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Is There a Role for Triglyceride Lowering? It Depends…

Cardiovascular Symposium India

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Sadiya S. Khan, MD, MSc, FACC, FAHA
Assistant Professor of Medicine and Preventive Medicine
Associate Program Director, CVD Fellowship
Director of Research, Section of Heart Failure
Northwestern University Feinberg School of Medicine
Associate Editor, *JAMA Cardiology*
@HeartDocSadiya

DISCLOSURES

No relevant COI/RWI

Grant support

- AHA
- NIH

CASE PRESENTATION

- 37-year-old South Asian man who presented with 3 hours of acute-onset abdominal pain.
- Vitals: BP 138/80, HR 66, BMI 36 kg/m^2
- Exam: CV: RRR, no murmurs; Abdomen: soft, moderately tender to palpation, no rebound tenderness or guarding

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Labs:
-- WBC 10.2, Hgb 15.1, PLT 303
-- Na 133, K 3.9, SCr 0.82, Glu 261
-- TC 154 mg/dL, HDL 15 mg/dL, non-HDL 139 mg/dL, TG 3505 mg/dL
-- Lipase: >3000 u/L

- CT A/P: Acute interstitial pancreatitis, with a diffusely enlarged pancreas with peripancreatic fat stranding and edema, no peripancreatic fluid collections; +Hepatic steatosis

CASE PRESENTATION

- 37 year old South Asian man who
- Vit
- Exam: CV: RRR, no murmurs;

- Labs:
- HDL 139 mg/dL, TG 3505 mg/dL
- no peripancreatic fluid collections;
+Hepatic steatosis

What are the benefits of TG lowering in this individual given the severe range?

What effective therapeutic options are available for TG lowering?

LEARNING OBJECTIVES

1. Define hypertriglyceridemia and its key causes
2. Discuss the evidence for the association of triglycerides and ASCVD risk: marker or mediator?
3. Discuss the available evidence for management strategies to lower triglycerides

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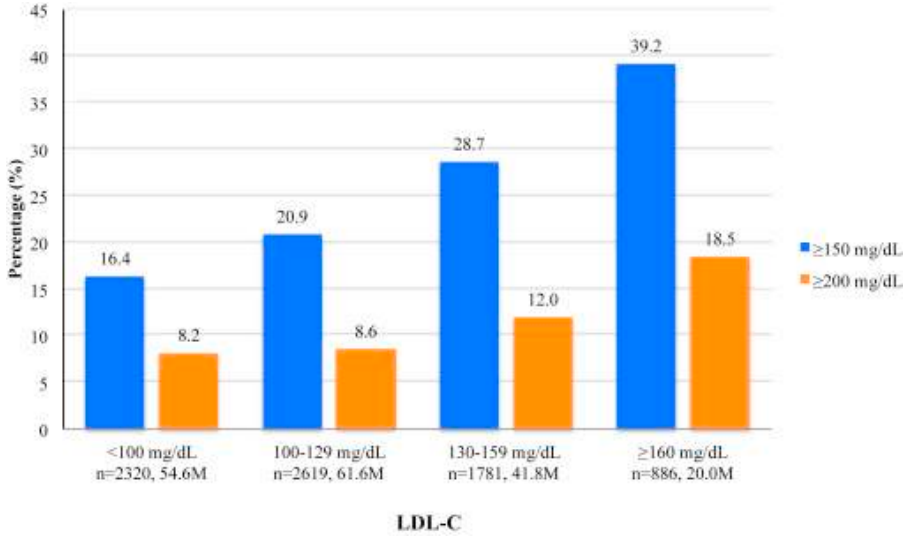
CLASSIFICATION OF TRIGLYCERIDE LEVELS

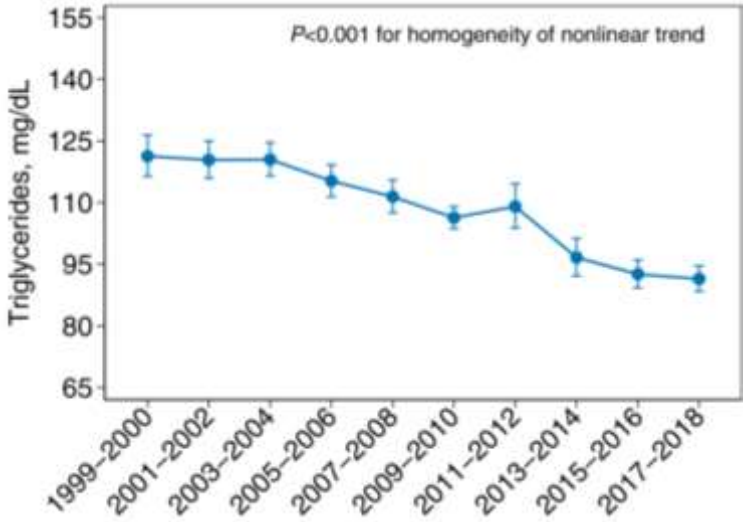
Classification	Triglyceride level mg/dL
Normal	<150
Moderate hypertriglyceridemia	150 to 499
Moderate to Severe hypertriglyceridemia	500 to 999
Severe hypertriglyceridemia	>1000

HYPERTG: HIGHLY PREVALENT BUT DECREASING

Prevalence of HyperTG by LDL-C
NHANES 2007-2014 (N=23,482)

