL

Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

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Fasting Glucose 118 mg/dl. HbA1c 6.9%.
TCh: 187 mg/dl; HDL: 44 mg/dl; LDL: 89 mg/dl; TG: 270 mg/dl

What lipid lowering therapy would you prescribe to this patient?

1) High intensity Statin
2) Moderate intensity Statin
3) Combination therapy (Statin + Ezetimibe)
4) Fibrate
5) Combination therapy (Statin + Fibrate)
6) None. Lifestyle changes

The patient was put on life style therapeutic changes and Atorvastatin 40 mg/day

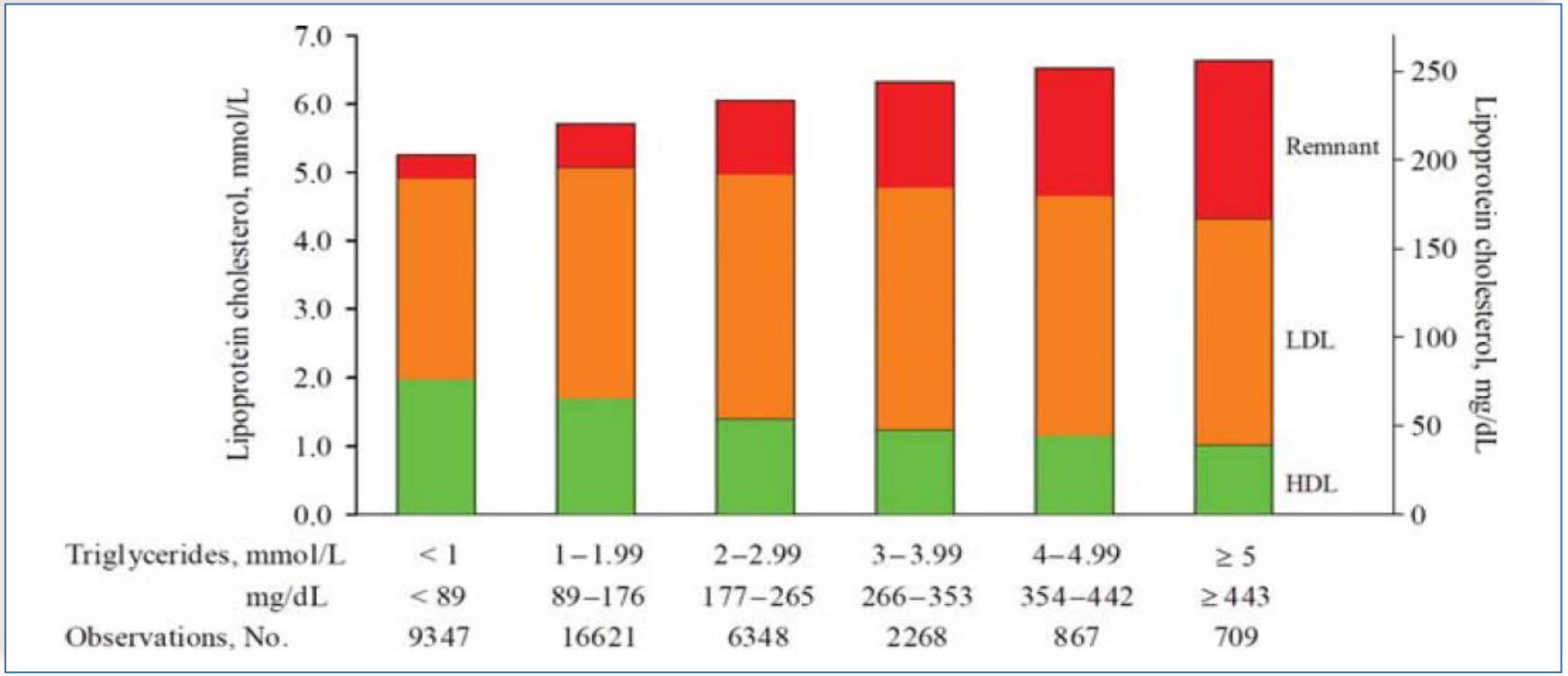
After 2 month:

BMI : 29.4
Fasting Glucose 127 mg/dl. HbA1c 7.1%.
TCh: 147 mg/dl; HDL: 31 mg/dl; LDL: 53 mg/dl; TG: 275 mg/dl; Apo B: 100 mg/dl

Would you change her treatment?

