Integrating Icosapent Ethyl in Cardiovascular Risk Reduction Strategies: Practical guidance

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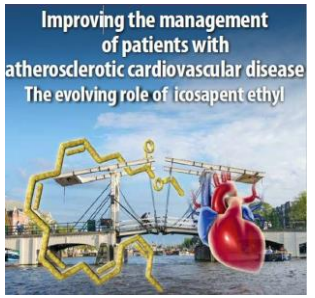
Improving the management of patients with atherosclerotic cardiovascular disease - The evolving role of icosapent ethyl



PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

Disclosures

- Consultant to Sanofi, Novo-Nordisk, Novartis, Boehringer-Ingelheim, Amgen, Bayer, Medtronic,
- Merck, Edwards and Esperion
- Founder and Shareholder of Epirium Bio

Research Funding:

Grants:

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  - Impact of time-restricted feeding (TRF) on glucose homeostasis and mitochondrial function in patients with metabolic syndrome – The TIMET Study (NCT0405733)
- Hillblom Network Grant (PI: Taub PR) (NCT05365529)
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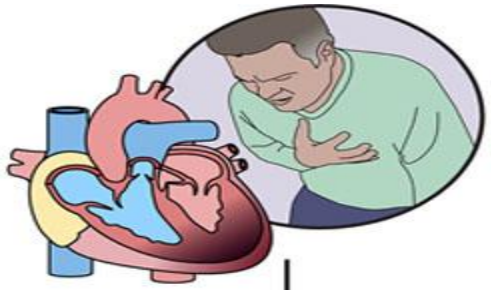
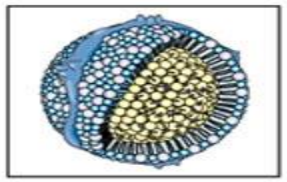
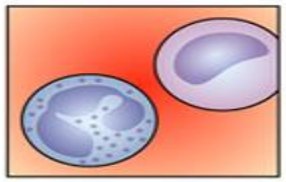
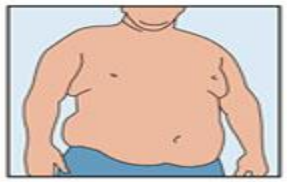
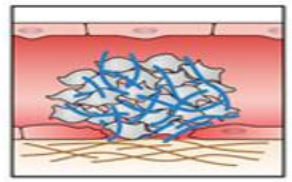
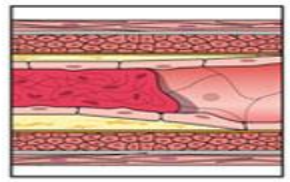
Clinical Trial Leadership:

- US National Lead/Steering Committee Member for: Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease (VICTORION-2P). (Sponsor: Novartis; NCT05030428)
- US National Lead/Steering Committee Member for: A Double-blind, Randomized, Placebo controlled, Multicenter Study Assessing the Impact of Olpasiran on Major Cardiovascular Events in Patients with Atherosclerotic Cardiovascular Disease and Elevated Lipoprotein (a). (Sponsor: Amgen NCT05581303)
- Executive Steering Committee for VICTORIAN-1P Trial (Sponsor: Novartis)
- National Principal Investigator for the NIH RECOVER COVID Initiative (recovercovid.org) and responsible for design and execution of studies related to Post COVID Postural Orthostatic Tachycardia Syndrome.
- US National Lead/Steering Committee Member for MK0616 (oral PCSK9 inhibitor) Phase 3 program (Sponsor: Merck)
- Executive Steering Committee Member for TRANSFORM Trial (Sponsor: Cleerly)

So Many Aspects of CV Prevention!