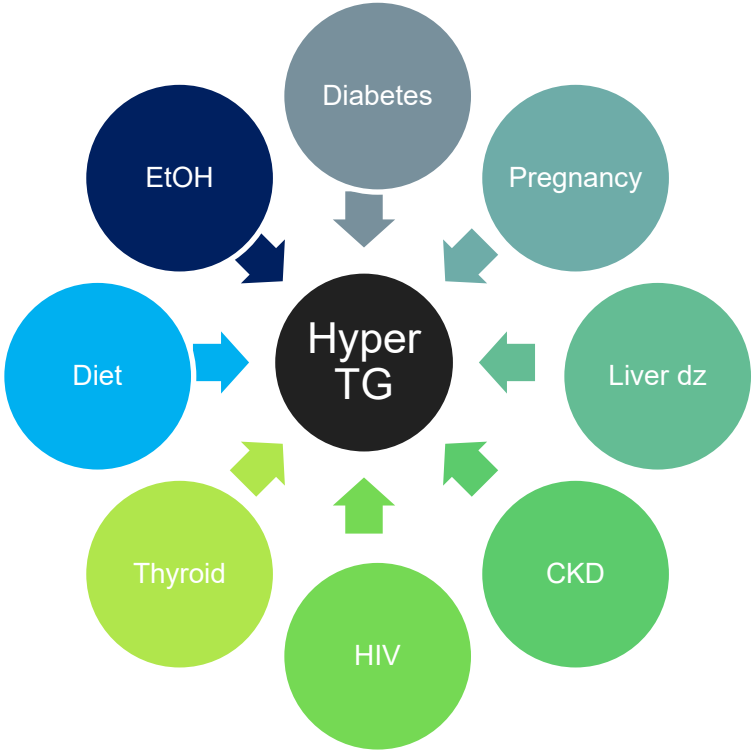


Trends in Fasting TG Levels
NHANES 1999-2018 (N=50928)



Fan et. al. *J Clin Lipidol* 2019
Gao et. al. *JAHA* 2023

SECONDARY (MODIFIABLE) CAUSES OF HYPERTG



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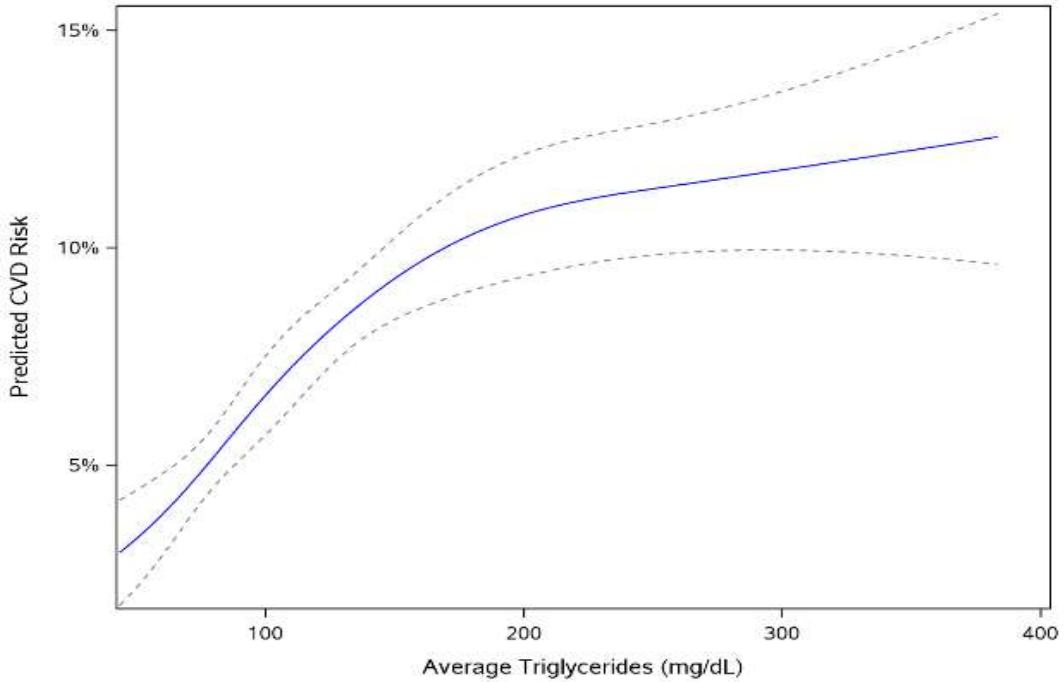
TRIGLYCERIDES ARE ASSOCIATED WITH CVD

