



A Closer Look at Women, Atherosclerosis, and Lipids

What Is Different?

WOMEN'S HEALTH:
Beyond the Annual Visit



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Identifying Women at Risk or With Cardiovascular Disease

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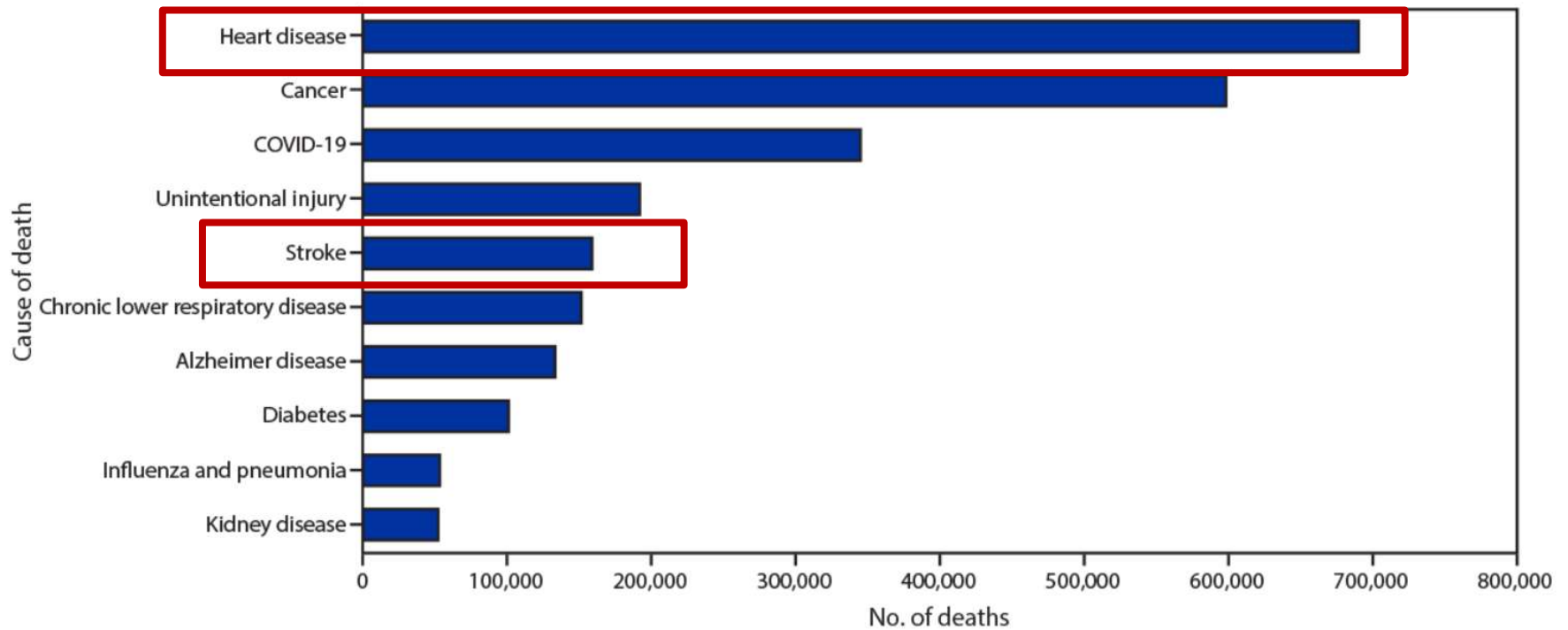
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Learning Objectives

- At the conclusion of this activity, learners should be better able to:
- Screen and diagnose female patients at high risk of cardiovascular events during their annual visit.
- Describe the importance of triglyceride management in ASCVD risk assessment and management.
- Apply evidence-based guidelines and recent randomized clinical trial evidence of icosapent ethyl in addition to statin therapy to manage women at risk of ASCVD events.

Heart Disease Remains the #1 Cause of Death

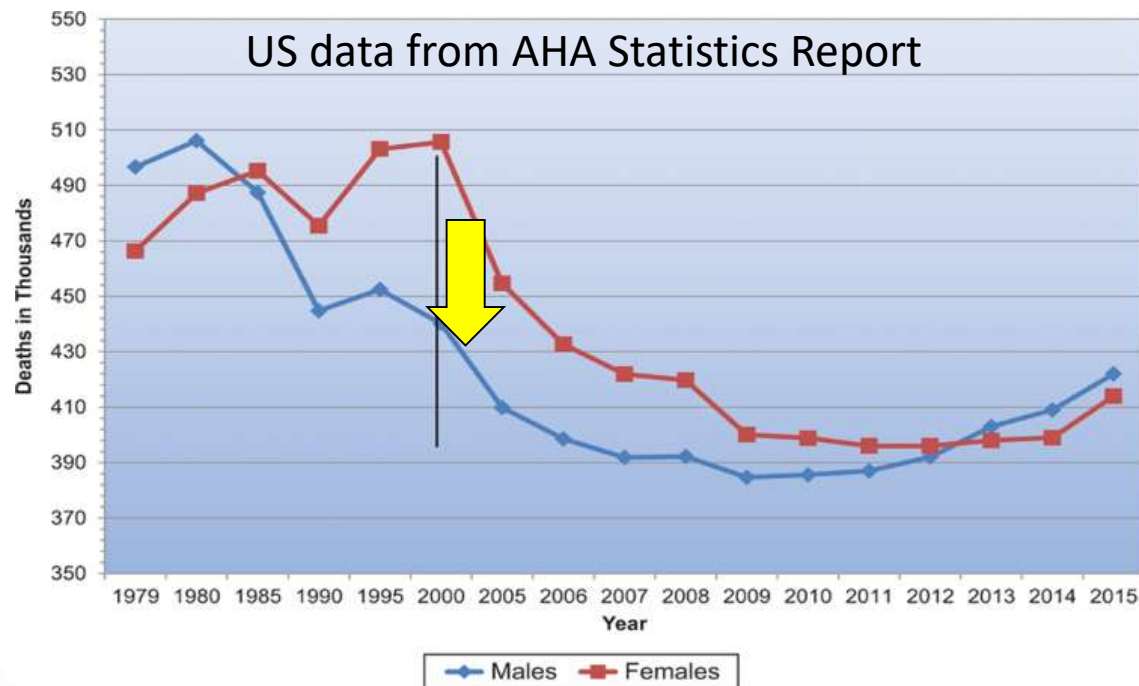
FIGURE 2. Provisional* number of leading underlying causes of death† — National Vital Statistics System, United States, 2020



* <https://www.cdc.gov/nchs/nvss/deaths.htm>

† Based on death records received and processed as of March 21, 2021, for deaths occurring in the United States among US residents. Data in this analysis include >99% of deaths that occurred in 2020. Ahmad FB, et al. *MMWR Morb Mortal Wkly Rep* 2021;70(14):519-522.

CVD Mortality Gap Between Men and Women Has Narrowed But Plateaued



- Additionally, CVD on rise in middle-aged women in US
- The heart disease death rate for women aged 45-64 declined 23% from 1999 (96.8) to 2011 (74.9) but then increased 7% in 2017 (80.1)

Female-Specific Risk Enhancers Are Across the Lifespan



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)


American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/the-american-journal-of-preventive-cardiology

State-of-the-Art Review

Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention

Petal Elder^a, Garima Sharma^b, Martha Gulati^c, Erin D. Michos^{b,*}



YOUNGER WOMEN

- Early or late menarche
- PCOS
- OCPs
- Premature menopause
- Primary ovarian insufficiency