1) Yes, I´ll increase the LDL lowering therapy?
2) Yes, I'll change her T2DM therapy regime?
3) Yes, I'll treat her hypertriglyceridemia?
4) No

Cholesterol distribution according triglyceride levels

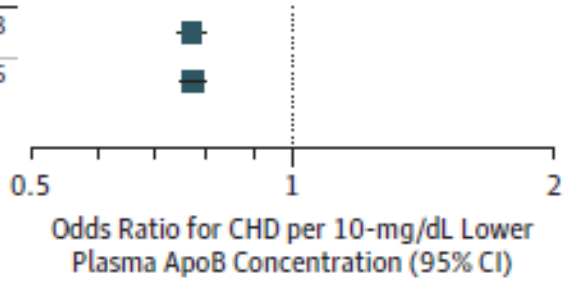


Chapman J.....Masana L et al . Eur Heart J 2011

Association of Triglyceride-Lowering LPL Variants and LDL-C–Lowering LDLR Variants With Risk of Coronary Heart Disease

Figure 1. Associations Between the Lipoprotein Lipase (*LPL*) and LDL Receptor Gene (*LDLR*) Genetic Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)–Containing Lipoproteins

Genetic Score	Δ Triglycerides (95% CI)	*P* Value	Δ Low-Density Lipoprotein Cholesterol (95% CI)	*P* Value	Odds Ratio for Coronary Heart Disease (95% CI)	*P* Value