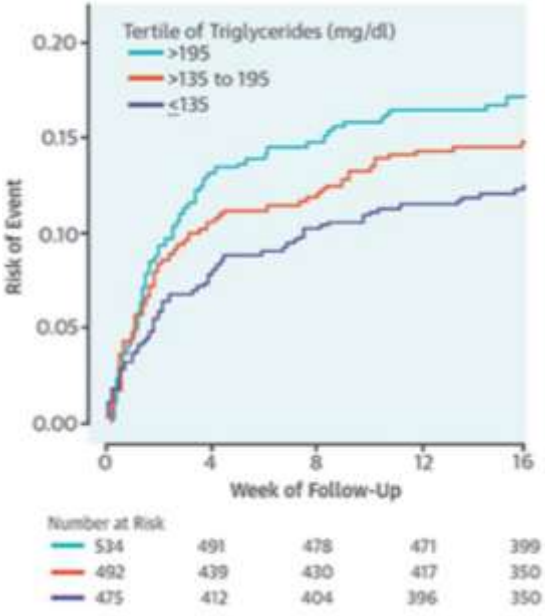


- N=8068 from two community-based US cohort studies (ARIC and FOS)
- Primary endpoint: composite of MI, stroke, and cardiovascular death
- Dose-dependent relationship even at ”normal” triglyceride levels <150 mg/dL in a primary prevention cohort with low statin utilization

Aberra T. et. al. *J Clin Lipidology* 2020

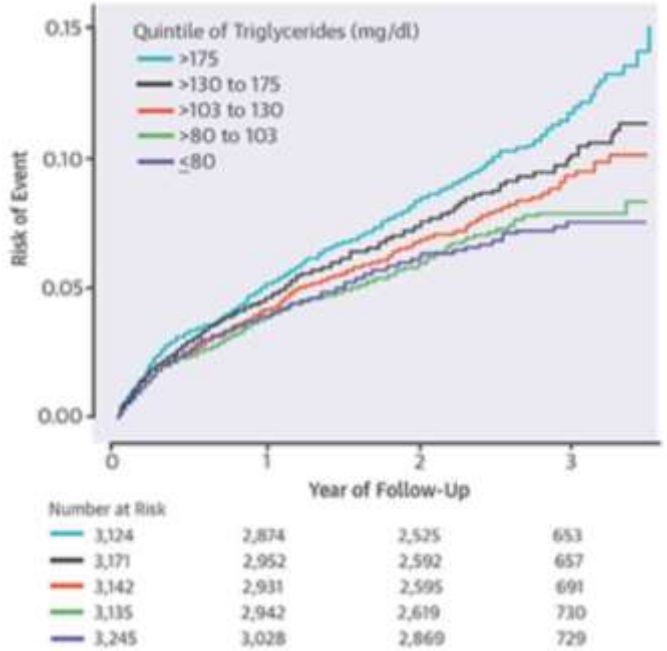
ELEVATED TG ASSOCIATED WITH MACE WITH ACS

Short-Term Risk after ACS



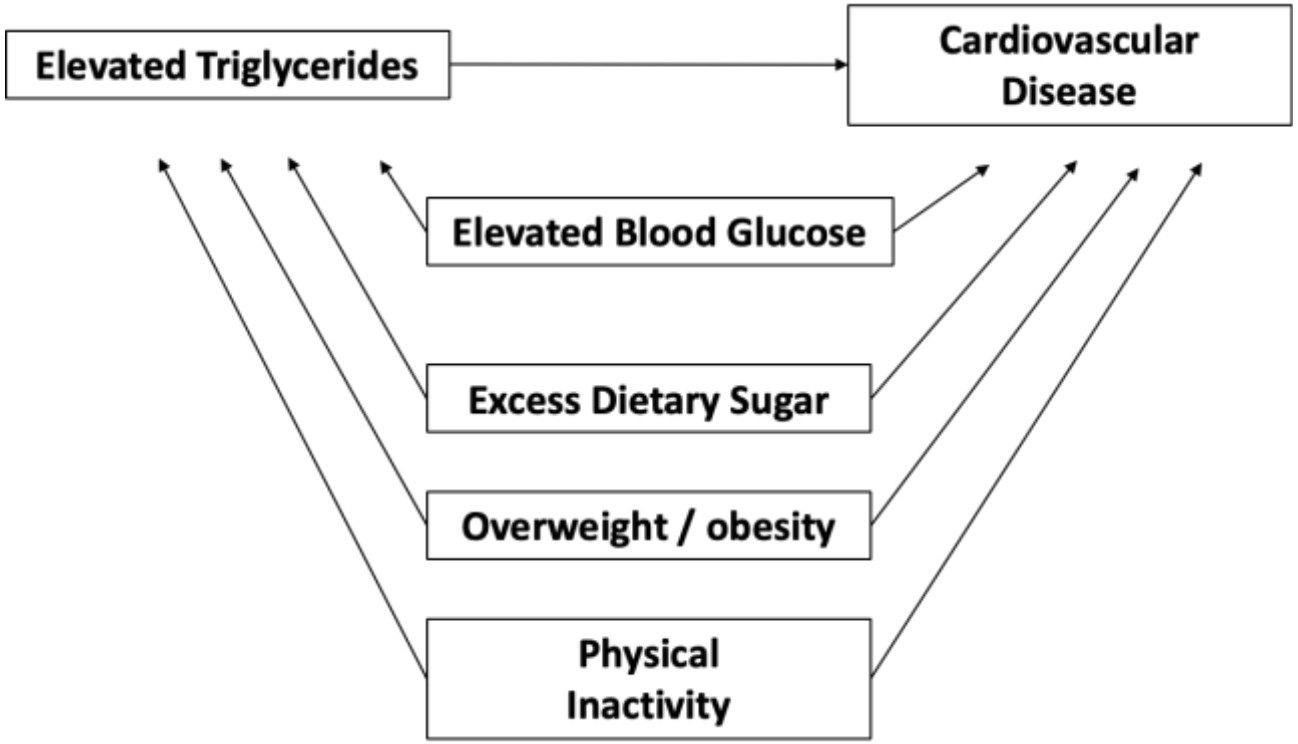
MACE defined as CHD death, non-fatal MI, stroke and UA