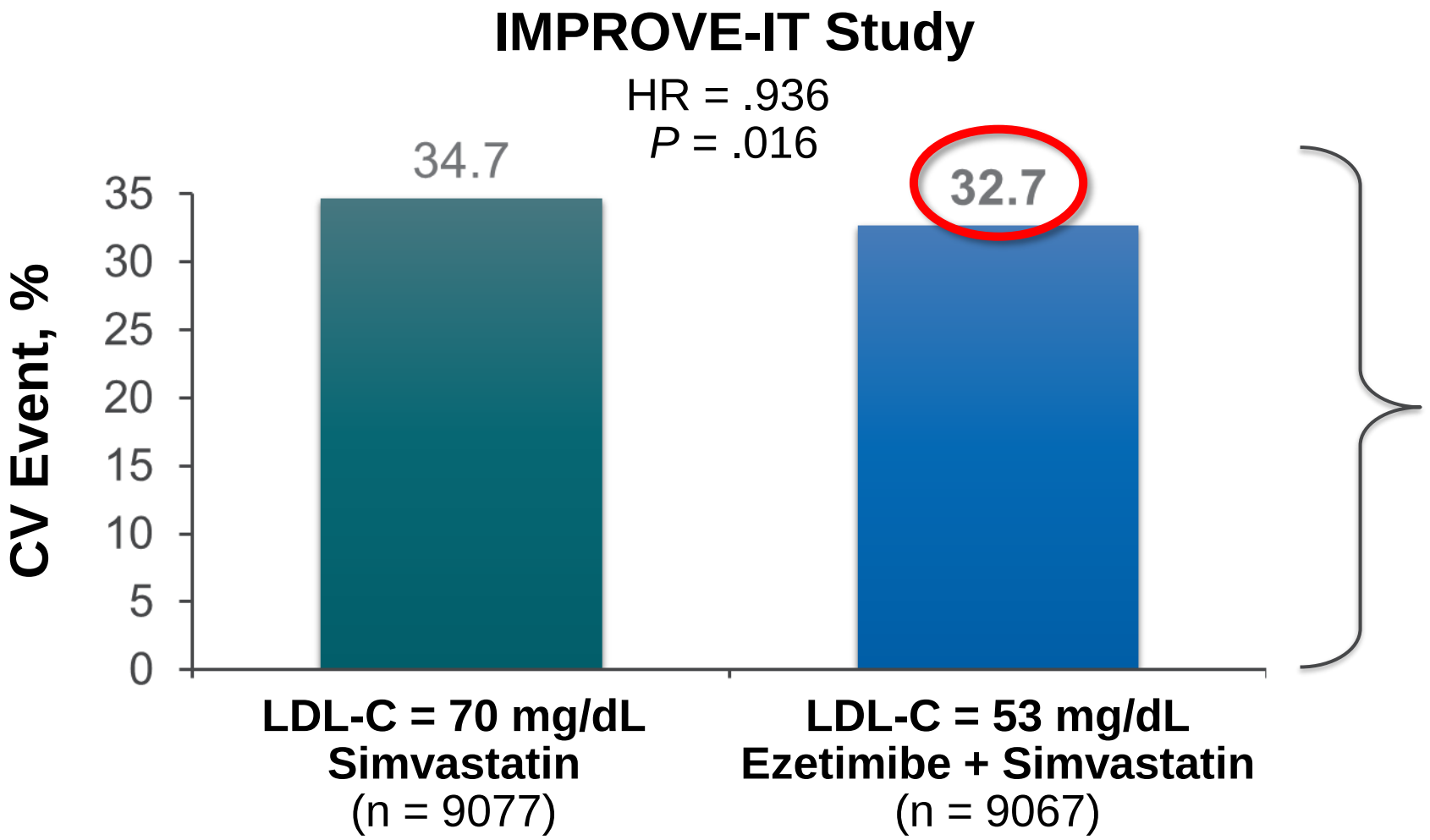


Lifestyle interventions, guideline-directed medical therapy

	Lipoproteins	Inflammation	Metabolism	Platelets	Coagulation
Residual risk target					
Residual risk-lowering therapies	Ezetimibe PCSK9 inhibitor *Omega-3 fatty acids*	Canakinumab *Methotrexate* *Colchicine*	SGLT2 inhibitor GLP-1 agonist	Extended DAPT Low dose ticagrelor	Low-dose rivaroxaban
Precision medicine toolbox	Standard lipids (e.g., LDL, HDL, TG), advanced lipid testing, Lp(a), HDL efflux capacity, genetic risk scores, atherosclerosis imaging	hs-CRP; biomarkers of inflammation, T cell and immune dysregulation, and clonal hematopoiesis; systemic inflammatory disease (e.g., psoriasis)	Prevalent type 2 DM, Hb A1c, HOMA-IR, BMI, visceral adiposity, liver fat	Antiplatelet risk scores (e.g., DAPT, PARIS, PRECISE-DAPT), platelet function testing, pharmacogenomics	PVD, prior VTE, thrombophilia, bleeding risk scores, coagulation biomarkers

Patel KV et al Circulation. 2018;137:2551–2553

Aggressive LDL-C Lowering Does Not Eliminate ASCVD Risk
Significant Residual Risk Remains Untreated



Residual risk due to increased triglycerides, elevated Lp(a), non – HDL, hyperglycemia and/or other untreated risk factors

Cannon CP, et al. *NEJM.* 2015;372(25)2387-97.

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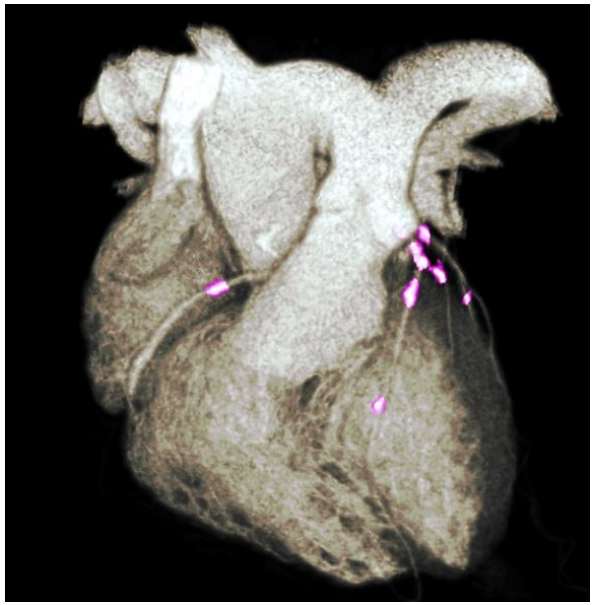
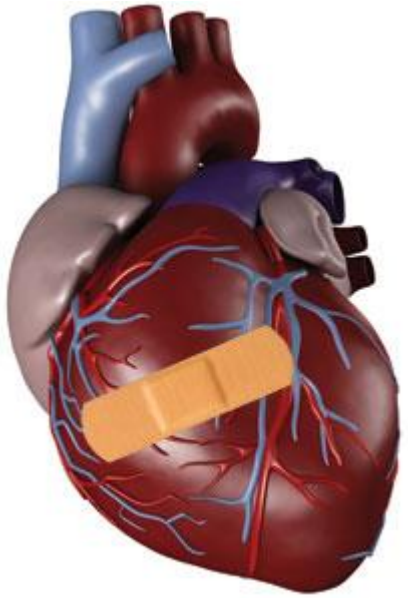
Continuum of ASCVD Risk