LPL	-69.9 (-71.6 to -68.3)	7.1×10^{-1363}	0.7 (0.0 to 1.4)	.04	0.771 (0.741 to 0.802)	3.9×10^{-38}
LDLR	-1.9 (-3.9 to -0.1)	.04	-14.2 (-14.8 to -13.6)	1.4×10^{-465}	0.773 (0.747 to 0.801)	1.1×10^{-46}



Conclusions

Triglyceride-lowering *LPL* variants and LDL-C–lowering *LDLR* variants were associated with similar lower risk of CHD per unit difference in ApoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in ApoB.

Ference BA at al JAMA. 2019;321(4):364-373

After 2 month:

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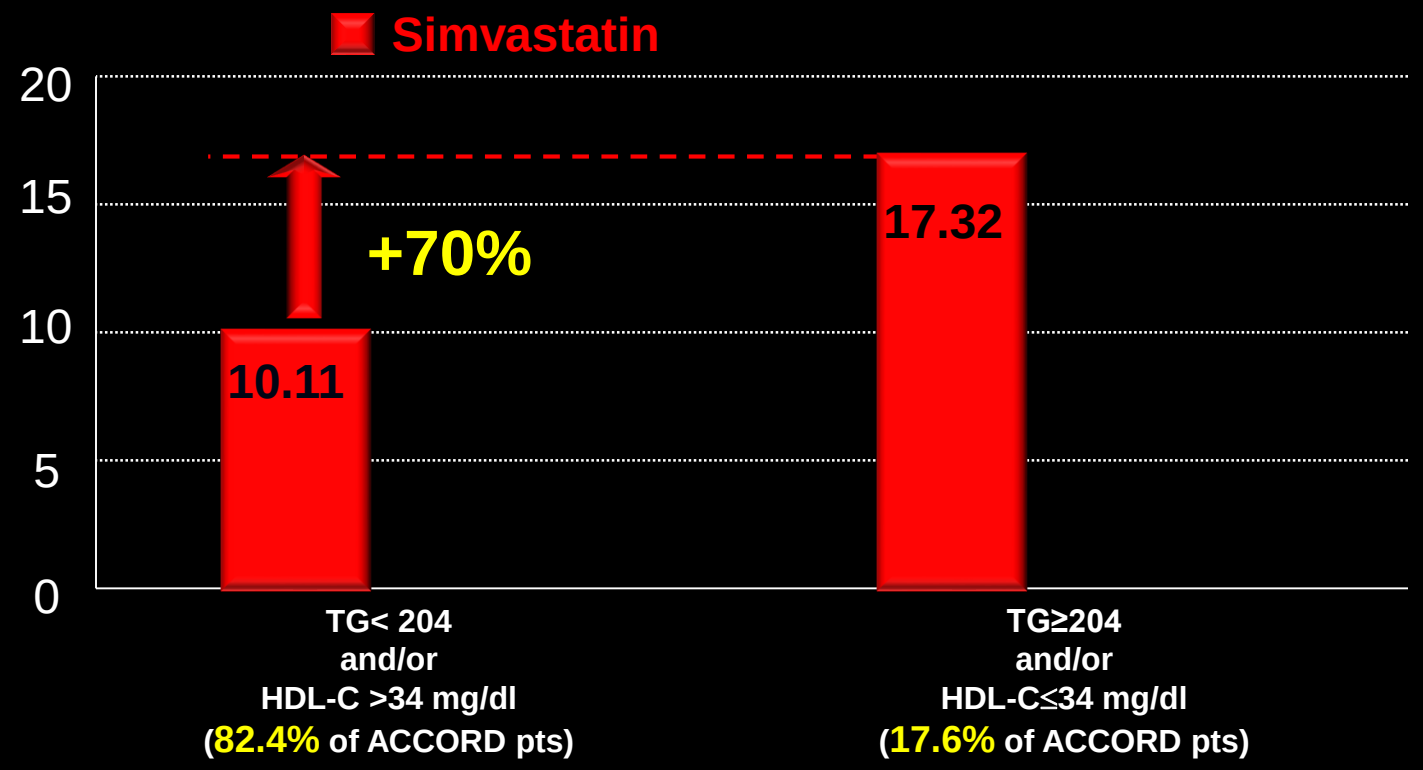
Fasting Glucose 127 mg/dl. HbA1c 7.1%.
TCh: 147 mg/dl; HDL: 31 mg/dl; LDL: 53 mg/dl; TG: 275 mg/dl; Apo B: 100 mg/dl