Long-Term Risk after ACS



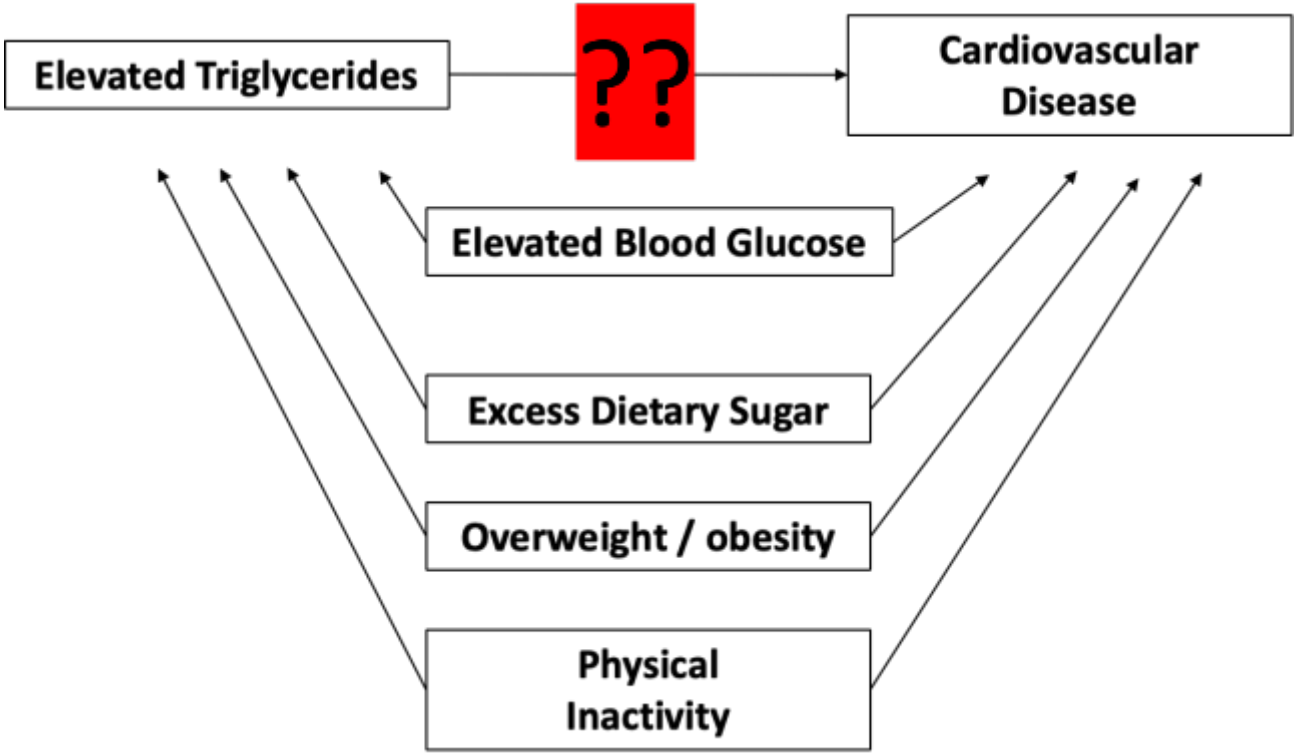
Schwartz et. al. *J Am Coll Cardiol* 2015

TRIGLYCERIDES ARE A MARKER OF CVD RISK



Adapted from Navar AM

BUT DOES MODIFYING TG LOWER CVD RISK?



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HILL'S CRITERIA FOR CAUSALITY

Sir Bradford Hill's Criteria
☐ Strength of association
☐ Consistency of effect by finding a similar direction and strength of association using different methods
☐ Specificity in the independent association without residual confounding
☐ Temporality with the exposure preceding the outcome
☐ Biological or dose-response gradient
☐ Biologic plausibility
☐ Reversibility whereby removing or reducing the exposure lead to decreased risk of outcome

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OUTCOME TRIALS WITH TG LOWERING

Agent	Trial	Sample Size	Demonstrated CV Benefit?
Fenofibrate	ACCORD[1]	5,518	No
	FIELD[2]	9,795	No
Niacin	AIM-HIGH[3]	3,414	No
	HPS2-THRIVE[4]	25,673	No
Omega-3-Fatty Acids	ORIGIN[5]	12,536	No
	R&P[6]	12,513	No
	OMEGA[7]	3,851	No
	ASCEND[8]	15,480	No
	VITAL[9]	25,871	No

1. ACCORD Study Group. *N Engl J Med*. 2010;362:1563-74. **2.** FIELD Study Investigators. *Lancet*. 2005;366:1849-61. **3.** AIM-HIGH Investigators. *N Engl J Med*. 2011;365:2255-67. **4.** HPS2-Thrive Collaborative Group. *N Engl J Med*. 2014;371:203-12. **5.** ORIGIN Trial Investigators. *N Engl J Med.* 2012;367:309-18. **6.** Risk and Prevention Study Collaborative Group. *N Engl J Med.* 2013;368:1800-8. **7.** Rauch B, et al. *Circulation.* 2010;122:2152-9. **8.** ASCEND Investigators. *JAMA Cardiol.* 2018;3(3):225-234. **9.** VITAL Study Investigators *N Engl J Med.* 2019;380:33-44. 10. Nicholls SJ et al. JAMA 2020. ;324(22):2268-2280