PREGNANCY

- Gestational diabetes
- Gestational hypertension
- Preeclampsia
- Preterm birth

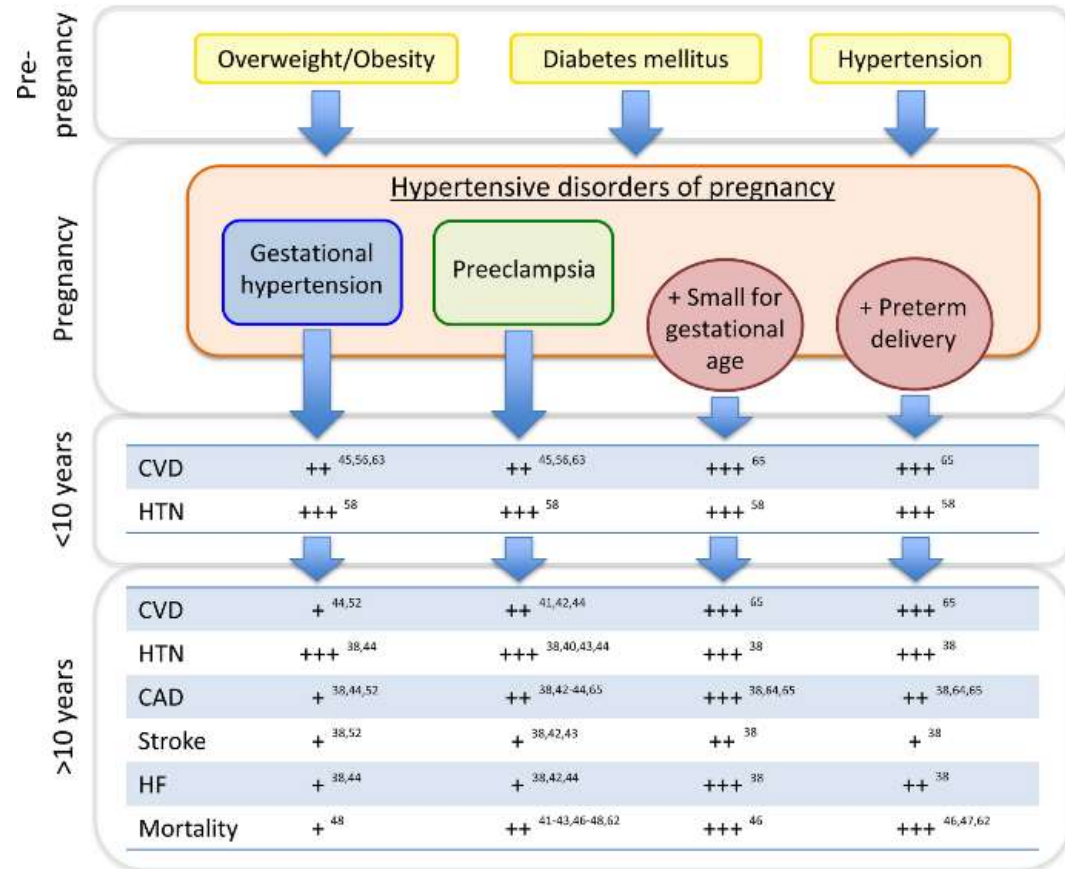


OLDER WOMEN

- Menopause

Adverse Pregnancy Outcomes (APOs) and Future Maternal CVD Risk

- Ask about pregnancy history
- Risk from adverse pregnancy seen even more than 10 years out

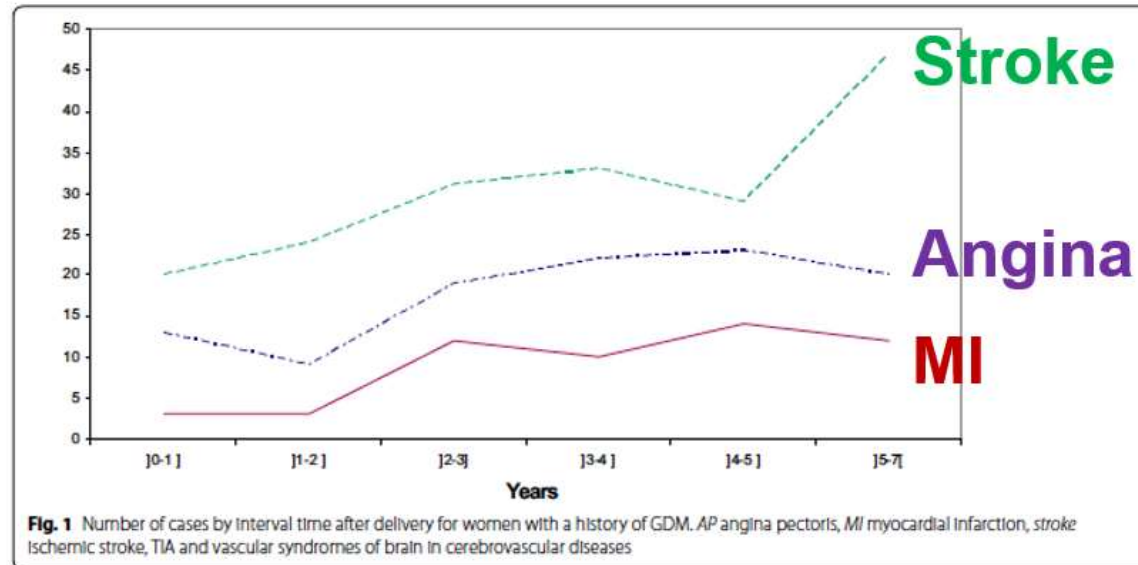


Ying W, et al. *J Am Heart Assoc.* 2018;7(17):e009382. doi:10.1161/JAHA.118.009382

Preeclampsia, Preterm Delivery, and Subsequent Maternal CVD: Meta-Analysis

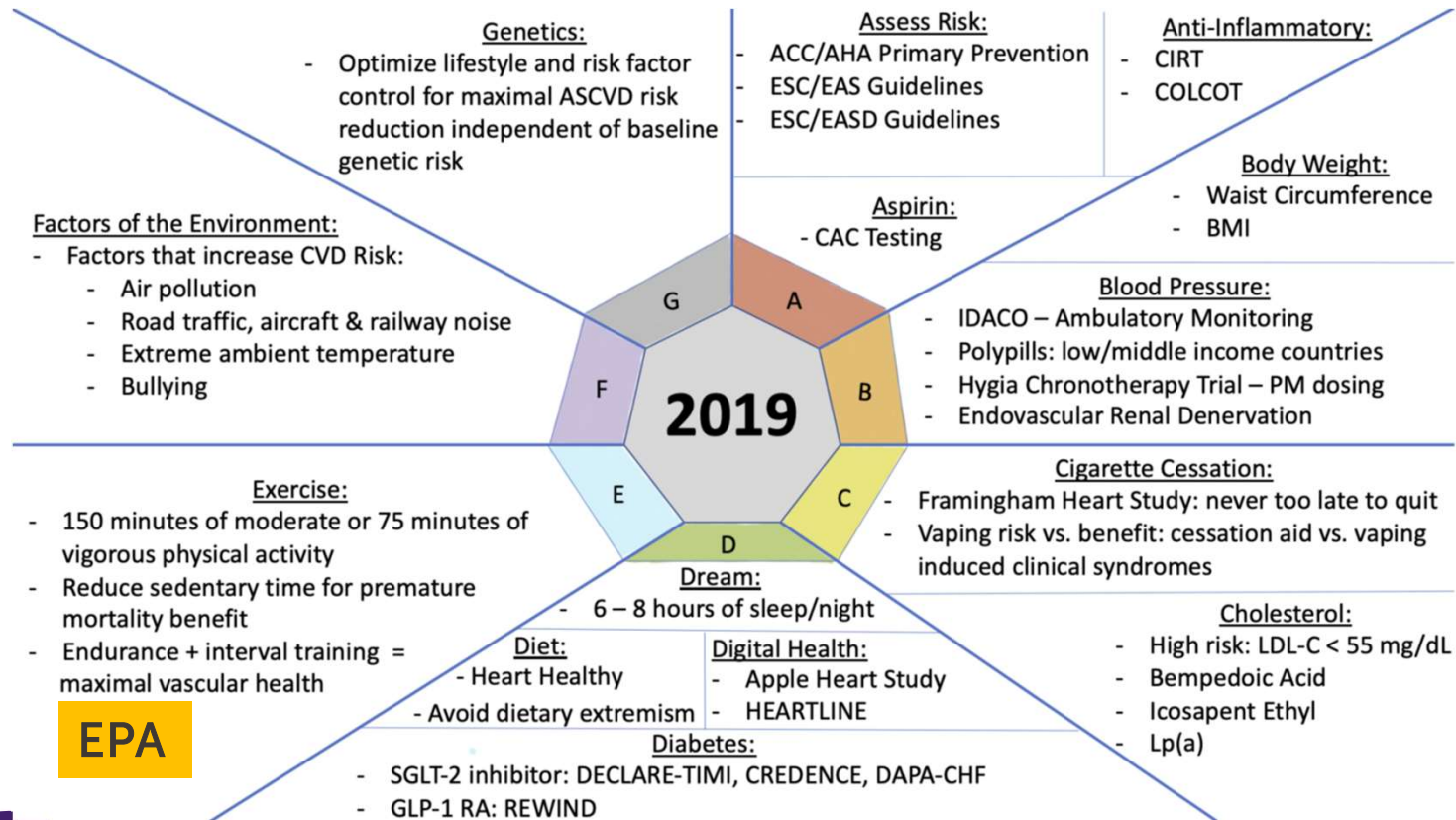
- >20 studies with ~6 million women including >25,800 with preeclampsia & 338,000 with previous preterm delivery (PTD)
- Preeclampsia is associated with a 4-fold increase in incident HF and a 2-fold increased risk in CHD, stroke, and CVD death
- Preterm delivery is associated with an increase in future maternal adverse CV outcomes, including a 2-fold increase in deaths caused by CHD
 - Highest risks occurred when the PTD was before 32 weeks' gestation or was medically indicated