Regarding her triglyceride levels and global cardiovascular risk

1) I won´t treat her high triglycerides
2) I´ll put her on Gemfibrozil
3) I'll put her on Fenofibrate
4) I'll put her on n-3 fatty acids

ACCORD Pre-Specified Endpoint
Patients with Elevated TG and Low HDL-C

- Patients with **Atherogenic Dyslipidaemia** had a **70% higher relative risk of major CV events**** compared to those without Atherogenic Dyslipidemia, despite achieving a mean **LDL-C of 80 mg/dl**



Major CV event (1º endpoint): CV death, nonfatal MI or nonfatal stroke

All groups LDL-C: 80 mg/dl (2.0 mmol/L)

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

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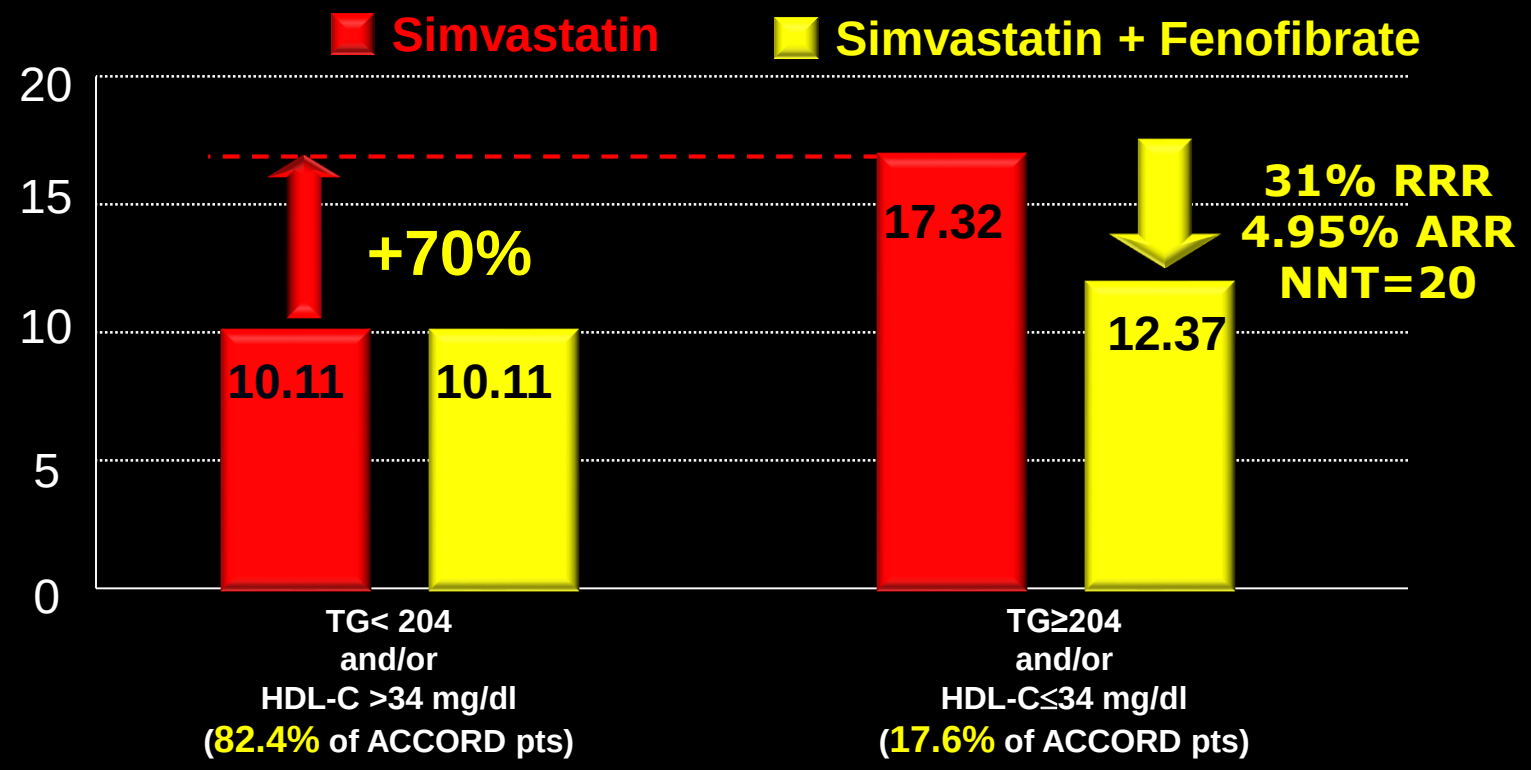

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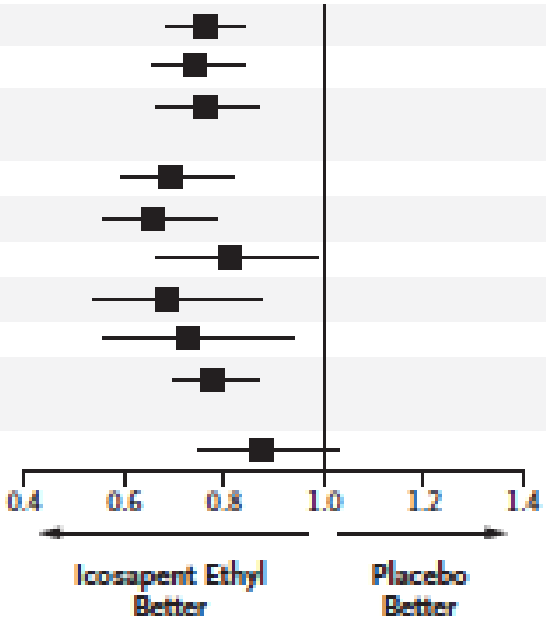
ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