HOPE FOR FIBRATES? SUBGROUP ANALYSES

Agent	Trial	RR in TG≥204 mg/dL
Fenofibrate	ACCORD[1]	-27% (p=0.005)
	FIELD[2]	-20% (p<0.05)

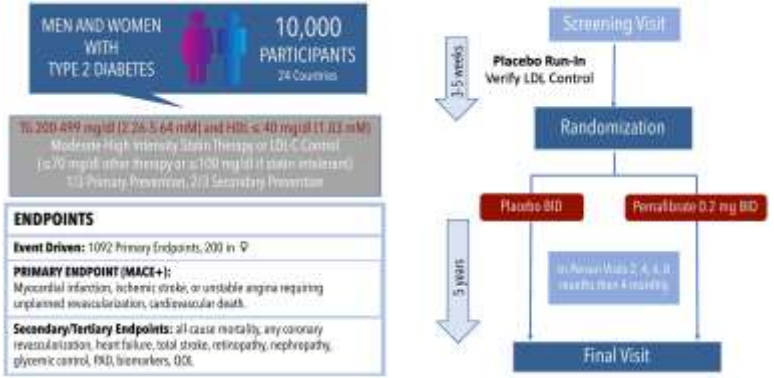
PROMINENT: NEGATIVE OUTCOME TRIAL, AGAIN

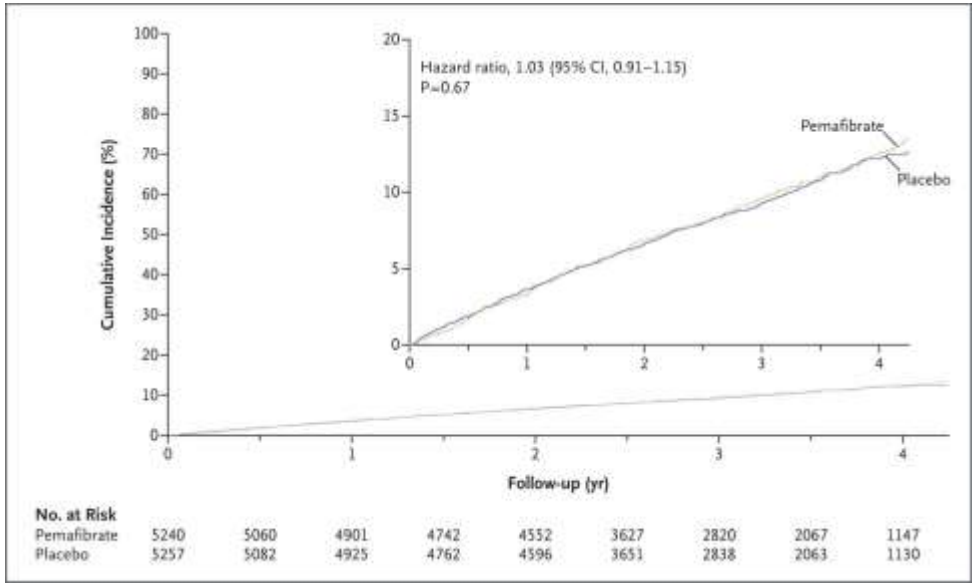
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 24, 2022 VOL. 387 NO. 21

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

A. Das Pradhan, R.J. Glynn, J.-C. Fruchart, J.G. MacFadyen, E.S. Zaharris, B.M. Everett, S.E. Campbell, R. Oshima, P. Amarenco, D.J. Blom, E.A. Brinton, R.H. Eckel, M.B. Elam, J.S. Felicio, H.N. Ginsberg, A. Goudev, S. Ishibashi, J. Joseph, T. Kodama, W. Koenig, L.A. Leiter, A.J. Lorenzatti, B. Mankovsky, N. Marx, B.G. Nordestgaard, D. Páll, K.K. Ray, R.D. Santos, H. Soran, A. Susekov, M. Tendera, K. Yokote, N.P. Paynter, J.E. Buring, P. Libby, and P.M Ridker, for the PROMINENT Investigators*