Gestational Diabetes Mellitus (GDM) and Risk of Maternal CVD



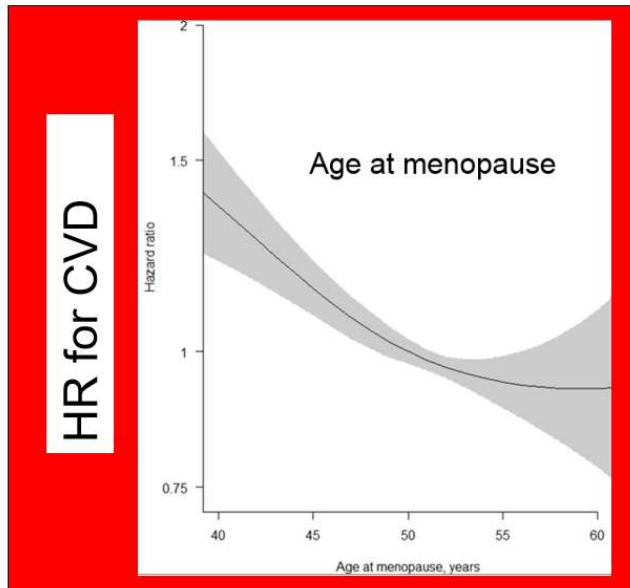
Nationwide: All births 2007-2008 in France: 7-year follow-up; 1,518,990 deliveries, 62,958 with GDM. After adjusting for age, DM, obesity, and hypertensive disorders in pregnancy, GDM was significantly associated with a higher risk of CVD (adjusted odds ratio = 1.25 [1.09–1.43])

Johns Hopkins Ciccarone Center's 'ABC' Approach for the Prevention of Cardiovascular Disease



Feldman DI, et al. *Am J Prev Cardiol.* 2020;2:100027.

Premature Menopause and Incident CVD in UK Biobank



Premature menopause (before age 40) was associated with increased risk of CVD (HR: 1.36; 95% CI: 1.19 to 1.56; $P < 0.001$) after adjustment for conventional risk factors

Analyses are adjusted for age, Townsend deprivation index, smoking status, systolic blood pressure, history of diabetes, and body mass index.

2019 ACC/AHA Guideline on Primary Prevention

Statins: Key Take-Home Message

- Statin therapy is first-line treatment for primary prevention of ASCVD in patients with:
 - Elevated LDL-C levels (≥ 190 mg/dL)
 - Diabetes mellitus who are age 40 to 75 years
 - Determined to be at sufficient ASCVD risk after a clinician-patient risk discussion

2019 ACC/AHA Primary Prevention Guidelines: Risk-Enhancing Factors

Risk-Enhancing Factors

- Family history of premature ASCVD (men, age <55 y; women, <65 y)
- Primary hypercholesterolemia
- Metabolic syndrome (increased waist circumference, elevated triglycerides, elevated blood pressure, elevated glucose, and low HDL-C
 - 3 or more of 5 factors = metabolic syndrome
- Chronic kidney disease
- Chronic inflammatory conditions

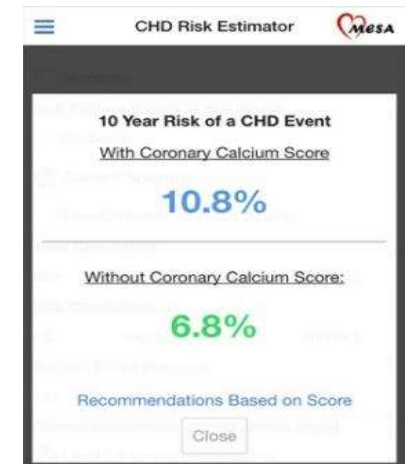
2019 ACC/AHA Primary Prevention Guidelines: Risk-Enhancing Factors (con't)

Additional Risk-Enhancing Factors

- History of premature menopause (before age 40 y) or pregnancy-associated conditions that ↑ASCVD risk (eg, preeclampsia)
- High-risk race/ethnicity (eg, South Asian, East Asian, Native American, Middle Eastern)
- High-risk levels of lipids or other biomarkers
- Persistent primary HTG
- If measured:
 - ↑high-sensitivity C-reactive protein
 - ↑Lp(a)
 - ↑apoB
 - ↓ABI

Using the CAC Score to Guide Statin Therapy

- CAC score predicts ASCVD events in a graded fashion
 - 0 is useful for reclassifying patients to a lower-risk group, often allowing statin therapy to be withheld or postponed unless higher-risk conditions are present
 - 1-99 favors statin therapy
 - 100+ initiate statin therapy
- For patients >75 y/o, RCT evidence for statin therapy is not strong, so clinical assessment of risk status in a clinician-patient risk discussion is needed to decide whether to continue or initiate statin treatment
- European Society of Cardiology guidelines also support CAC scoring:
 - “CAC score assessment with CT should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.”





ACC Risk Calculator *Plus* to Assess Risk Category

1. For primary prevention, use the calculator to assess risk category

<5% "Low Risk"	5% to <7.5% "Borderline Risk"	≥7.5% to <20% "Intermediate Risk"	≥20% "High Risk"
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- Estimates 10-year hard ASCVD (nonfatal MI, CHD death, stroke) for ages 40-79 and lifetime risk for ages 20-59
- Intended to promote patient-provider risk discussion and best strategies to reduce risk
- ≥7.5% identifies statin eligibility, not a mandatory prescription for a statin

2. Then use the new ACC/AHA Primary Prevention guideline algorithms to guide management

Nutrition Lifestyle Recommendations: Lipids and BP

- Emphasis on dietary *patterns* (esp. Mediterranean or DASH-style):
- ↑Fruits, vegetables, and whole grains
- ↑Fiber and ↓Sugar
- Fat intake
 - 30%-35% total calories
 - <6% saturated fats (avoid *trans* fats)
- *Regular* fish intake
- ↓Highly processed/pre-prepared food
- Low sodium (<2400 mg/day)
- Healthy eating for a *lifetime*



Best evidence for ↓ MI risk is with the Mediterranean diet

Physical Activity Guidelines: Lipids and BP

Regular aerobic activity and strength training:



- 3+ sessions per week
- Average ~40 min per session
- Moderate to vigorous intensity
- Strength training *also* helpful
- *Patient* chooses most enjoyable and sustainable activities

Best evidence is brisk walking ~30 min/day ~5 days/week



Evidence-Based Approaches for Managing Women at High Risk of CVD Events

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Statin...statin...statin...

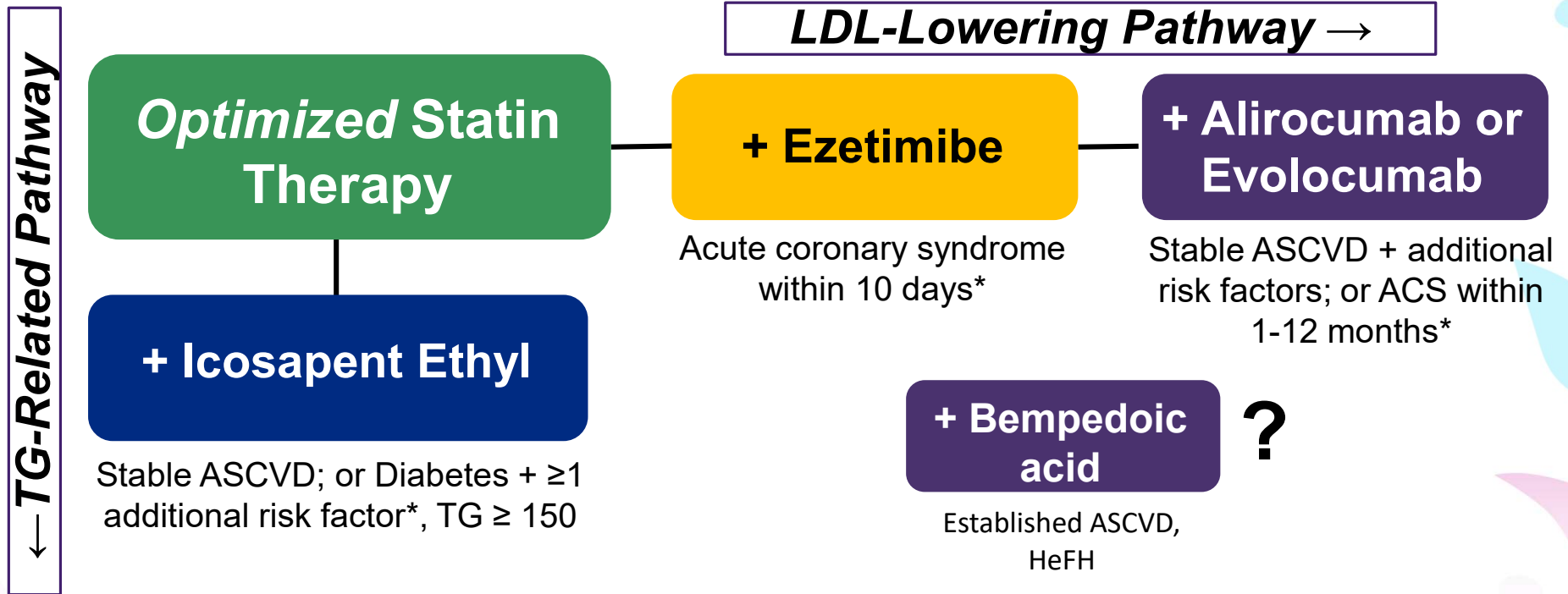
Selecting the Appropriate Statin

	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering [†]	≥50%	30% to 49%	<30%
Statins	Atorvastatin (40 mg [‡]) 80 mg Rosuvastatin 20 (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg [§]	Simvastatin 10 mg
	-	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