Primary Prevention → **High Risk Primary Prevention** **Advanced Subclinical Atherosclerosis?** → **Secondary Prevention**

Blaha MJ, *AJC* 2016

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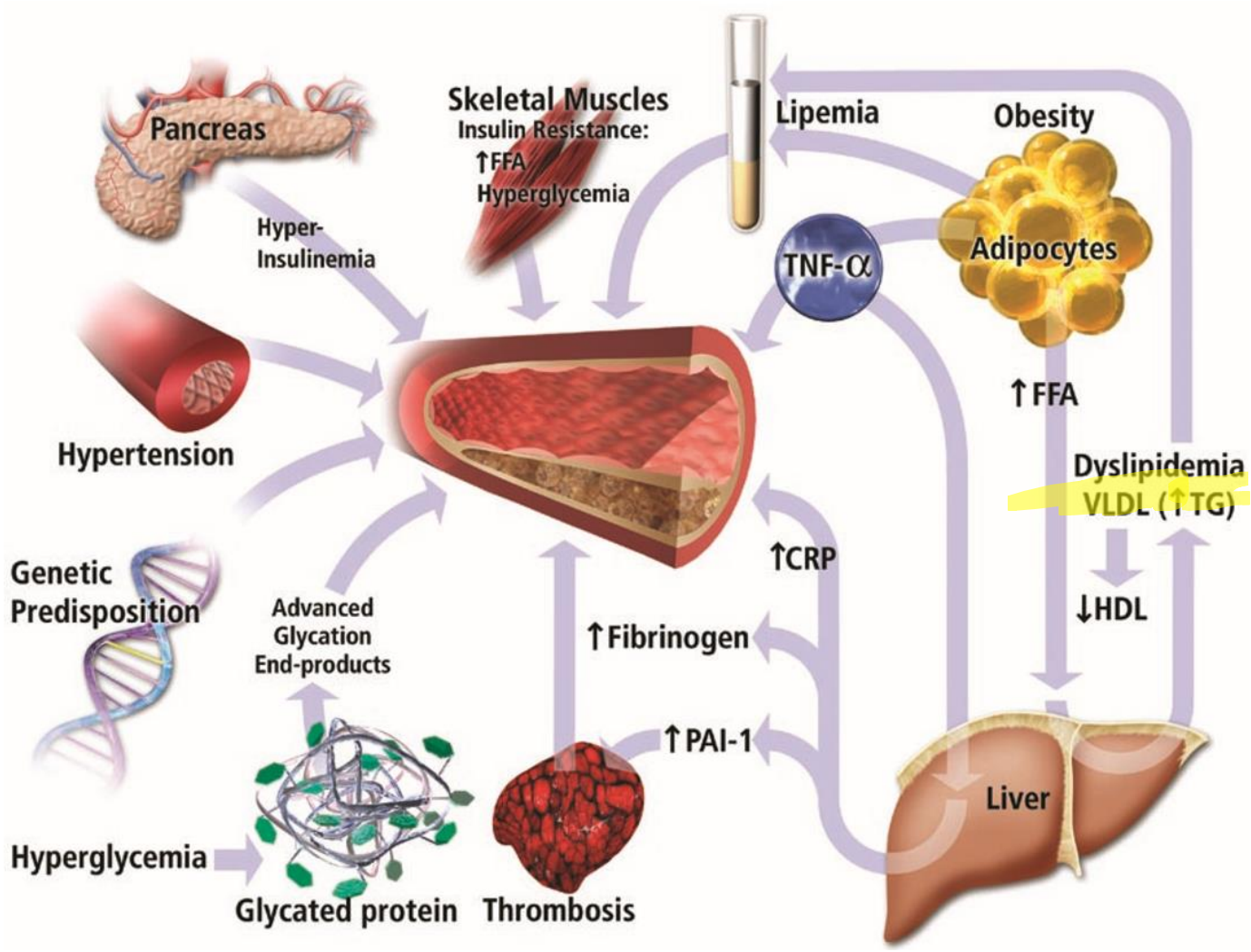
Type 2 Diabetes is a Cardiovascular Disease

