"How Low Should We Go with Lipids?"

ATDC - July 17, 2021

University of Colorado
Anschutz Medical Campus

Robert H. Eckel, M.D.

Professor of Medicine, Emeritus

Division of Endocrinology, Metabolism & Diabetes

Divsion of Cardiology

S/P Charles A. Boettcher II Chair in Atherosclerosis

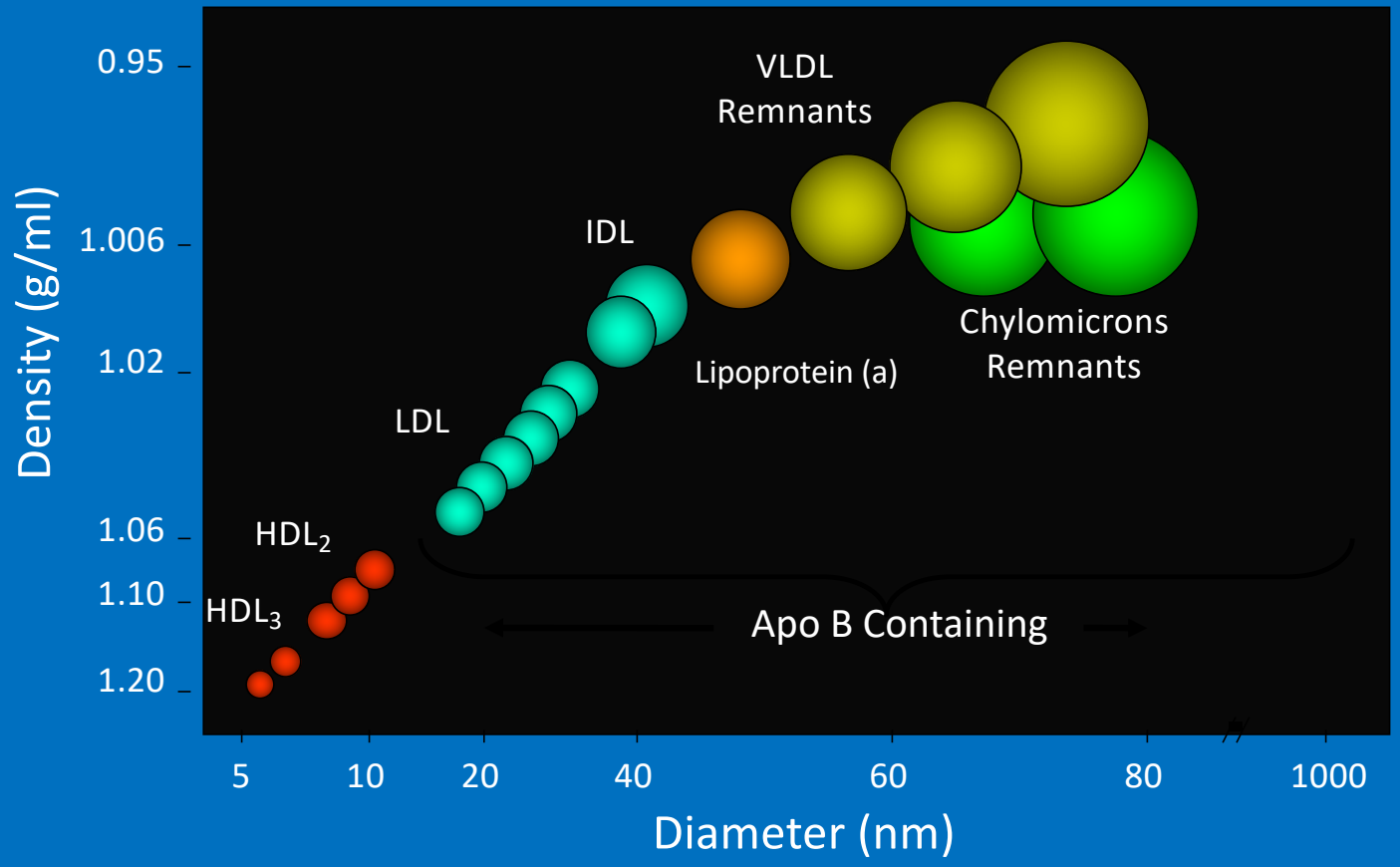
University of Colorado Anschutz Medical Campus

Duality of Interests

– ***Consultant/Advisory Boards***
  - Kaleido
  - Kowa - PROMINENT
  - Provention Bio
  - The Healthy Aging Co.

– ***Medical Education***
  - CMHC
  - Medtelligence
  - VOX Media

Lipoprotein Classes



What's Left to be Accomplished with Lipids and Lipoproteins in Patients with Diabetes?

- How much LDL-C lowering is needed?
  - Should we be concerned about the absence RCTs for LDL lowering in patients with T1DM?
- Are elevated triglycerides truly a risk factor for ASCVD in patients with or without diabetes (T2DM or T1DM)?
  - What's the optimal treatment goal for patients with severe hypertriglyceridemia?

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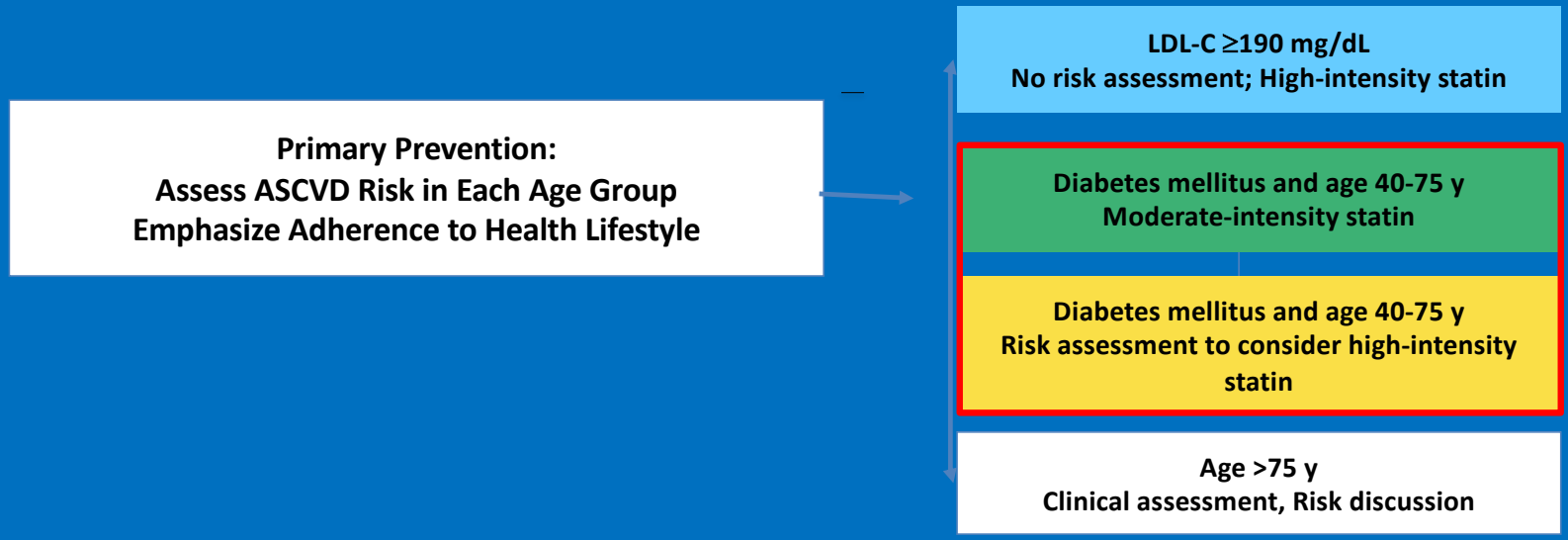
So, if my patient with T2DM has experienced an ASCVD event or is at very high CVD risk, what is the treatment goal for LDL-C ?