Another Nail in the Coffin for Fish Oil Supplements

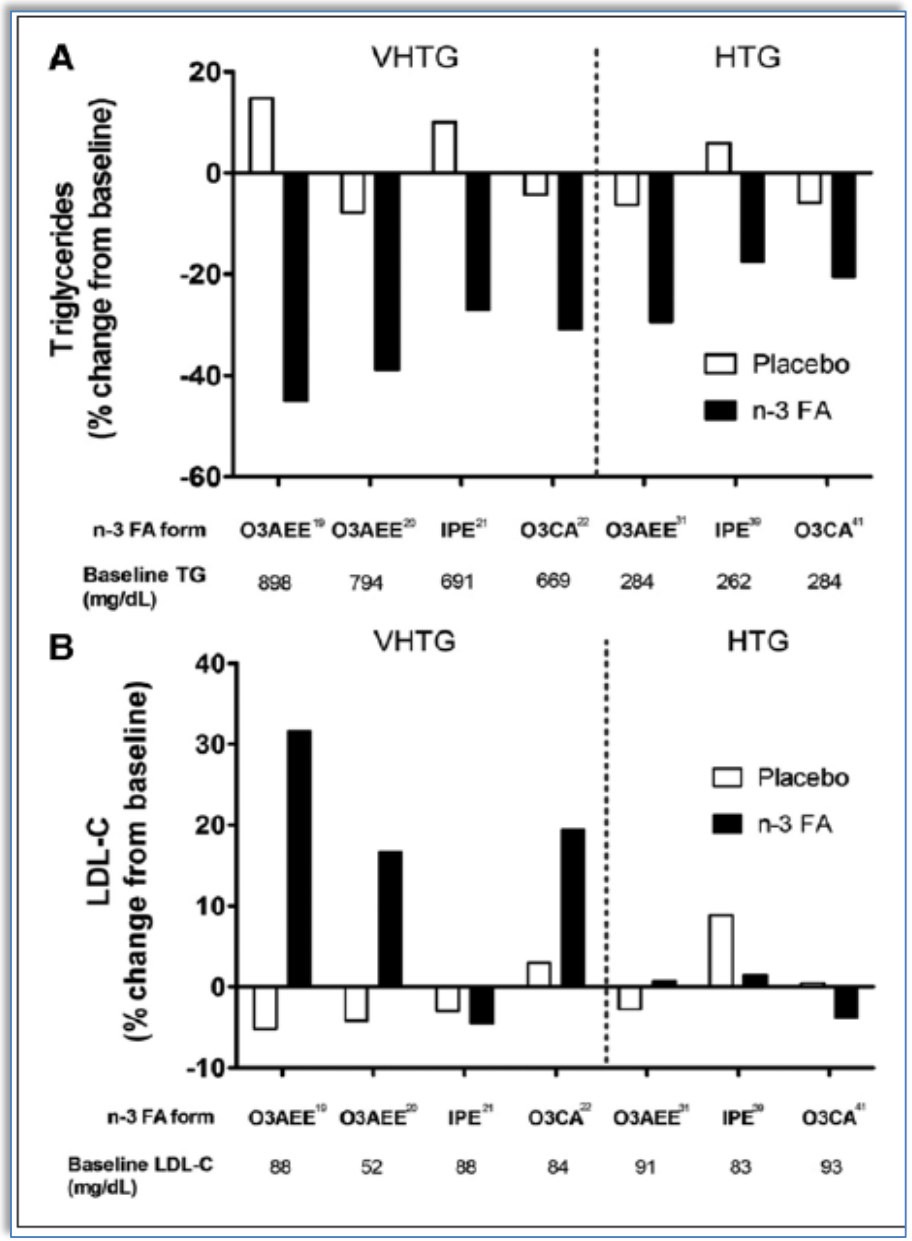
Jennifer Abbasi JAMA. 2018;319(18):1851-1852. doi:10.1001/jama.2018.2498

Cardiovascular Risk Reduction with Eicosapent Ethyl for Hypertriglyceridemia

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—



Bhatt DL et al. NEJM , 2018, Nov 10.



Skulas-Ray AC et al Circulation 2019; 140: e673-91

Circulation

AHA SCIENCE ADVISORY

Omega-3 Fatty Acids for the Management of Hypertriglyceridemia

A Science Advisory From the American Heart Association

	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
Children/adolescents	Apparently safe but more research needed to further evaluate efficacy
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

ESC/EAS 2019 guidelines: Treatment of hypertriglyceridemia

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

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The patient was put on Empagliflozine 25 mg/day + Metformin 2g/day

Because Eicosapent Ethyl was not available, Fenofibrate 145 mg/day was added

After 2 month:

BMI : 28.7
Fasting Glucose 122 mg/dl. HbA1c 6.9 %.
TCh: 128 mg/dl; HDL: 45 mg/dl; LDL: 52 mg/dl; TG: 155 mg/dl; Apo B: 83 mg/dl