Many factors contribute to increased CV risk in T2D



Libby P and Plutzky J, Circulation. 2002;106:2760–276

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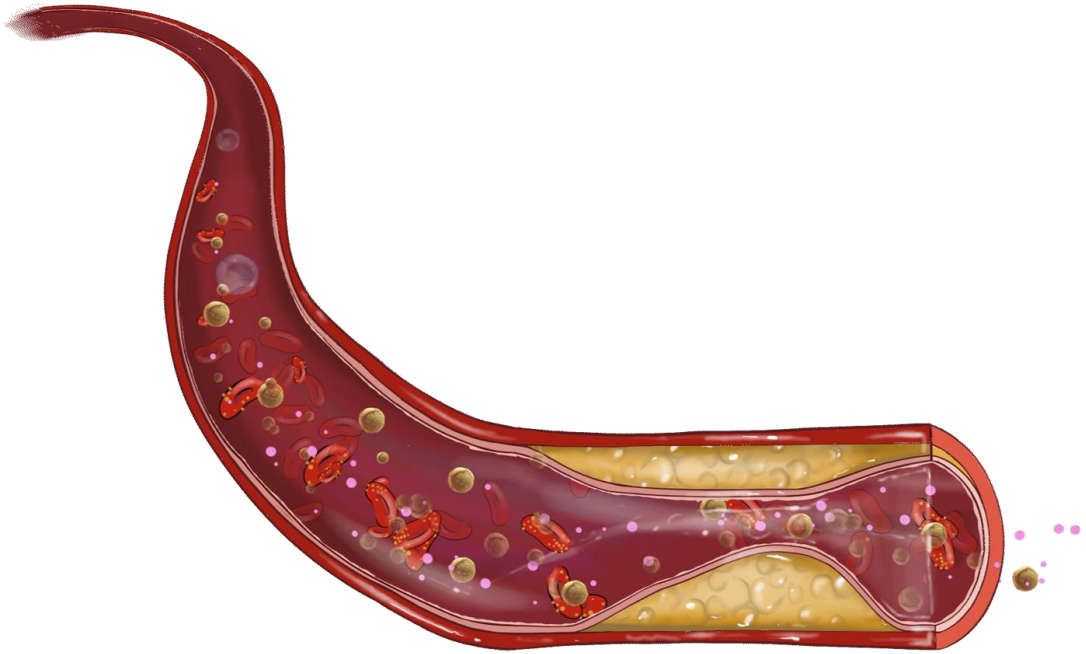
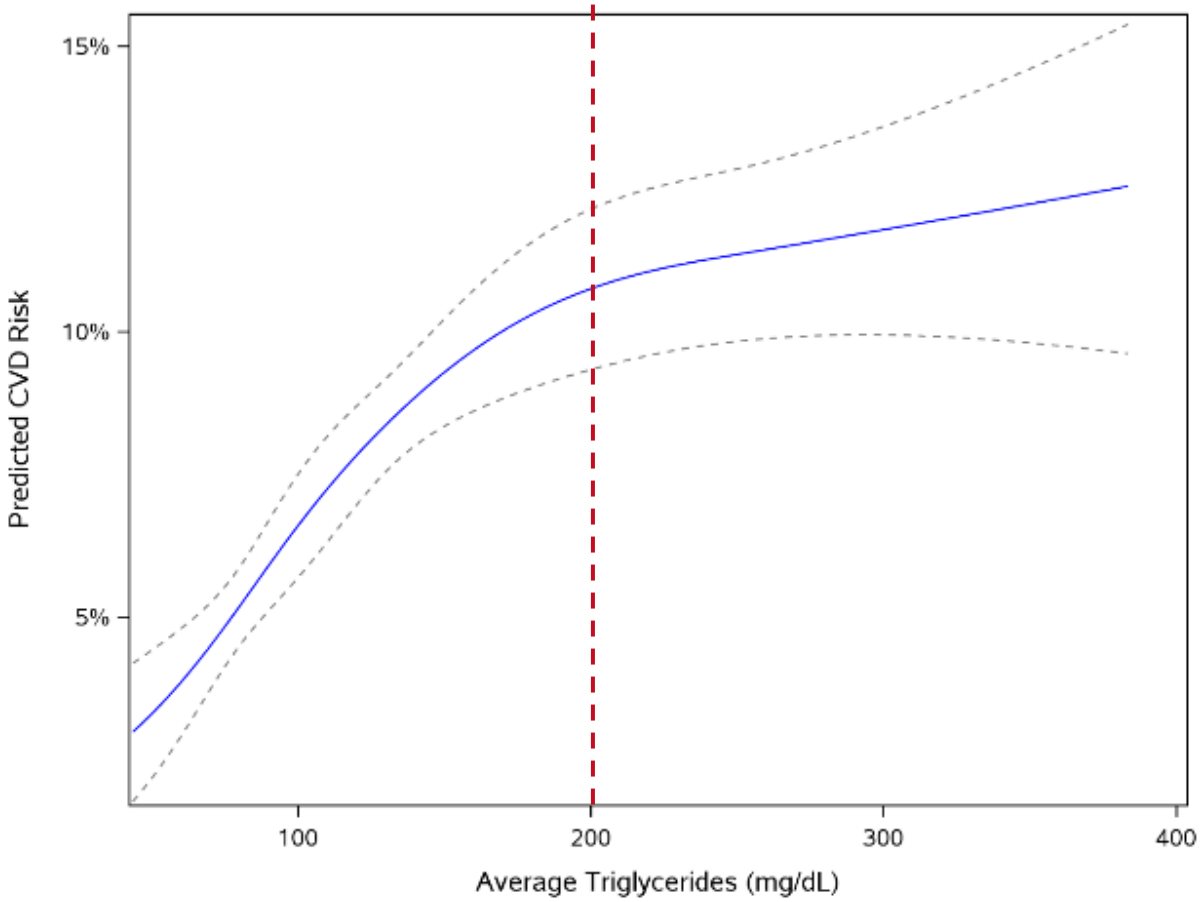
Triglycerides are a Reflection of the Bad Company they Keep