2019 ACC/AHA Guidelines: High Risk of CVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Grundy SM et al, *Circulation* 139:1083, 2019

AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/ PCNA Guideline (2018) on the Management of Blood Cholesterol: Primary Prevention

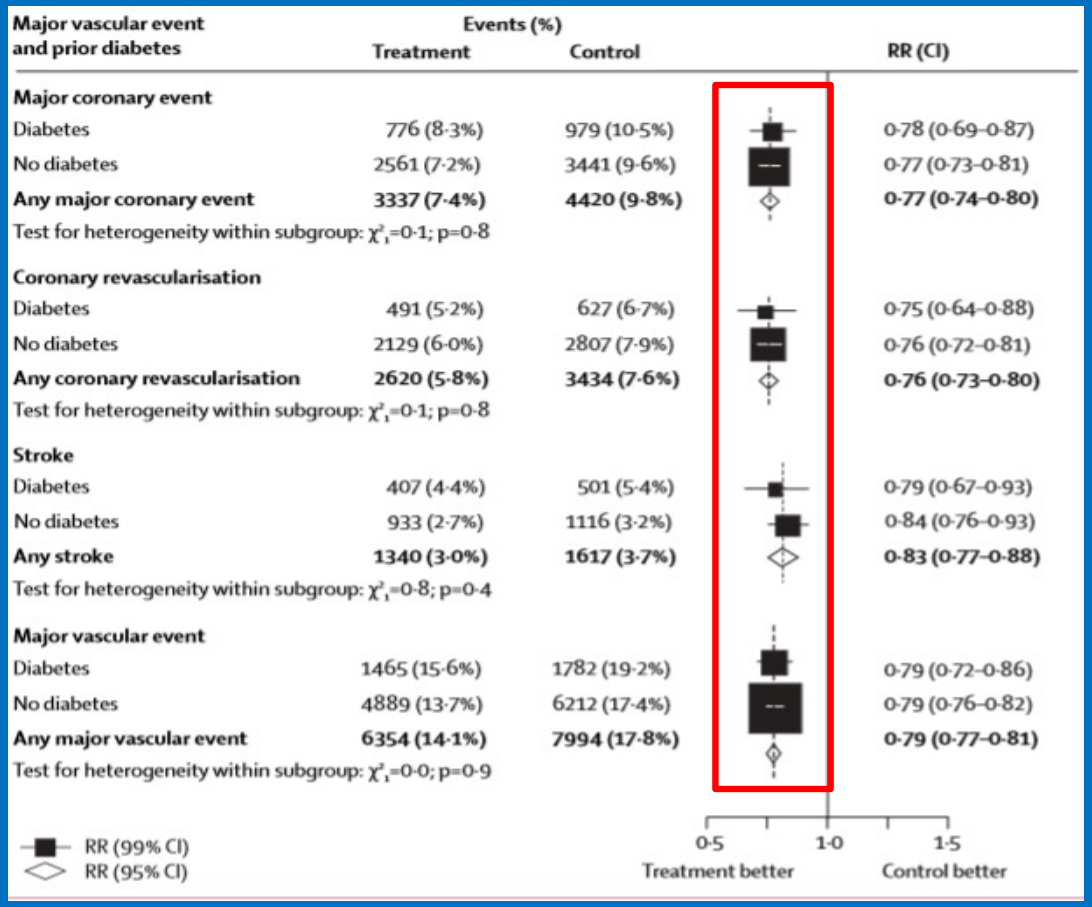


- Class I (Strong). Benefit >>> Risk.
- Class IIa (Moderate). Benefit >> Risk.
- Class IIb (Weak). Benefit ≥ Risk.

Grundy SM et al, *Circulation* 139:1083, 2019

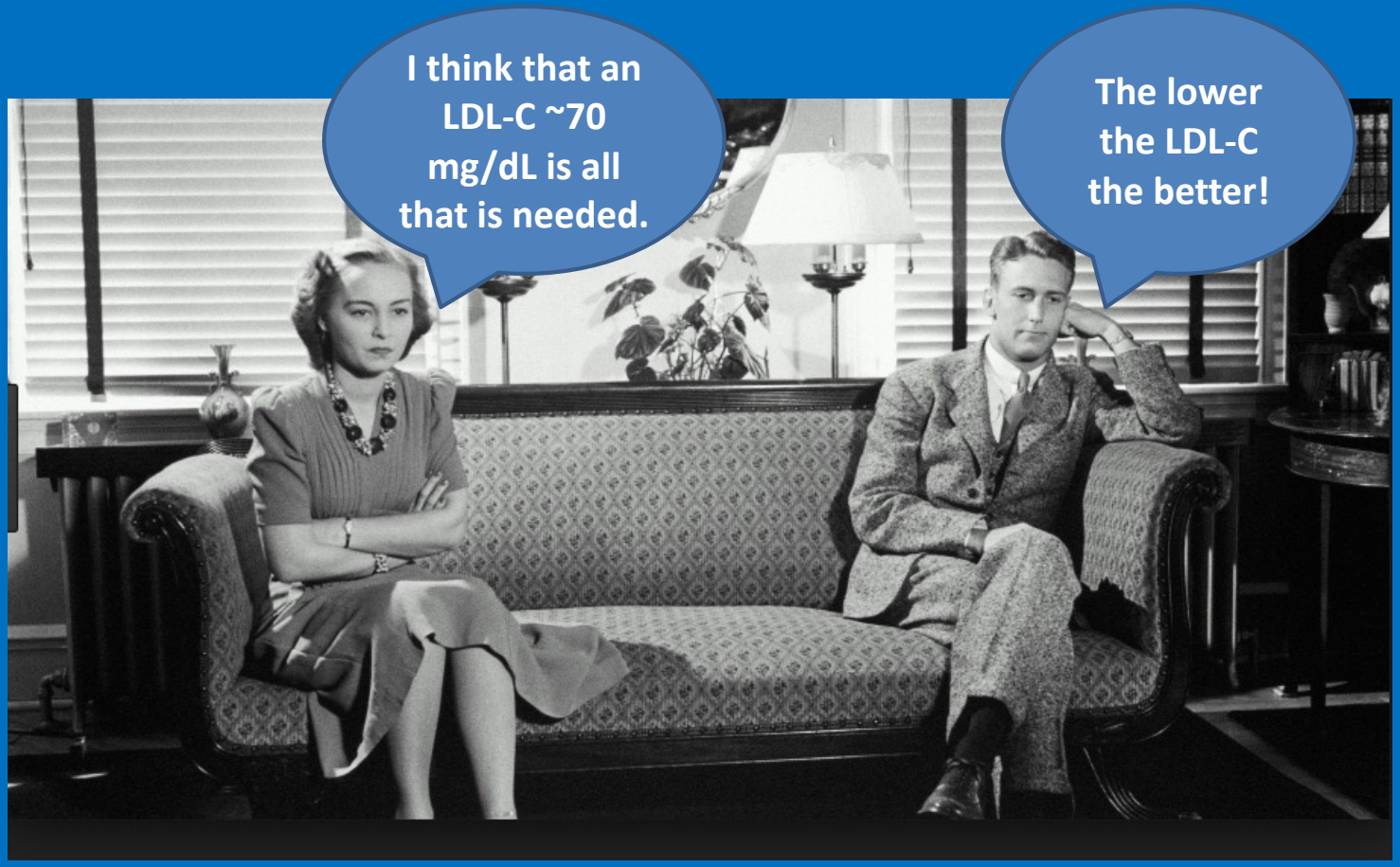
Statins in Patients with Diabetes: CTT 2008