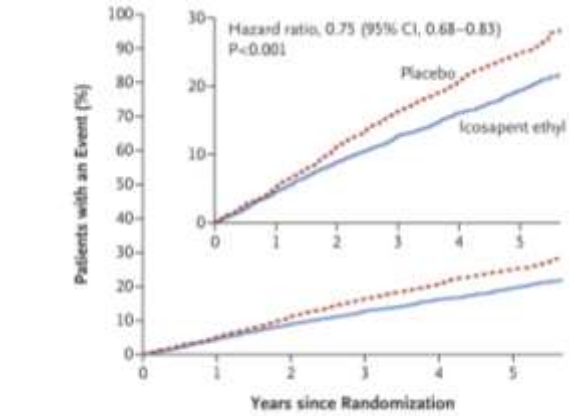




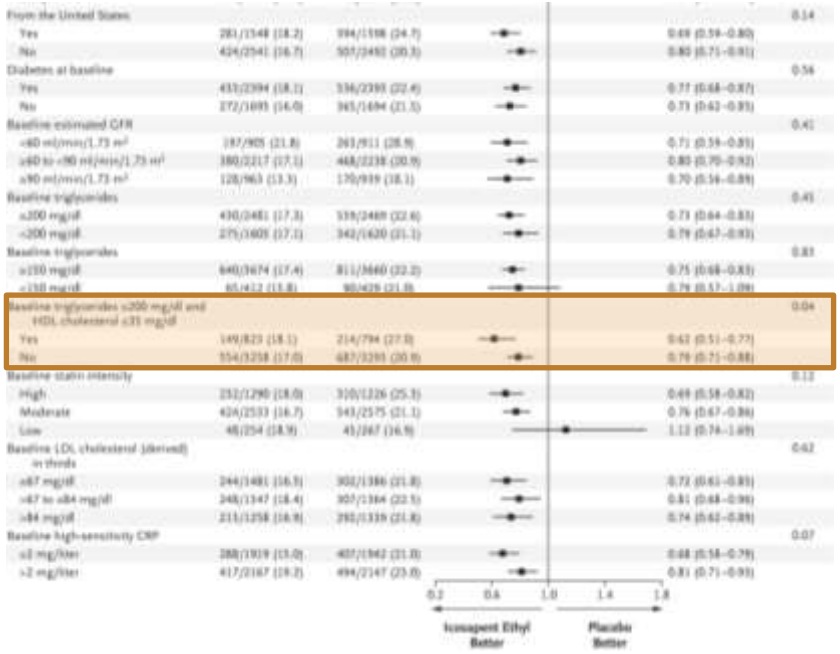
REDUCE-IT: POSITIVE OUTCOME TRIAL

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

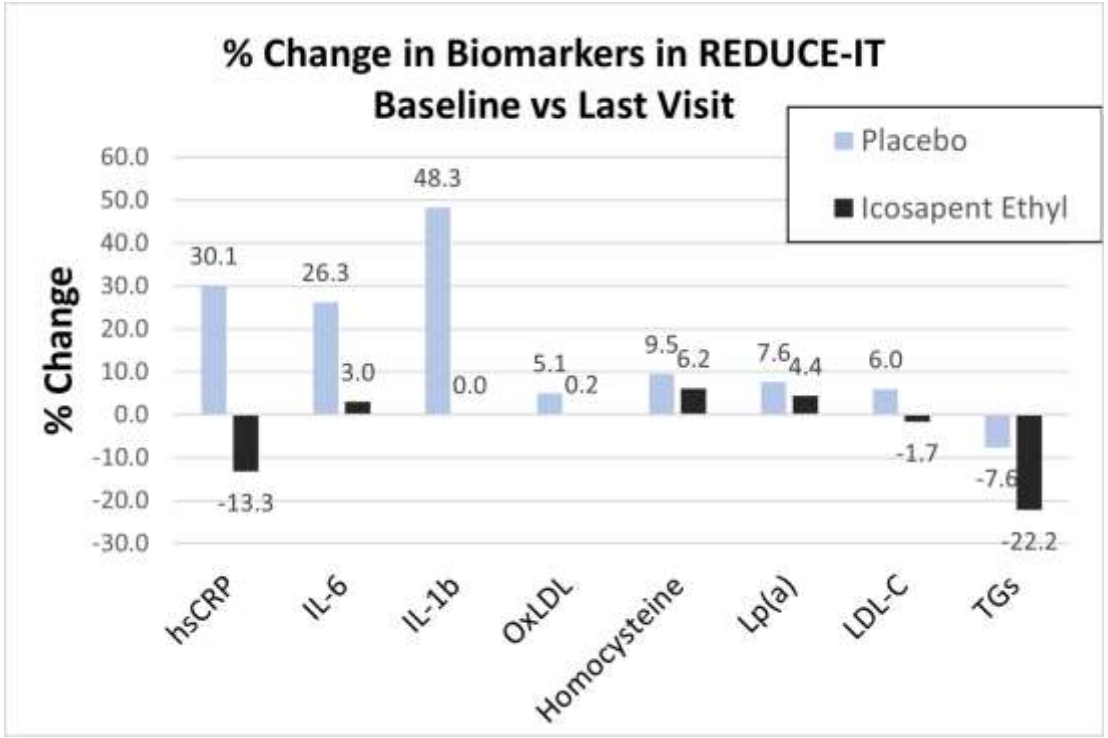
Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D.,



No. at Risk						
Placebo	4090	3743	3327	2807	2347	1358
Icosapent ethyl	4089	3787	3431	2951	2503	1430