- “It is what is flowing with it.”
- Capturing an atherogenic phenotype

CVD Increases Dramatically w/ TG Increases Even Just "Normal" to "Upper Normal" Range



- 8,068 primary prevention patients in Atherosclerosis Risk in Communities Study (ARIC) and Framingham Offspring Study
  - 40 to 65 years old
  - No CVD
- ≥2 TG measurements on record
- Endpoint: Time to MI, stroke, or CV death
- Follow-up for up to 10 years to first event

CVD events steeply increase across the entire range of TG levels to ~200 mg/dL, above which the relationship is less graded.

95% confidence intervals shown as dotted lines.

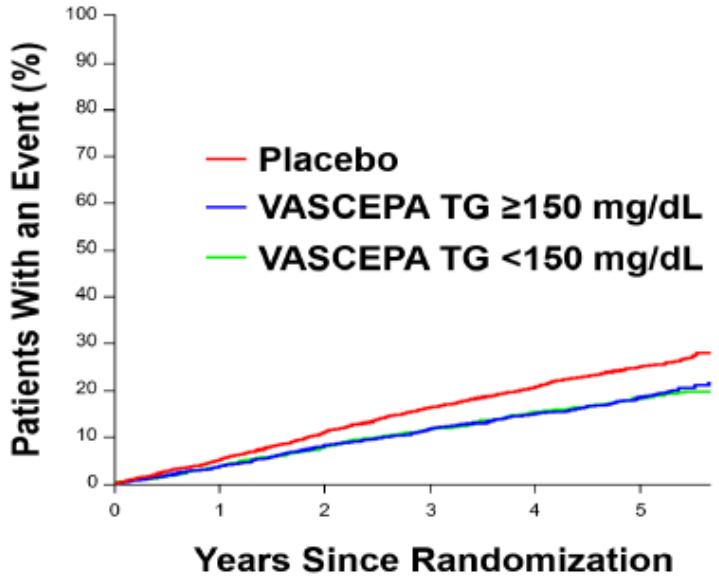
Aberra T, et al. *J Clin Lipidol*. 2020;14(4):438-447.e3.

CVD Reduction with EPA Comparable with *On-Treatment* TG Above vs Below 150 mg/dl

1.7 mmol/L

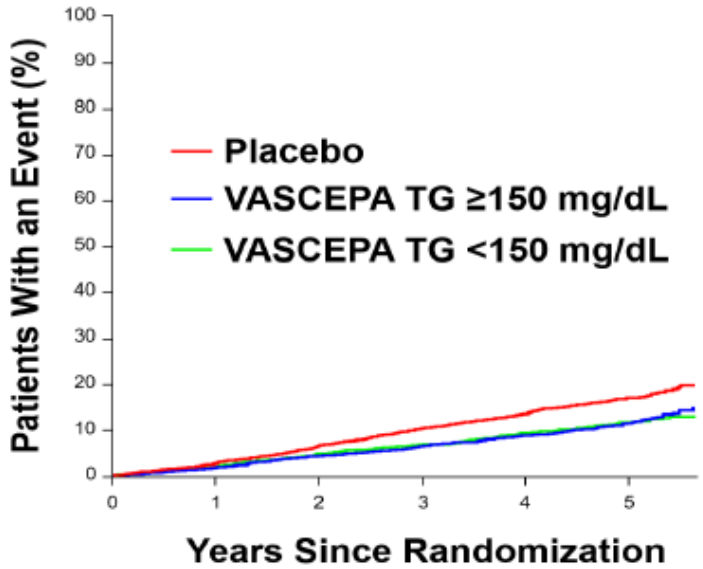
Primary Endpoint by Achieved TG Level at 1 Year

VASCEPA TG	HR (95% CI)
<150 vs ≥150 mg/dL	0.99 (0.84–1.16)
≥150 mg/dL vs Placebo	0.71 (0.63–0.79)
<150 mg/dL vs Placebo	0.70 (0.60–0.81)