(n=3247 major CVD events)

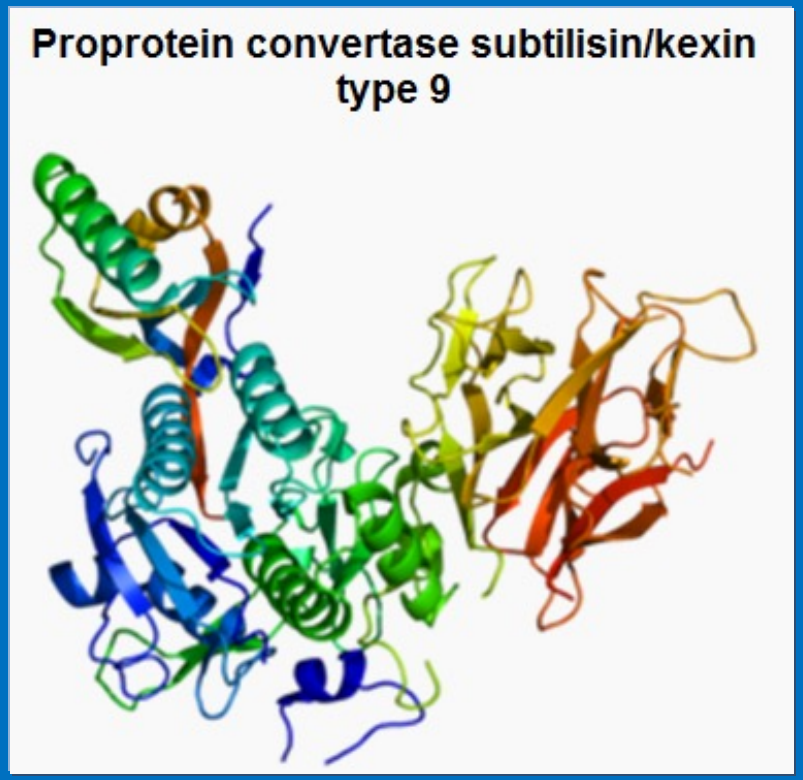


Major vascular event and prior diabetes	Events (%) Treatment	Control	RR (CI)
Major coronary event			
Diabetes	776 (8·3%)	979 (10·5%)	0·78 (0·69–0·87)
No diabetes	2561 (7·2%)	3441 (9·6%)	0·77 (0·73–0·81)
Any major coronary event	**3337 (7·4%)**	**4420 (9·8%)**	**0·77 (0·74–0·80)**
Test for heterogeneity within subgroup: χ^2_1=0·1; p=0·8			
Coronary revascularisation			
Diabetes	491 (5·2%)	627 (6·7%)	0·75 (0·64–0·88)
No diabetes	2129 (6·0%)	2807 (7·9%)	0·76 (0·72–0·81)
Any coronary revascularisation	**2620 (5·8%)**	**3434 (7·6%)**	**0·76 (0·73–0·80)**
Test for heterogeneity within subgroup: χ^2_1=0·1; p=0·8			
Stroke			
Diabetes	407 (4·4%)	501 (5·4%)	0·79 (0·67–0·93)
No diabetes	933 (2·7%)	1116 (3·2%)	0·84 (0·76–0·93)
Any stroke	**1340 (3·0%)**	**1617 (3·7%)**	**0·83 (0·77–0·88)**
Test for heterogeneity within subgroup: χ^2_1=0·8; p=0·4			
Major vascular event			
Diabetes	1465 (15·6%)	1782 (19·2%)	0·79 (0·72–0·86)
No diabetes	4889 (13·7%)	6212 (17·4%)	0·79 (0·76–0·82)
Any major vascular event	**6354 (14·1%)**	**7994 (17·8%)**	**0·79 (0·77–0·81)**
Test for heterogeneity within subgroup: χ^2_1=0·0; p=0·9			

CTT Analysts, *Lancet* 371:117, 2008


I think that an LDL-C ~70 mg/dL is all that is needed.
The lower the LDL-C the better!

PCSK9 is proprotein convertase subtilisin/kexin type 9 (PCSK9)