Adherence to Statin Therapy Is Difficult But Important

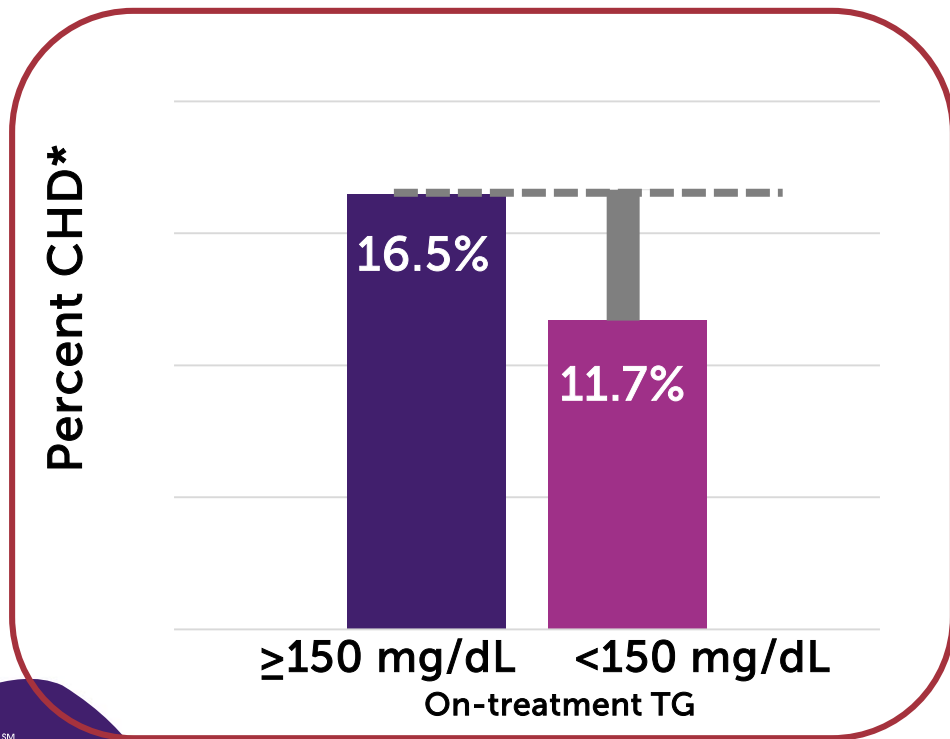
- Statins are generally well tolerated
 - >Three-quarters of the general population tolerates statin therapy, but
 - 10%-20% of patients prescribed a statin report statin intolerance
- Statins are very effective in preventing 1st/recurrent ASCVD across all LDL-C levels
- Rates of serious adverse events are very low
 - The risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%
 - The risk of serious hepatotoxicity is \approx 0.001%
 - The risk of statin-induced newly diagnosed diabetes mellitus is \approx 0.2% per year of treatment
- Large proportion (40%-70%) of patients discontinue statin therapy within 1-2 years, with resulting large increase in CVD risk
- Perceived vs real effect may play a role as multiple studies show nocebo effect
 - Many patients can tolerate statins on rechallenge after reported statin intolerance

Statin Therapy Adjuncts *Proven* to Reduce ASCVD



*Major inclusion criteria for respective CVOTs.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia.
After Orringer CE. *Trends in Cardiovasc Med.* 2019;30(3):151-157.

Residual HTG Predicted Residual ASCVD Risk Despite *LDL-C at Goal* on Statin Monotherapy

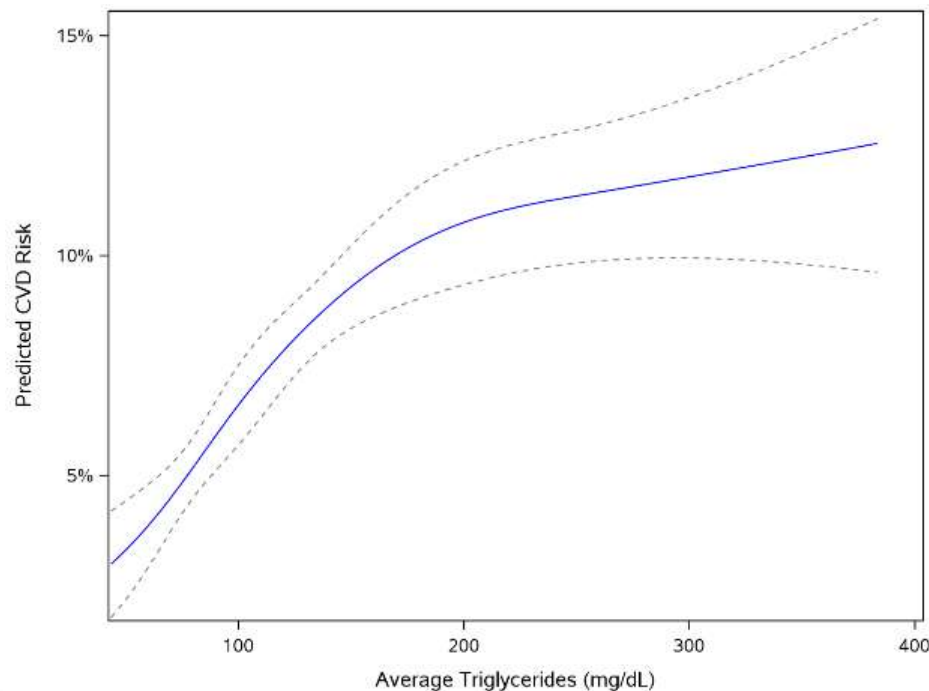


↑41% CVD risk w/
mild HTG

Despite LDL-C <70 mg/dL on high-dose statin, patients with TG ≥150 have a 41% higher risk of coronary events*

*Death, myocardial infarction, or recurrent acute coronary syndrome, PROVE IT-TIMI 22
Miller M, et al. *J Am Coll Cardiol.* 2008;51(7):724-730.

Fasting TG Is Strongly Related to CVD Risk, Even at Very Low Levels



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

CVD events increased across the range of TG levels ~50 to ~200 mg/dL, above which the relationship flattened out

Classification of Fasting TG Levels (2011 AHA/2014 NLA)

Fasting Triglycerides (mg/dL)	
<100	Optimal
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

Current Guidance Regarding Available Statin Adjuncts: Fibrates & Niacin

Negative Studies	
ACCORD Fenofibrate	HR=0.92 (95% CI, 0.79-1.08) P=0.32
FIELD Fenofibrate	HR=0.89 (95% CI, 0.75-1.05) P=0.16
AIM-HIGH Extended-release niacin	HR=1.02 (95% CI, 0.87-1.21) Log-rank P=0.79
HPS2-THRIVE Extended-release niacin/laropiprant	HR=0.96 (95% CI, 0.90-1.03) Log-rank P=0.29

- Combination therapy (statin/fibrate) has not been shown to improve ASCVD outcomes and is generally not recommended. (A)
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. (A)

(A), high evidence.

Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

ACCORD Study Group, et al. *N Engl J Med*. 2010;362(17):1563-1574.