Key Secondary Endpoint by Achieved TG Level at 1 Year

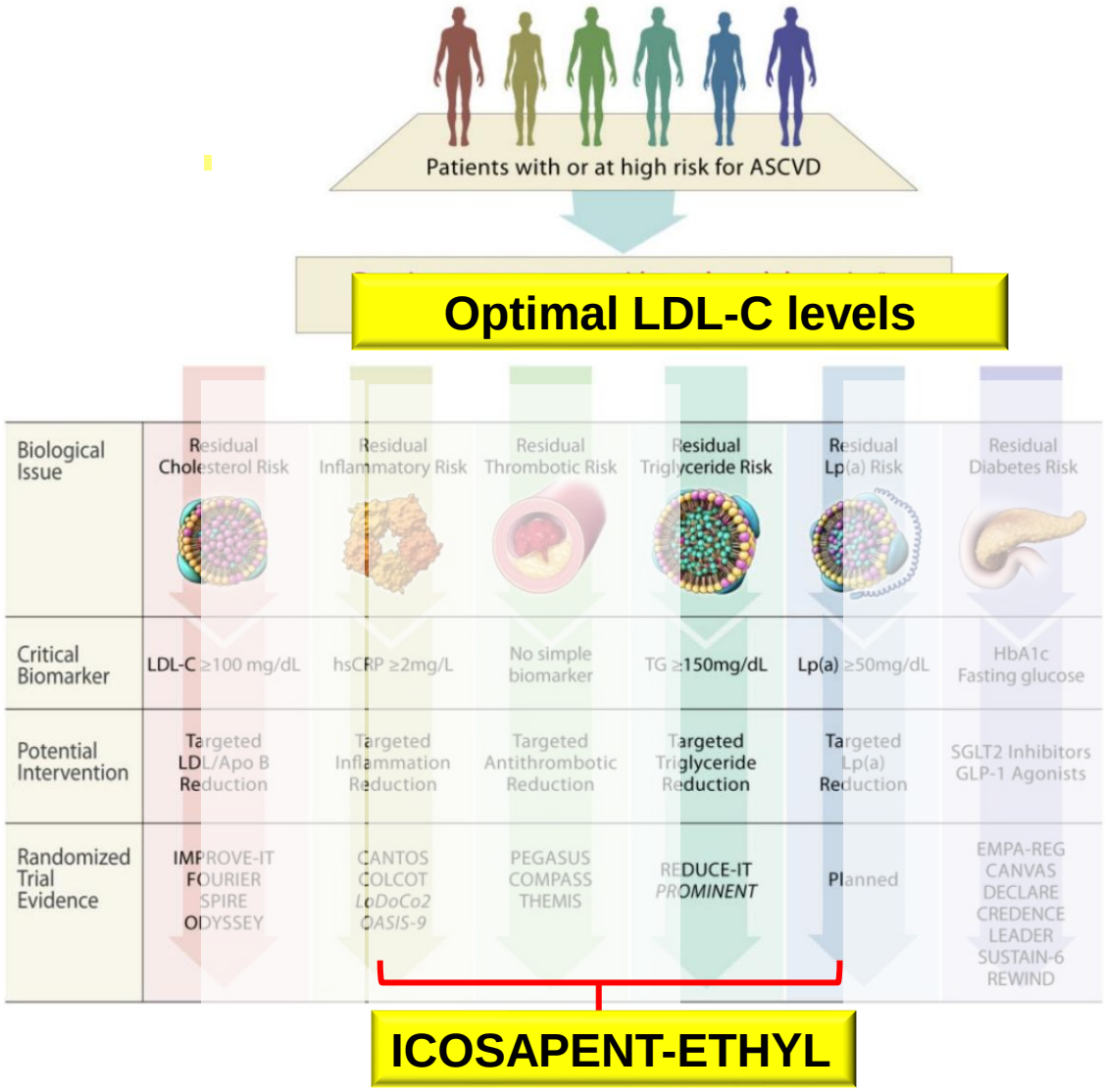
VASCEPA TG	HR (95% CI)
<150 vs ≥150 mg/dL	1.00 (0.82–1.23)
≥150 mg/dL vs Placebo	0.67 (0.56–0.80)
<150 mg/dL vs Placebo	0.66 (0.57–0.77)



1. REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. Nov 2018. doi:10.1056/NEJMoa1812792.

reduce-it™

Icosapent-ethyl (IPE): Impact on Multiple Components of CV Residual Risk



Review

Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement

Ian J Neeland, Robert Ross, Jean-Pierre Després, Yuji Matsuzawa, Shizuya Yamashita, Iris Shai, Jaap Seidell, Paolo Magni, Raul D Santos, Benoit Arsenault, Ada Cuevas, Frank B Hu, Bruce Griffin, Alberto Zambon, Philip Barter, Jean-Charles Fruchart, Robert H Eckel, for the International Atherosclerosis Society and the International Chair on Cardiometabolic Risk Working Group on Visceral Obesity

Lancet Diabetes Endocrinol 2019; 7: 715–25
Published Online July 10, 2019
http://dx.doi.org/10.1016/S2213-8587(19)30084-1

Mild to moderate Hypertriglyceridemia

Impaired glucose tolerance

Type 2 diabetes

Cardiovascular disease
- Hypertension
- Heart failure
- Coronary heart disease, myocardial infarctions
- Valve diseases
- Arrhythmias

Pro- atherothrombotic phenotype

Modest elevation of hsCRP – Subclinical inflammation

Brain health
- Stroke, necrosis
- Reduced brain size
- Reduced grey matter
- Reduced cognitive function
- Dementia