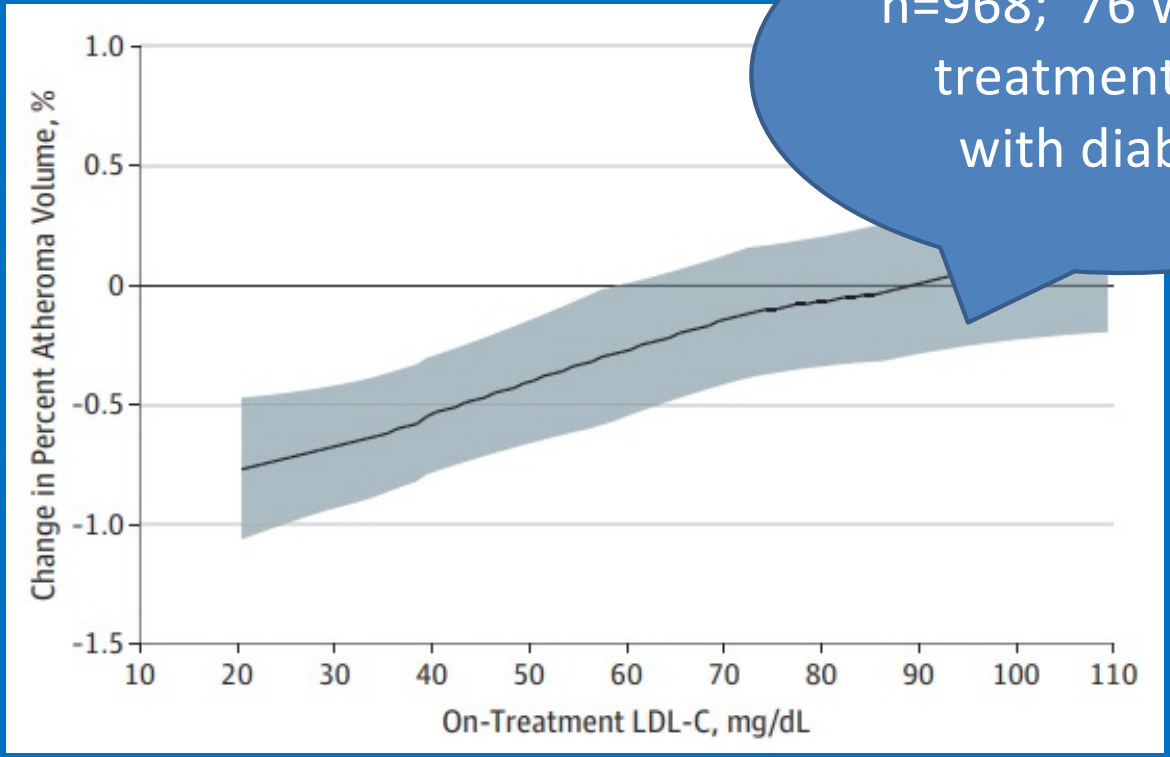
Can LDL-C Be Too Low?

- Abetalipoproteinemia & homozygous hypobetalipoproteinemia
  - Autosomal recessive
    - MTP, and/or apo B and LIMA1 gene mutations
  - Absent apo B-containing lipoproteins
    - Chylomicrons, VLDL, LDL
  - Neurological and ophthalmological sequela prevented by fat-soluble vitamins
  - Malabsorption prevented by low fat diet + essential fatty acids
  - Hepatic steatosis and AST/ALT elevations
  - No ASCVD
- PCSK9 inhibitor trials without adverse effects

Lee J & Hegele RA, *J Inherit Metab Dis* 37:333, 2014

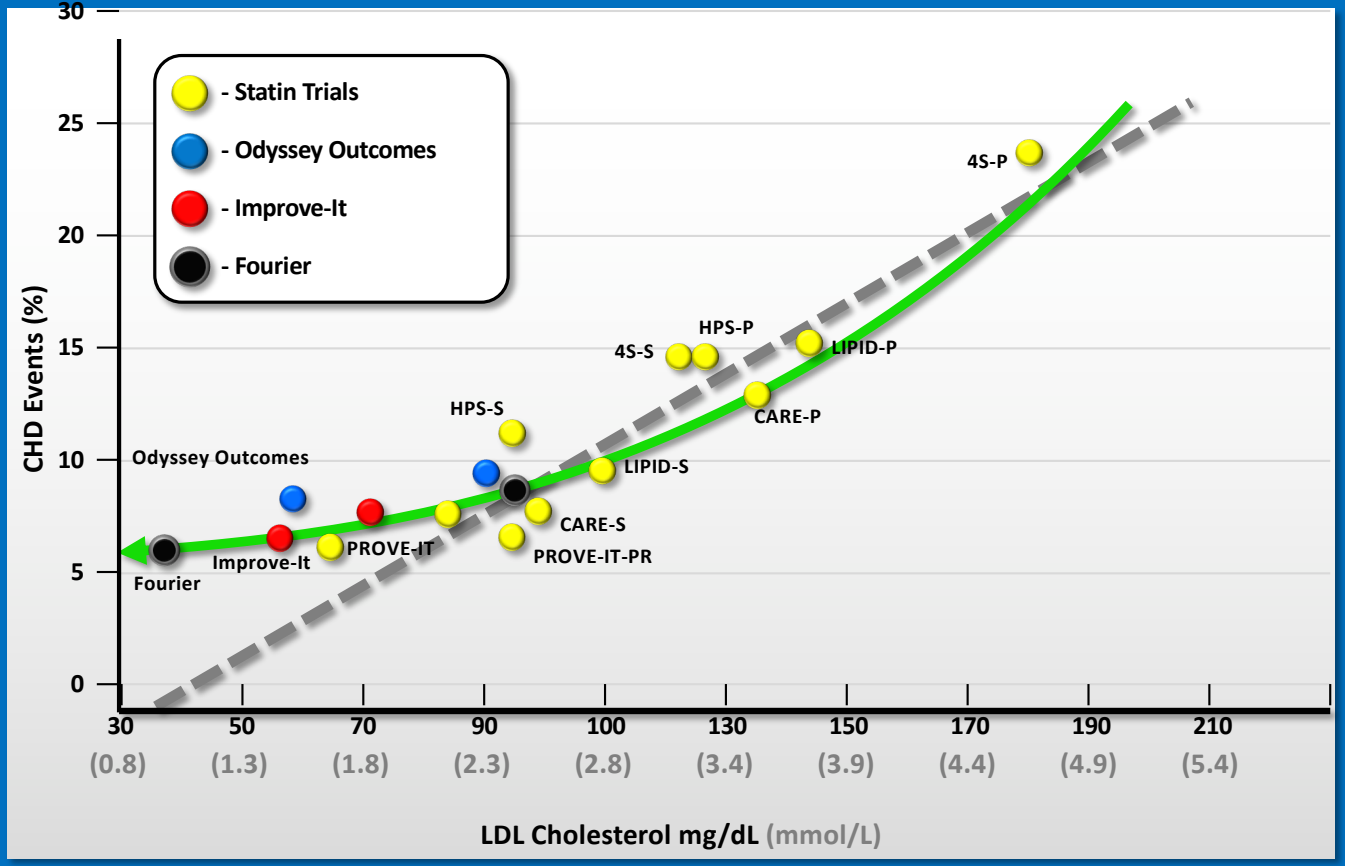
Post Hoc Analysis of the Relationship Between Evolocumab-achieved LDL-C and Change in Percent Atheroma Volume

n=968; 76 weeks of treatment, 20% with diabetes



Nicholls SJ et al, *JAMA* 316:2373, 2018

Absolute Risk Reduction of LDL-C Lowering Begins to Plateau



Adapted from O'Keefe, J. et al., *JACC* 43:2142, 2004 + RHE 2019

Now let's turn to the statin/T1DM data!