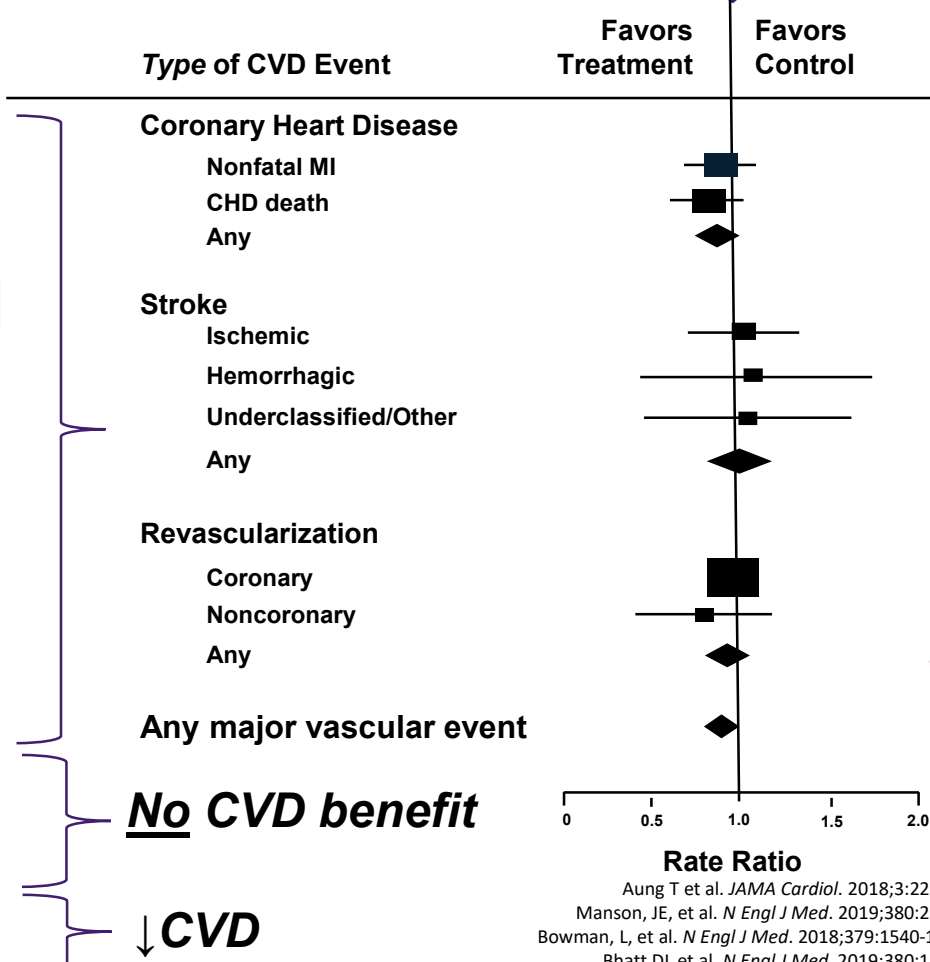
Keech A, et al. *Lancet*. 2005;366(9500):1849-1861.

Boden WE, et al. *N Engl J Med*. 2011;365(24):2255-2267.

HPS2-THRIVE Collaborative Group. *N Engl J Med*. 2014;371(3):203-212.

Lack of ↓ CVD with Omega-3 FA: Due to Low Doses, Use of Dietary Supplements, Presence of DHA, and/or Lack of Focus on HTG Subjects?

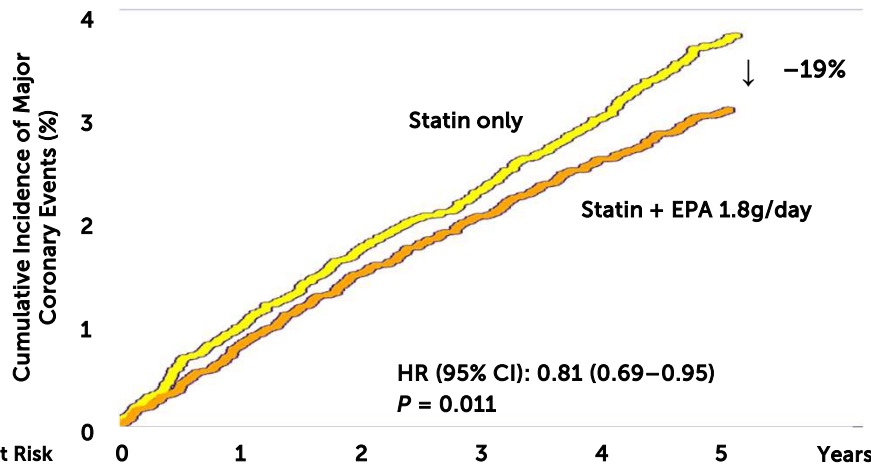
Study (Year)	EPA/DHA Dose (mg/d)	EPA / DHA Source
DOIT (2010)	1150 / 800	Dietary supplement
AREDS-2 (2014)	650 / 350	Dietary supplement
SU.FOL.OM3 (2010)	400 / 200	Dietary supplement
JELIS (2007)	1800 / 0	Pure EPA Rx
Alpha Omega (2010)	226 / 150	Margarine with dietary supplement
OMEGA (2010)	460 / 380	Rx EPA/DHA
R&P (2013)	500 / 500	Rx EPA/DHA
GISSI-HF (2008)	850 / 950	Rx EPA/DHA
ORIGIN (2012)	465 / 375	Rx EPA/DHA
GISSI-P (1999)	850 / 1700	Rx EPA/DHA
VITAL (2018)	465 / 375	Rx EPA/DHA
ASCEND (2018)	465 / 375	Rx EPA/DHA
REDUCE-IT (2018)	4000 / 0	Rx EPA



No CVD benefit

↓ **CVD**

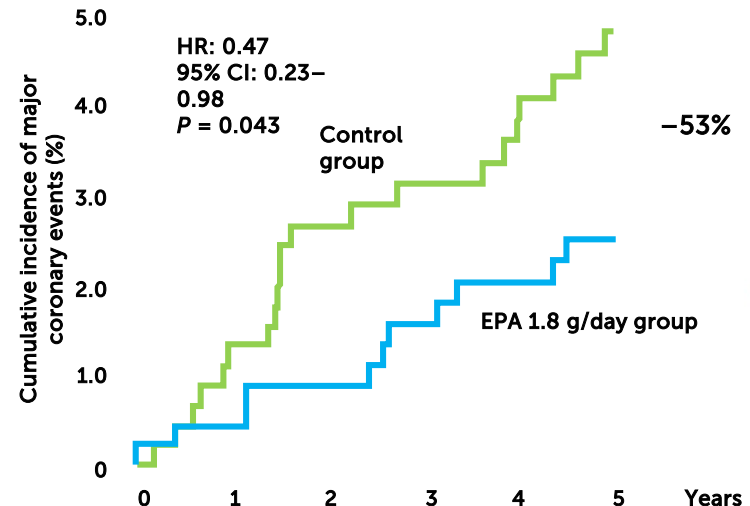
JELIS: Rx Pure EPA + Statins Led to ↓ Major Coronary Events* in Hypercholesterolemic Patients on Statins and in HTG Subgroup†



No. at Risk	0	1	2	3	4	5	Years
Control	9319	8931	8671	8433	8192	7958	
EPA	9326	8929	8658	8389	8153	7924	

N=18,645 Japanese pts with TC ≥251 mg/dL prior to baseline statin Rx. Baseline TG=153 mg/dL. Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.

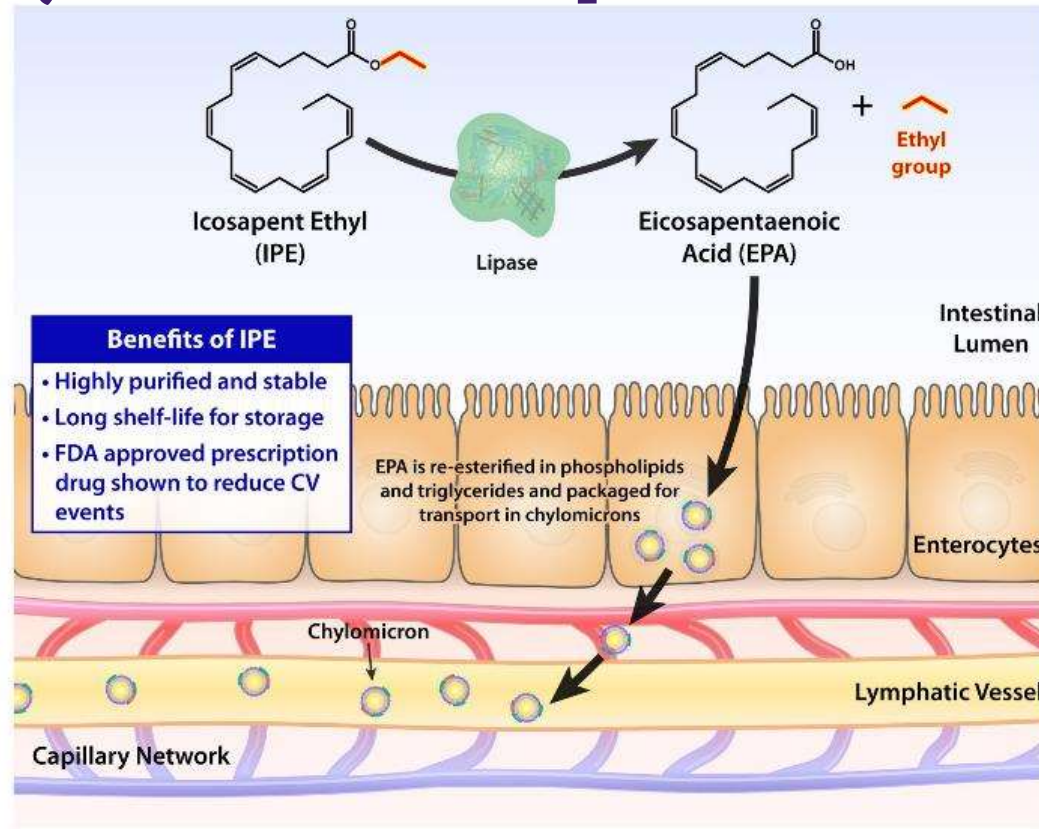
*Primary endpoint: Sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.