Cancers

Others
- Reduced bone density
- Polycystic ovary syndrome
- HIV infection and antiretroviral therapy*

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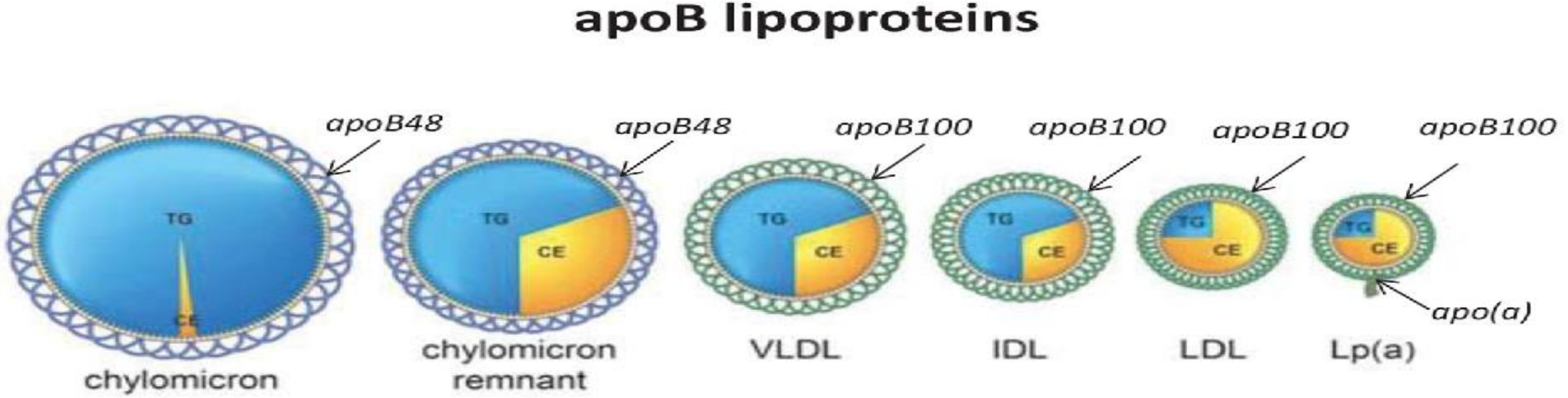
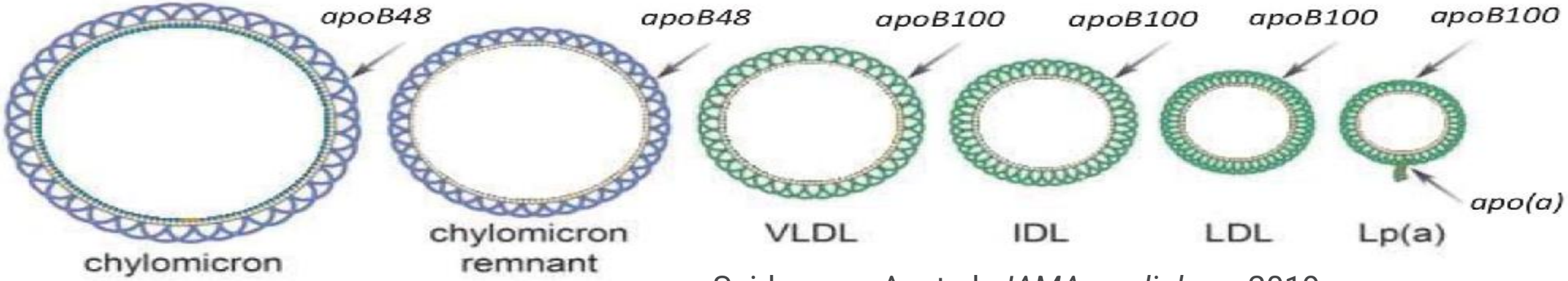
REDUCE-IT
Effects on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (n = 4089) Median		Placebo (n = 4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change *P*-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	< 0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	< 0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	< 0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	< 0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	< 0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	< 0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	< 0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	**+358.8**	< 0.0001