Lipid-Lowering Therapy and CVD and Death in Patients with T1DM

- Swedish National Diabetes Registry
  - n = 24,230 patients from 2006-2008
    - No history of CVD
    - Followed until December 31, 2012
      - 18,843 untreated
      - 5,387 treated **(97% statins)**
  - Propensity score balanced 32 covariates
    - No differences between groups

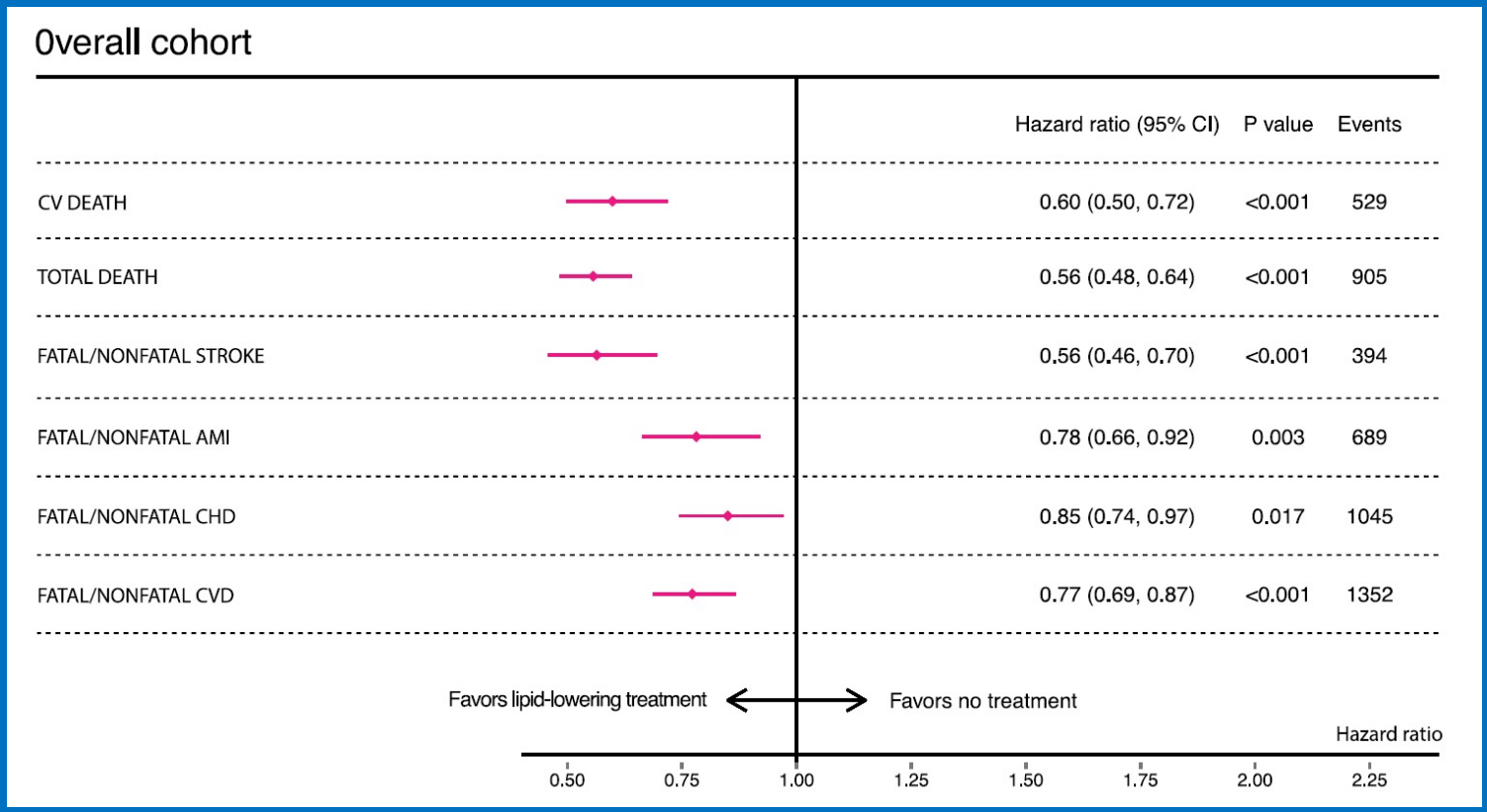
Hero C et al, *Diabetes Care*, 39:996, 2016

Swedish National Diabetes Register: Baseline Data

Variable	Untreated	'Statin'-Treated
Male	53.0%	56.6%
Age	36.3±12.7	50.4±11.7
Diabetes Duration	21.0±13.2	34.0±12.8
Smokers	12.1%	12.8%
BMI	25.1±4.3 kg/m^2	26.8±4.5 kg/m^2
HbA1c	8.0±1.4%	8.2±1.3%
eGFR	96.5±26.5 mL/min	79.9±27.3 mL/min
Systolic BP	125±15 mm	135±17 mm
Triglycerides	1.07±0.8 mmol/L	1.34±1.08 mmol/L
HDL-C	1.62±0.49 mmol/L	1.65±0.52 mmol/L
LDL-C	2.60±0.77 mmol/L	2.66 ±0.89 mmol/L

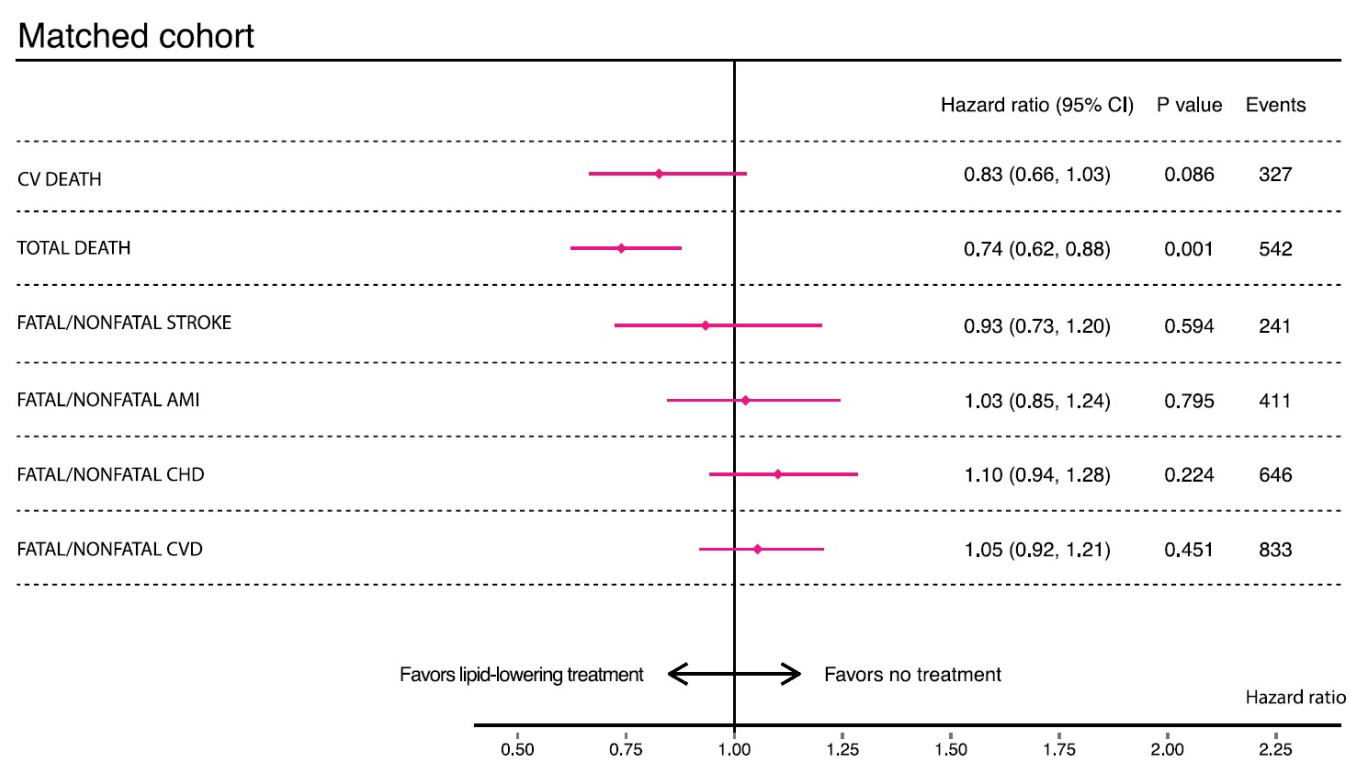
Hero C et al, *Diabetes Care*, 39:996, 2016