No. of patients	0	1	2	3	4	5	Years
Control	475	444	432	414	400	392	
EPA	482	455	443	427	413	403	

HR and P value adjusted for age, gender, smoking, diabetes, and HTN
† Pre-specified, TG ≥150 mg/dL and HDL-C <40 mg/dL (high TG/low HDL-C group).

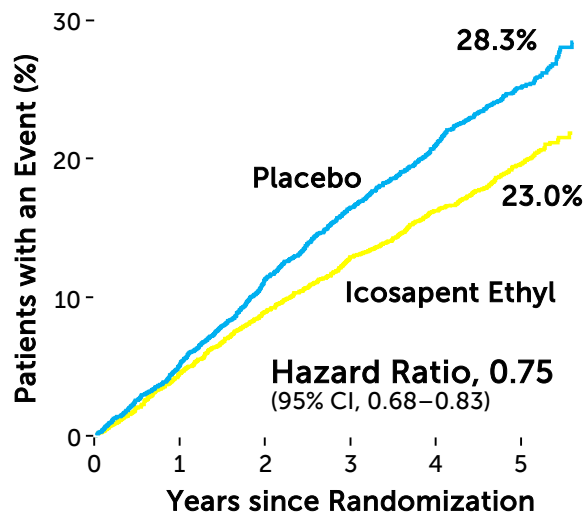
Icosapent Ethyl (IPE) and Eicosapentaenoic (EPA)



REDUCE-IT Primary and Secondary Endpoints

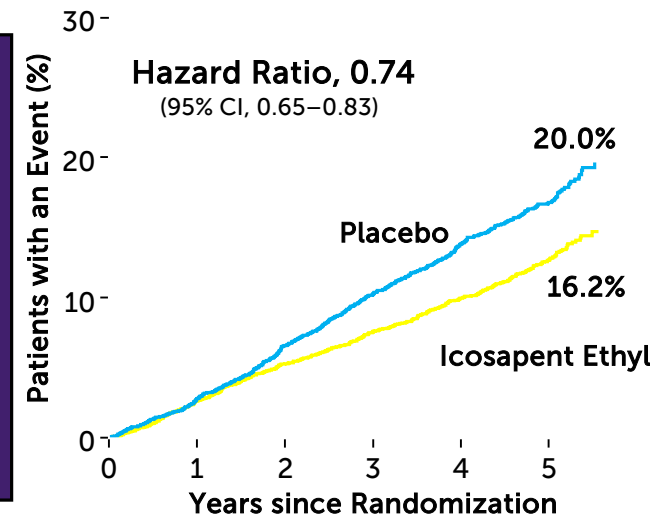
Primary Endpoint: CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina

Key Secondary Endpoint: CV Death, MI, Stroke



Key Inclusion Criteria

- Statin-treated men and women ≥ 45 yrs
- Established CVD (~70% of patients) or DM + ≥ 1 risk factor
- TG ≥ 150 mg/dL and < 500 mg/dL
- LDL-C > 40 mg/dL and ≤ 100 mg/dL

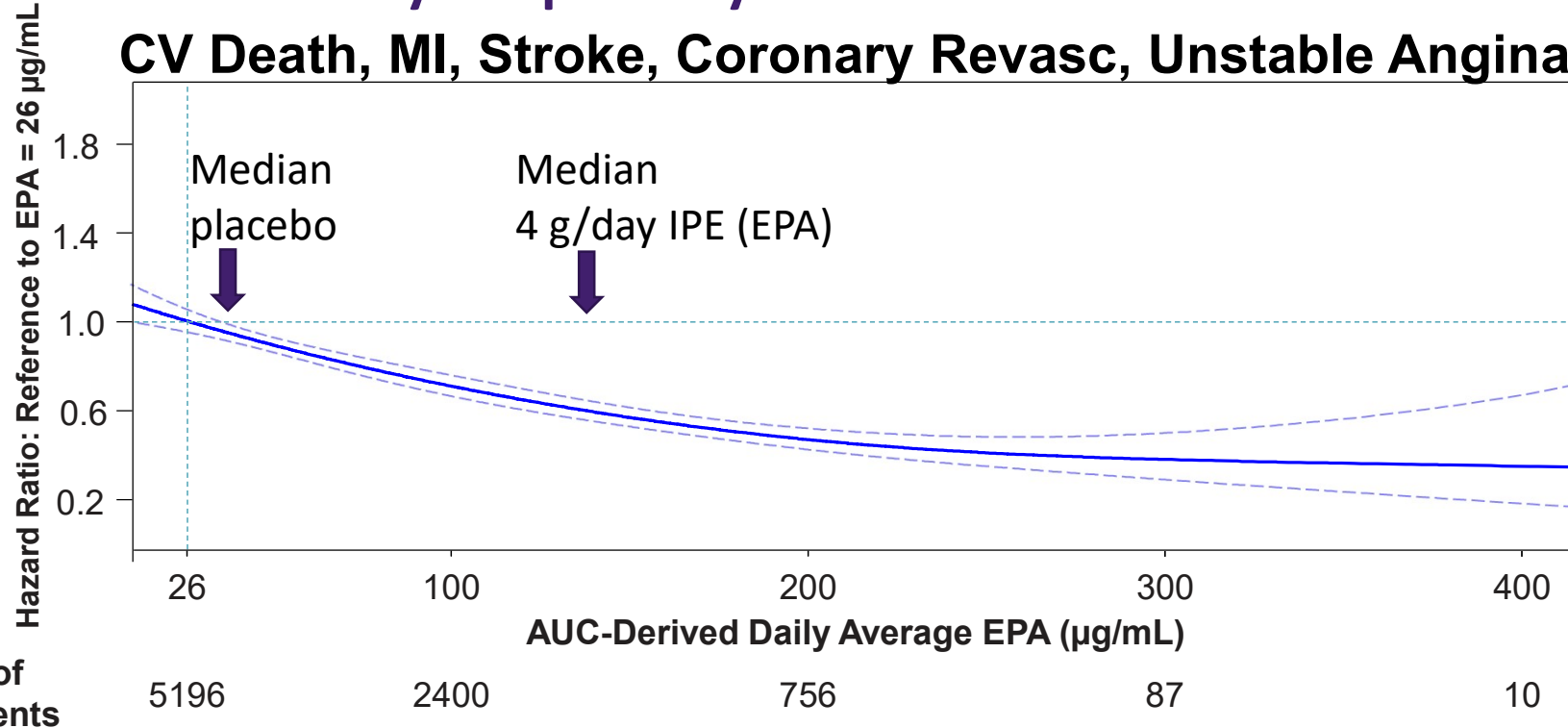


RRR = 24.8%
 ARR = 4.8%
 NNT = 21 (95% CI, 15–33)
 P = 0.00000001

RRR = 26.5%
 ARR = 3.6%
 NNT = 28 (95% CI, 20–47)
 P = 0.0000006

REDUCE-IT Primary Endpoint by On-treatment Serum EPA

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



No. of Patients

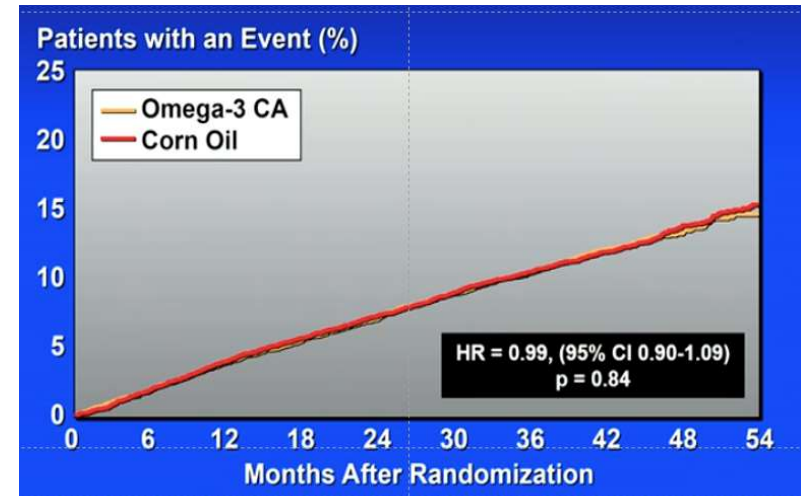
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Adapted from Bhatt DL. Abstract presented at: ACC.20/WCC Virtual Meeting; March 30, 2020.