REDUCE-IT: POSITIVE OUTCOME TRIAL, BUT…



Ridker P. et. al. *Circulation* 2022

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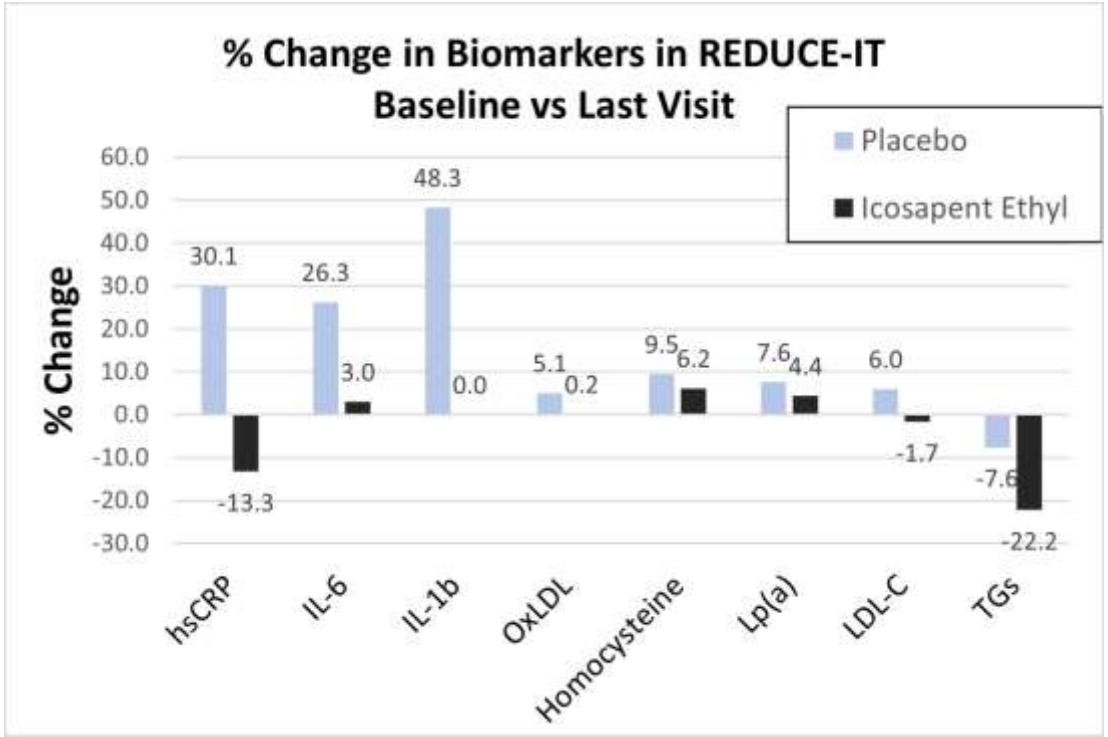


Adverse Events of Interest: Serious Bleeding

By Baseline Medications of Interest

Antithrombotic therapy (at baseline)	Patients with bleeding/ at risk % Icosapent Ethyl n/N (%)	Placebo n/N (%)	P-value*
All Randomized Patients	111/4089 (2.7)	85/4090 (2.1)	0.06
No Antithrombotics	8/584 (1.4)	6/601 (1.0)	0.60
One Antiplatelet	58/2416 (2.4)	43/2408 (1.8)	0.16
Two or More Antiplatelets	31/841 (3.7)	19/828 (2.3)	0.11
Anticoagulant	27/385 (7.0)	27/390 (6.9)	>0.99
Single Antiplatelet Plus Anticoagulant	8/114 (7.0)	8/123 (6.5)	>0.99

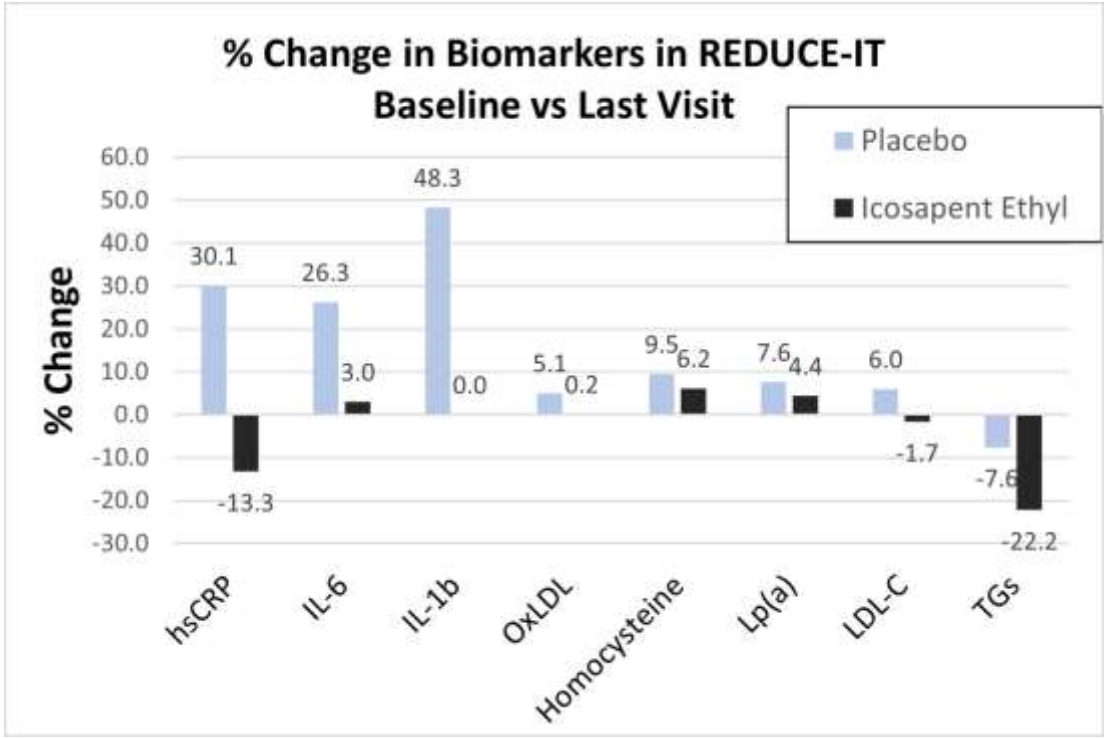
Atrial Fibrillation / Flutter

- Atrial fibrillation/flutter requiring hospitalization ≥24 hours was an adjudicated efficacy endpoint
- All other atrial fibrillation/flutter events reside in the safety database