‘Statin’ Therapy on CVD and Death in Patients with T1DM: Overall Cohort



Hero C et al, *Diabetes Care*, 39:996, 2016

‘Statin’ Therapy on CVD and Death in Patients with T1DM: Matched Cohort (n=4025 each)



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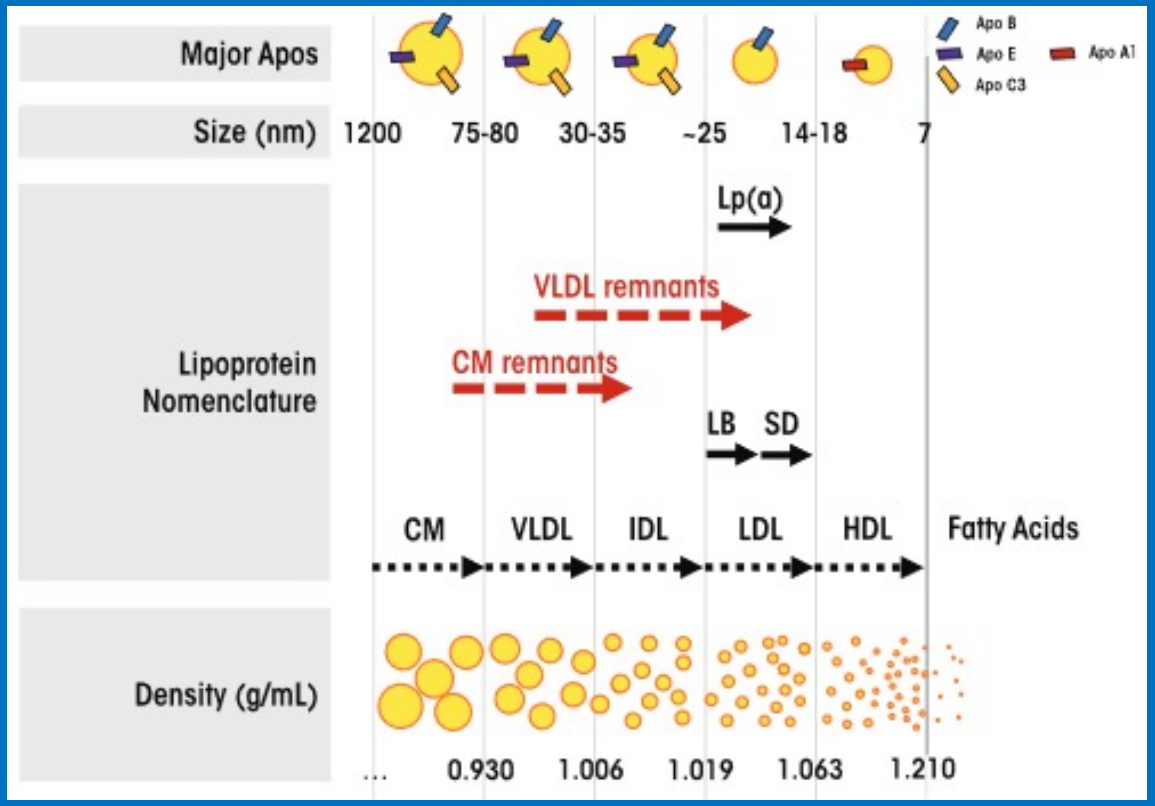
But, hypertriglyceridemia + reduced levels of HDL-C is the most common lipid/lipoprotein disorder in patients with T2DM!

But increasing evidence from basic science and CVOTs indicate that hypertriglyceridemia is simply associated with but does not cause ASCVD in patients with T2DM, or even without diabetes!



It's likely the Cholesterol Content of VLDL and Chylomicron Remnants

The plaque is mostly cholesteryl ester not TG!

Duran EK & Pradhan AD, *Clin Chem* 67:183, 2021

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REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Mechanistic Insights from REDUCE-IT STRENGTHen the Case Against Triglyceride Lowering as a Strategy for Cardiovascular Disease Risk Reduction

R. Preston Mason, PhD,[a] Robert H. Eckel, MD[b]

[a]Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; [b]University of Colorado Anschutz Medical Campus, Aurora.

ABSTRACT

Elevated triglyceride (TG) levels have been linked to residual atherosclerotic cardiovascular risk in patients with controlled low-density lipoprotein cholesterol. However, outcome trials testing TG-lowering agents have failed to demonstrate cardiovascular risk reduction in statin-treated subjects. One such example is the recent STRENGTH trial, which tested mixed omega fatty acids (n3-FAs, 4 g/d) in high-risk patients with elevated TGs. Similar to trials using fibrates and niacin, the STRENGTH trial failed despite effective TG lowering. Results from these studies have contributed to skepticism about the use of TG-lowering therapy for cardiovascular risk. However, new mechanistic insights are provided by the REDUCE-IT trial that used icosapent ethyl (IPE), a purified formulation of the n3-FA eicosapentaenoic acid. In high-risk patients, IPE reduced a composite of cardiovascular events (25%, $P < .001$) in a manner not predicted by TG lowering. Benefits with IPE appear linked to broad pleiotropic actions associated with on-treatment eicosapentaenoic acid levels. These studies indicate that although TGs are a potential biomarker of cardiovascular risk, there is no evidence that TG lowering itself is an effective strategy for reducing such risk.
 • The American Journal of Medicine (2021) 000:1–6

KEYWORDS: Atherosclerosis; cholesterol; docosahexaenoic acid; eicosapentaenoic acid; low-density lipoprotein; omega-3 fatty acid; statin; triglyceride