Bhatt DL, et al. *NEJM.* 2019;380(1):11-22

Apo B is the Structural Backbone of all Atherogenic Lipids

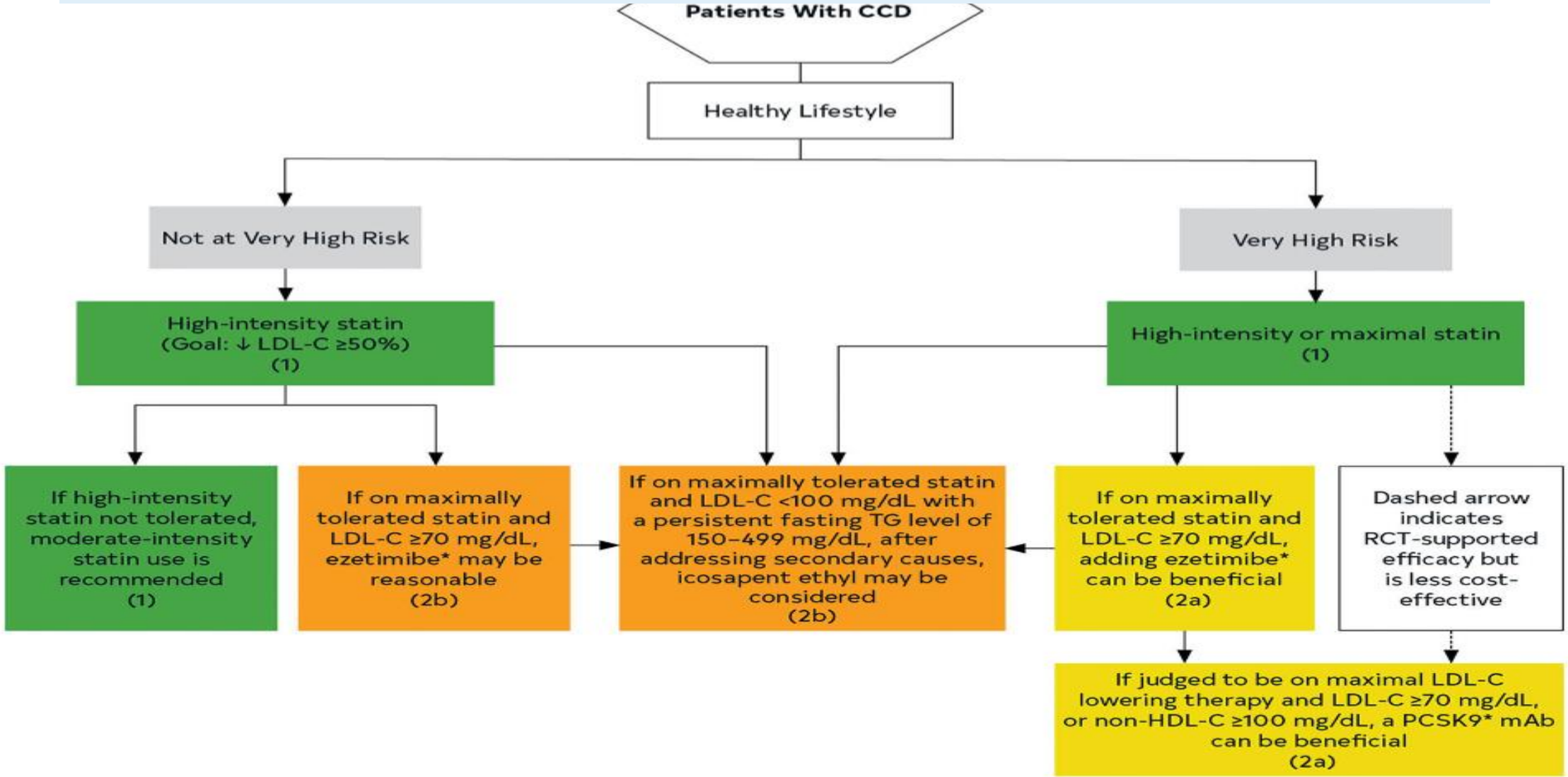




Sniderman, A. et al. *JAMA cardiology*, 2019

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease

A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines



Case Presentation

- 66 year old female with a history of CAD, PCI of LAD 8 months ago, HTN, T2DM, atrial fibrillation, and hypothyroidism.
- Current medications: atorvastatin 40 mg qd, amlodipine 10 mg qd, aspirin 81 mg qd, clopidogrel 75 mg qd, levothyroxine 75 mcg qd apixaban 5 mg bid, metformin 1000 mg bid, empagliflozin 10 mg qd
- Exam: Blood Pressure: 130/85 HR 70; BMI 30 kg/m^2
- Laboratory Data:

  Total Cholesterol: 140 mg/dL (3.6 mmol/L)

  HDL: 30 mg/dL (0.7 mmol/L)

  Calculated LDL: 53 mg/dL   (1.4 mmol/L)

  Triglycerides: 287 mg/dL (3.24 mmol/L)

  Non-HDL: 110 mg/dL (1.24 mmol/L)

  HbA1c: 7.6

  Creatinine 1.4 mg/dL; eGFR 55 mL/min

Management of this patient

- Optimize Lifestyle Strategies
  - Discuss lifestyle management including: aerobic exercise, Mediterranean diet avoidance of concentrated sugars/alcohol and improved glycemic control

- Get the LDL-C/non HDL-C “as low as you can go” with a minimum goal of less than 55 mg/dL in this very high-risk patient
  - Optimize statin therapy and utilize non-statin agents

- Concomitantly add Icosapent Ethyl for Global CV Risk Reduction
  - In addition to triglyceride lowering icosapent ethyl will have an impact on multiple aspects of residual risk.

Summary

- Triglycerides are marker for increased CV risk and risk increases with even with mild elevation >100 mg/dL (1.1 mmol/L).
- In clinical trials in which only triglycerides are lowered no benefit in CV outcomes.
- In clinical trials where triglycerides were lowered concomitantly with ApoB improvement in CV outcomes was seen.
- The benefit of icosapent ethyl goes beyond triglyceride-lowering and it should be considered as an agent for global CV risk reduction.

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