STRENGTH Trial Design, Details, and Primary Endpoint

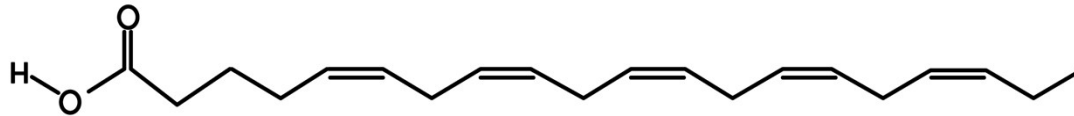
- Randomized 13,078 patients Oct 2014 – June 2017 (686 sites, 22 countries)
- Trial stopped by data monitoring board for “futility” Jan 8, 2020, after review of 1,384 MACE outcomes
- 1,580 MACE endpoints accrued by last patient visit May 14, 2020
- Median follow-up time 42.0 months, and study drug 38.4 months

Primary Endpoint: MACE (CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina)

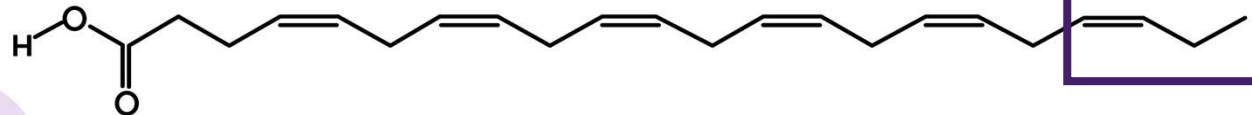


Omega-3 Fatty Acid Structure

Eicosapentaenoic acid (EPA) 20:5



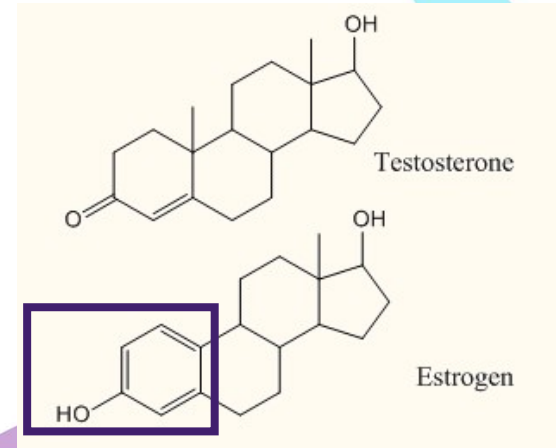
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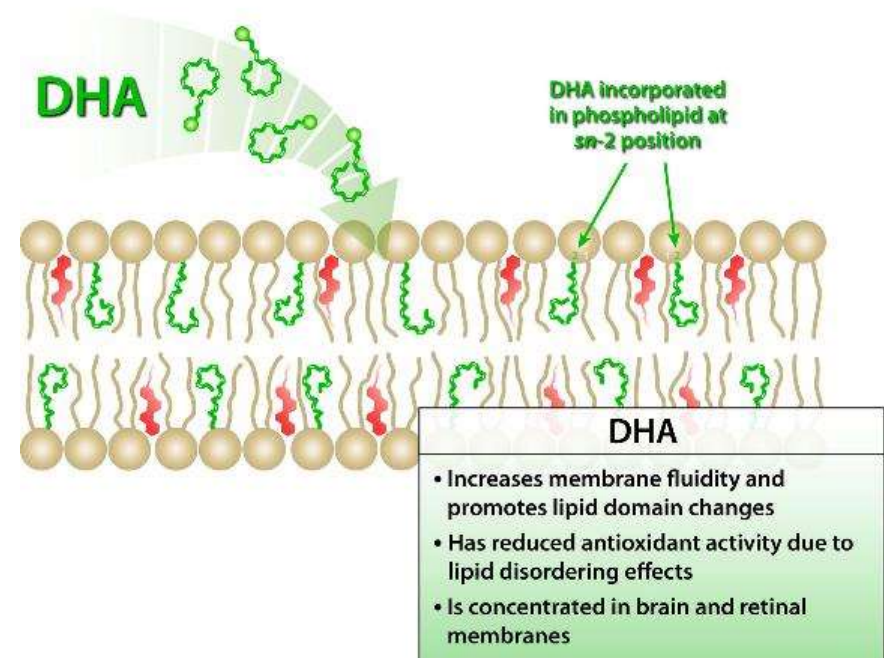
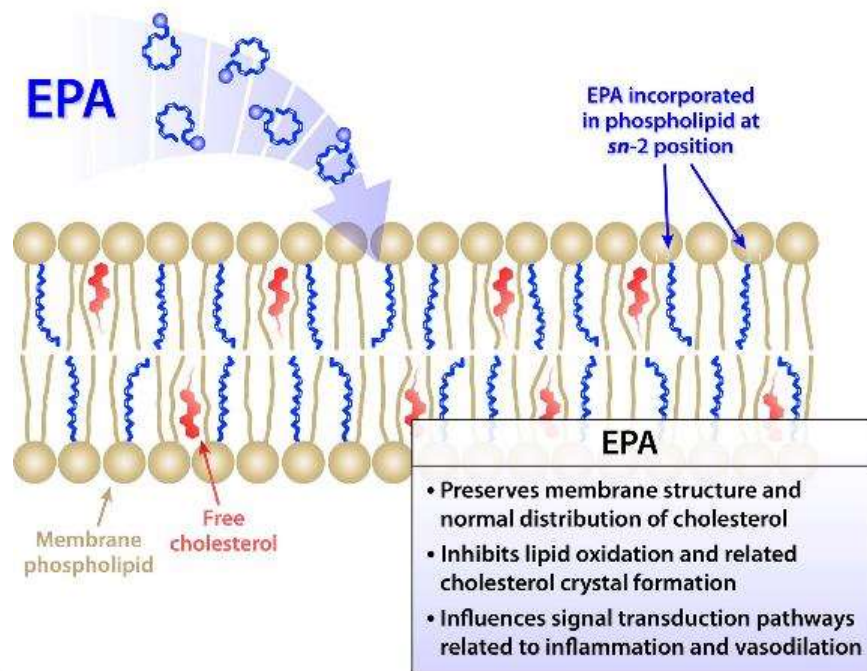
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**Omega-3
PUFA**

Docosahexaenoic acid (DHA) 22:6



Contrasting Effects of EPA and DHA



Distinct Differences Exist Between Marine Omega-3 Fatty Acids EPA and DHA

- Membrane stabilization and fluidity are very different
- Different resolvins are engaged
- Activity on oxidized LDL-C is different
- Different effects of anti-inflammatory biomarkers such as hsCRP

What Have We Learned from the Marine Omega-3 Fatty Acid Clinical Trials?

EPA only vs EPA/DHA Omega-3 Fatty Acid Trials

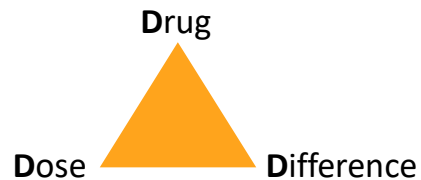
Trial		↓ CVD risk?
REDUCE-IT	EPA	✓
JELIS	EPA	✓
CHERRY	EPA	✓
EVAPORATE	EPA	✓
ASCEND	EPA/DHA	✗
VITAL	EPA/DHA	✗
STRENGTH	EPA/DHA	✗
OMEMI	EPA/DHA	✗

The Bottom Line for Patients with Elevated Triglycerides and High Risk of ASCVD

REDUCE-IT has shown that

Icosapent ethyl at 4 g/day should be prescribed across a broad spectrum of ASCVD risk with HTG

Rx IPE has unique, well-documented MOA profile for benefit in ASCVD: atherogenic lipid-lowering, anti-inflammatory, anti-plaque effects, membrane stabilization, oxidation, endothelial dysfunction, etc.