Fibrate Triglyceride Lowering CVOTs in Patients with T2DM

Study	Drug	'n'	TG (Criteria)	TG ↓	Primary Endpoint ↓
VA-HIT (DM)	Gemfibrozil	2531 (550)	160 mg/dl (<300)	31%	24%*
BIP (DM)	Bezafibrate	3090 (330)	145 mg/dl (<300)	21%	7%
FIELD (DM)	Fenofibrate	9795	156 mg/dl (90-450)	29%	11%
ACCORD-LIPID (DM)	Simvstatin ± Fenofibrate	2532	162 mg/dl (<400)	20%	8%

Recent CVOTs with Omega-3 Fatty Acids

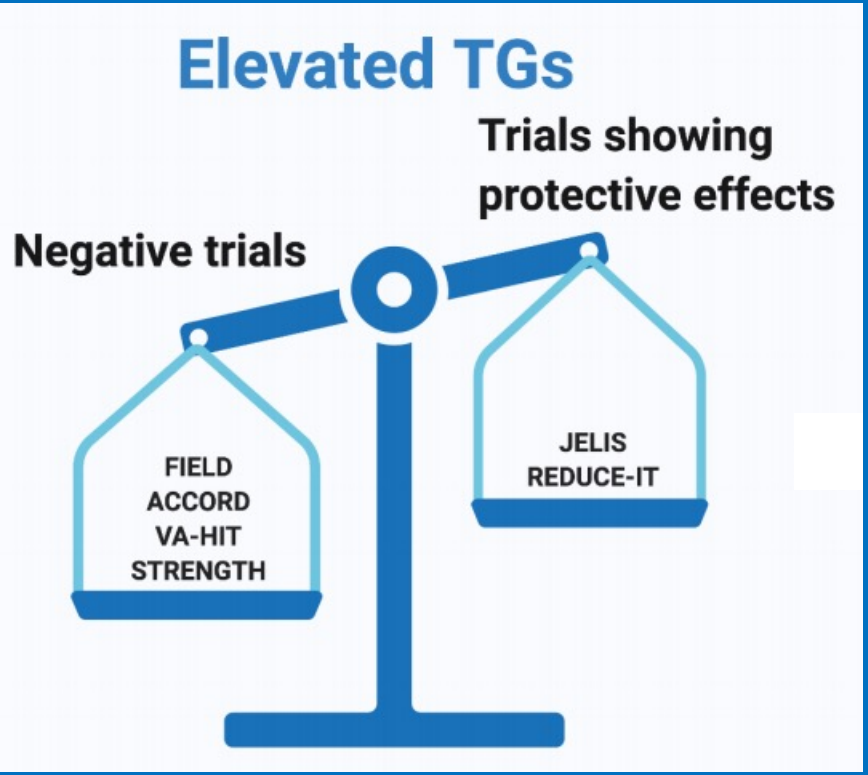
	JELIS (18,645)	REDUCE-IT (8179)	STRENGTH (13,078)
Population*	Hypercholesterolemic	High cardiovascular risk, Elevated TG	High cardiovascular risk, Elevated TG, low HDL
Formulation	IPE (1.8 g/d EPA)	IPE (4 g/d EPA)	EPA/DHA carboxylic acids (4 g/d)
Baseline median TG (mg/dL)	153	216	240
Baseline EPA (μg/mL)	97	26.1	21.0
Achieved EPA (μg/mL)	169	144	89.6
Increase in achieved EPA levels (%)	70	394	269
TG lowering (%)	9	17	19
Primary endpoint	Major coronary events	Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina
HR, 95% CI of primary endpoint	0.81, 0.69-0.95 (P = .011)	0.75, 0.68-0.83 (P = .00000001)	0.99, 0.90-1.09 (P = .84)

Mason RP, Eckel RH, *Am J Med* 2021, In press

CLINICAL SIGNIFICANCE

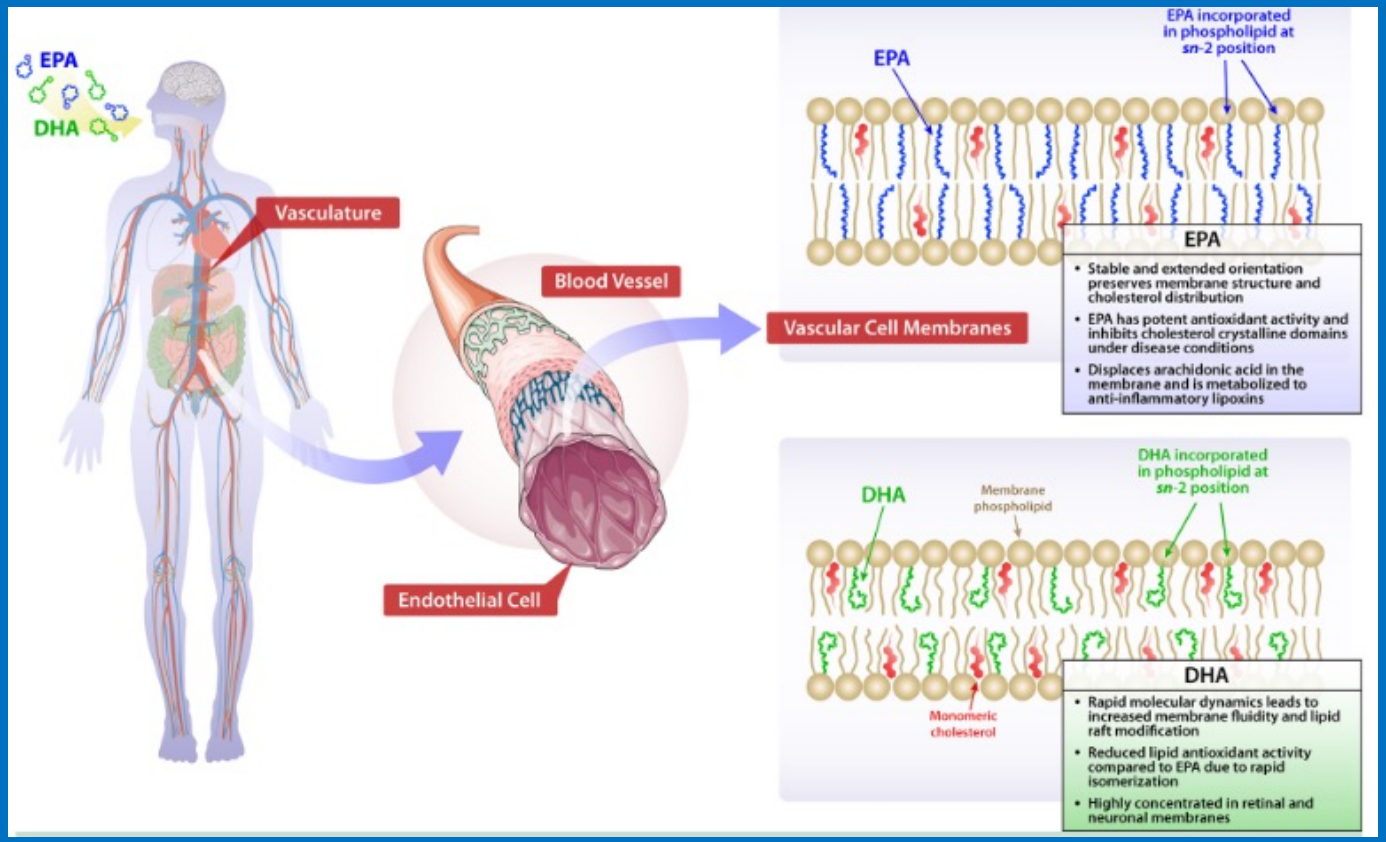
- Elevated triglycerides (TGs) are associated with increased cardiovascular risk; however, current TG-lowering therapies are ineffective in reducing such risk.
- Icosapent ethyl, highly purified eicosapentaenoic acid, was recently shown to reduce cardiovascular events by 25% and was not associated with TG lowering.
- Icosapent ethyl appears to have broad pleiotropic effects associated with on-treatment eicosapentaenoic acid levels.
- Evidence against TG lowering in reducing cardiovascular risk should guide other therapeutic strategies to lower residual risk.