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value*
Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization	321 (7.9)	248 (6.1)	0.002
Afib/Aflutter TEAEs[1]	236 (5.8)	183 (4.5)	0.008
Serious Afib/Aflutter TEAEs[2]	22 (0.5)	20 (0.5)	0.76
Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization[3]	127 (3.1)	84 (2.1)	0.004

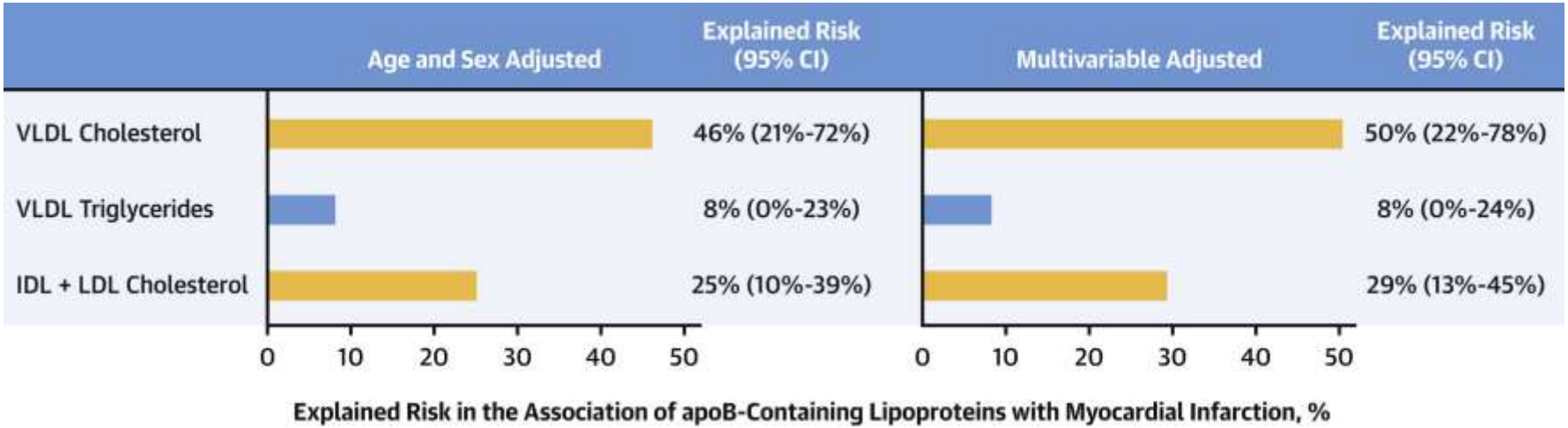
Ridker P. et. al. *Circulation* 2022
https://www.fda.gov/media/132768/download

REDUCE-IT: POSITIVE OUTCOME TRIAL, BUT…



Ridker P. et. al. *Circulation* 2022

CHOLESTEROL CONTENT MATTERS, NOT TG



Balling M. et. al. *J Am Coll Cardiol* 2020

2018 AHA/ACC Guidelines on the Management of Blood Cholesterol, hypertriglyceridemia is regarded as a risk-enhancing factor for ASCVD with recommendation to measure ApoB

COR	LOE	Recommendations
I	B-NR	In adults ≥20years with moderate hyperTG (175-499 mg/dL), **address lifestyle** (obesity, metabolic syndrome), **secondary** factors (diabetes, liver dz, kidney dz, hypothyroid, nephrotic syndrome) and **medications** that increase TG
IIa	B-R	In adults 40-75 years with moderate to severe hyperTG and ASCVD risk ≥7.5%, reevaluate ASCVD risk after lifestyle and secondary factors addressed with **persistently elevated TG≥175 noted as a risk-enhancing factor**
IIa	B - R	In adults 40-75 years with severe hyperTG (≥500) and ASCVD risk ≥7.5%, address reversible causes and **initiate statin therapy**
Iia	B-NR	In adults with severe hyperTG (≥500), identify other causes to focus on reduction of TG (e.g., very low-fat diet, alcohol avoidance, omega-3 fatty acids, fibrates) to prevent pancreatitis

KEY TAKEAWAYS: TG PLAY A ROLE IN CVD RISK

1. Assessment of triglyceride levels are important to identify people at risk for pancreatitis (>500 mg/dL)

2. Elevated triglycerides are a marker of ASCVD risk and should prompt lifestyle, risk factor modification, and apoB assessment

3. Recommendation for icosapent ethyl in the right patient may be considered but controversy remains about benefit

Thank you.

Questions?

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