CVOTs in T2DM



Mason RP, Eckel RH, *Am J Med* 2021, In press.

Comparative Effects of EPA vs. DHA on Membrane Structure, Fatty Acid Oxidation and Tissue Distribution

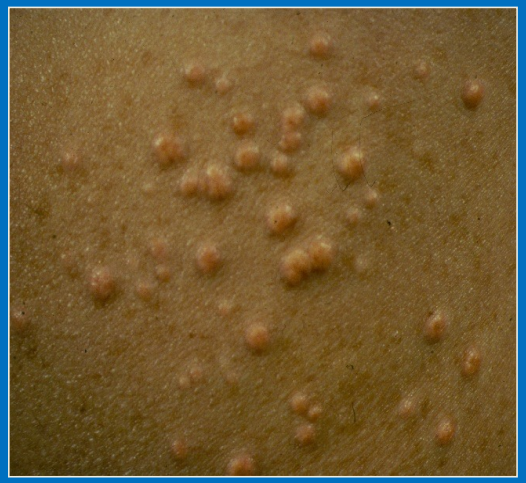


Mason RP, Eckel RH, *Am J Med* 2021, In press

Clinical Findings Associated with Severe Hypertriglyceridemia

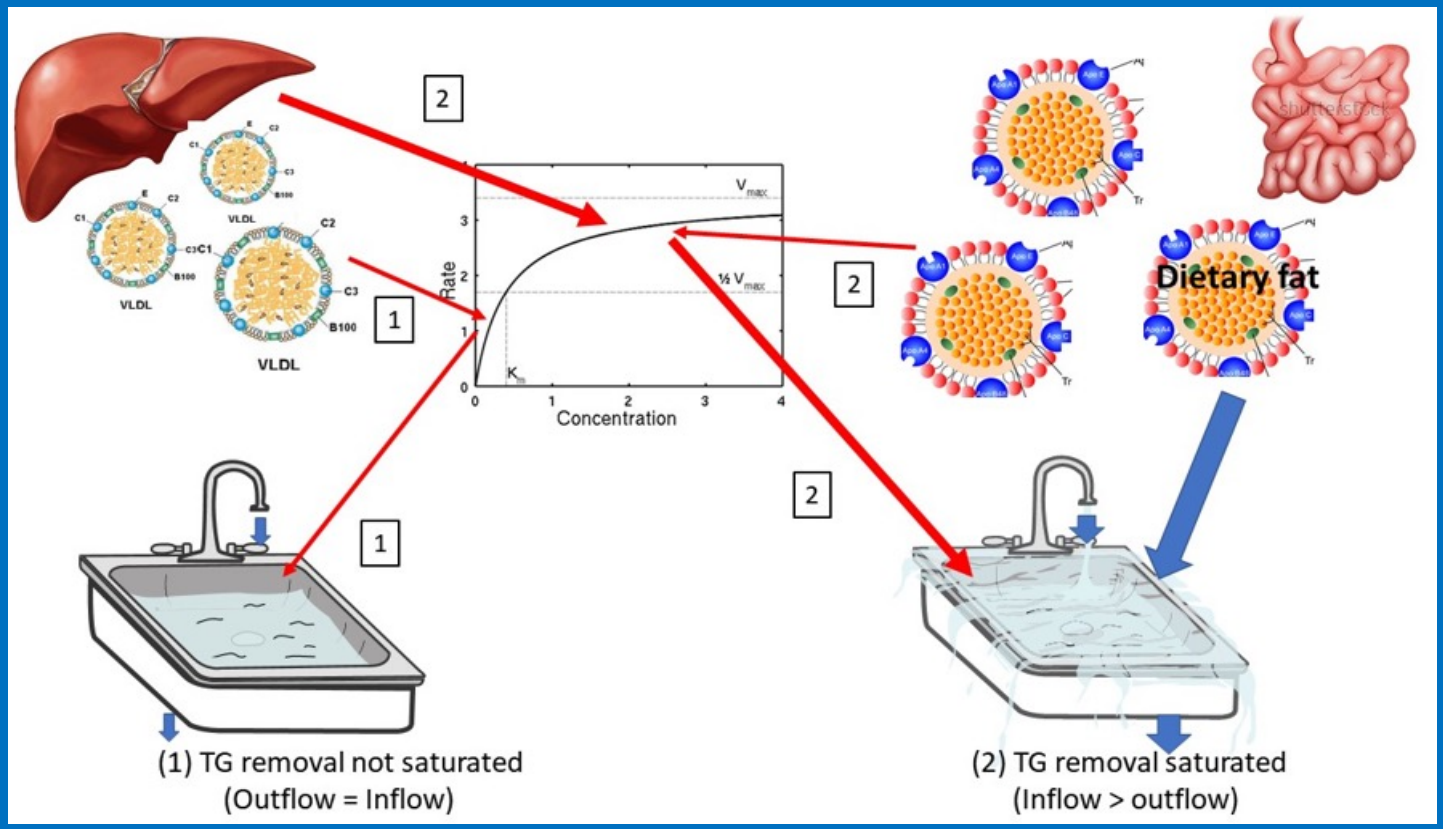
Lipemia Retinalis

Eruptive Xanthomas



Lipemic Serum

Triglyceride Clearance is Saturable



Chait A, Eckel RH, *Ann Int Med*, April 30, 2019

Summary and Conclusions

- Based on absolute risk reduction, LDL-C levels of <55 mg/dL provide maximum benefit for CVD risk reduction; lower levels do not appear to be harmful.
  - Are studies of lipid lowering therapy ethical in patients with T1DM?
- Triglyceride elevations are strongly associated with ASCVD but are not etiologic and the amount of reduction in triglycerides by fibrates or omega-3 fatty acids does not relate to reduced CVD.
  - Data suggest that EPA alone and EPA levels achieved reduce CVD by alternative mechanisms.
- In patients with severe hypertriglyceridemia, triglycerides should be reduced to <500 mg/dL to reduce the risk for acute pancreatitis.


Thank You!