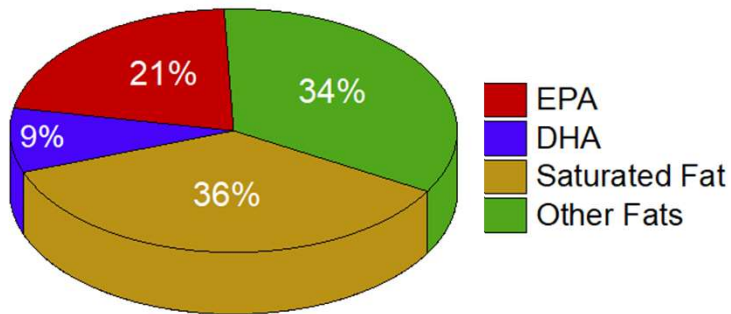


Fish Oil Dietary Supplements: Poorly Regulated But Widely Used

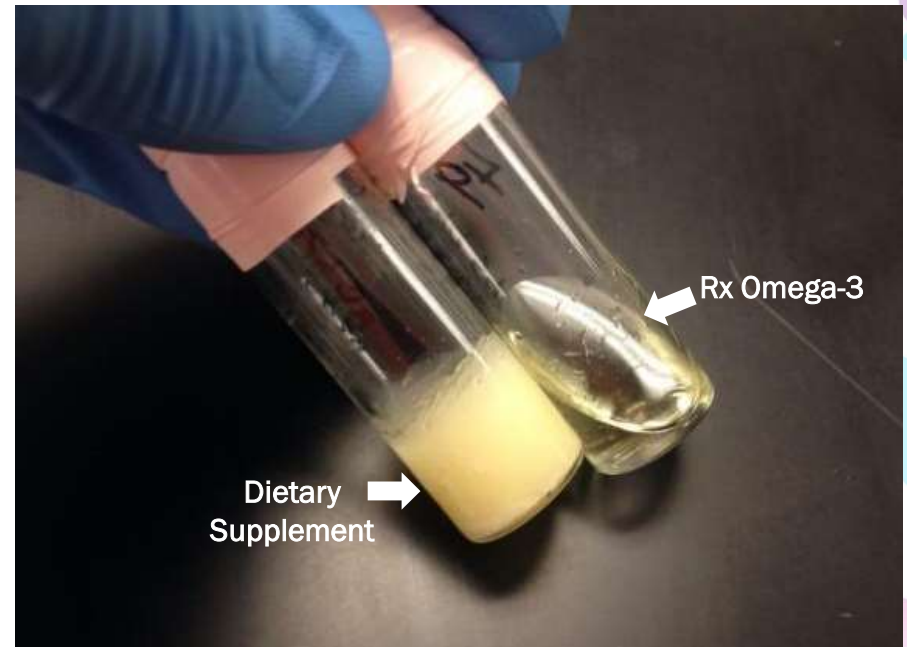


- Approximately 8% of US adults (19 million) take fish oil dietary supplements, but
- There are NO over-the-counter omega-3 products in USA (FDA-regulated and non-prescription), and
- Only non-Rx omega-3s in USA are dietary supplements
 - Minimal FDA oversight, lots of saturated fat, etc.
- Dietary supplements are NOT recommended to treat diseases, yet
- Benefits claimed for heart, brain, weight, etc., etc.
- NO CVD benefits seen in dietary supplement trials!

Problems w/ Content of *Leading* US Fish Oil Dietary Supplements



- Up to 36% of content may be saturated fat
- Omega-3 FA content often overstated
- Oxidation of omega-3 FA content tends to be high (even those meeting industry standards are more oxidized than Rx meds)
- Contamination risk (pesticides, PCBs, etc.)
- Difficult to achieve EPA+DHA doses similar to Rx meds



High saturated fatty acid content of common fish oil dietary supplement makes it **solid at room temperature**

Don't Even Try It! Achieving the Recommended 4 g/day Dose of EPA with Prescription IPE vs Leading Fish Oil Dietary Supplements

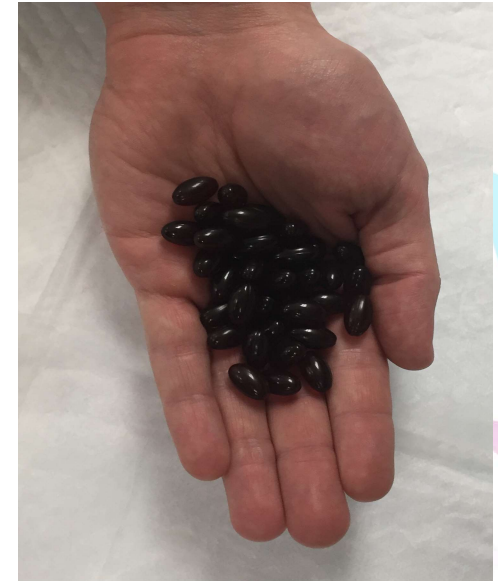
Prescription pure, stable EPA
(Icosapent ethyl)



EPA/DHA dietary supplement
(per label)



Krill oil dietary
supplement (per label)



Icosapent Ethyl (IPE), Rx Only, Now Indicated by the FDA for CVD Event Reduction

New

- As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
 - Established cardiovascular disease or
 - Diabetes mellitus and 2 or more additional risk factors for cardiovascular disease

Prior

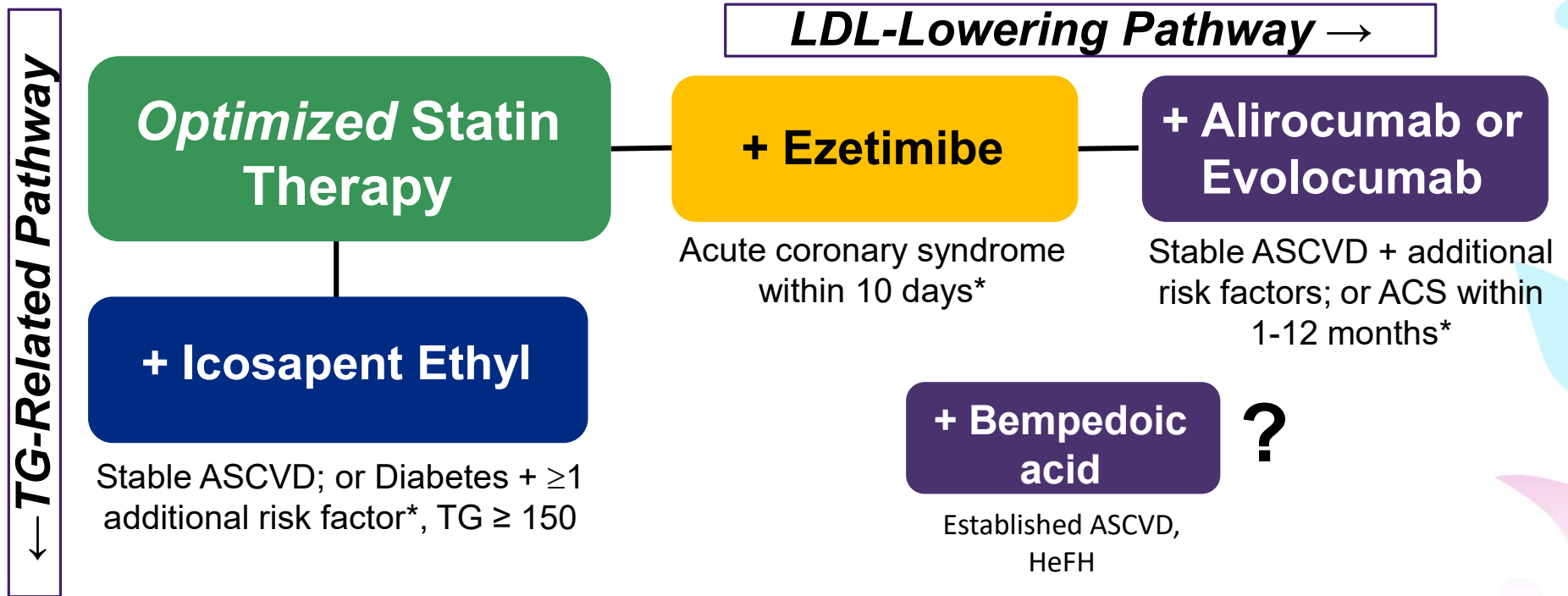
- As an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia
- Limitations of Use: The effect of IPE on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined
- The daily dose is 4 g per day

New Guidelines/Recommendations for IPE to Prevent ASCVD in Patients with TG 135-500 mg/dL (*mild to moderate HTG*)*

Scientific Society	Publication	Treatment with Statin and IPE for ASCVD Risk Reduction
American Diabetes Association (ADA)	<i>#10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019</i>	In patients with ASCVD or other cardiac risk factors with controlled LDL-C but elevated triglycerides (135-499)
European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS)	<i>2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce CV Risk</i>	In high-risk (or above) patients with TG levels between 135-499 mg/dL, n-3 PUFAs (icosapent ethyl 2x2 g/day) should be considered in combination with a statin
National Lipid Association (NLA)	<i>NLA Scientific Statement on the Use of Icosapent Ethyl in Statin-treated Patients with Elevated Triglycerides and High- or Very-high ASCVD Risk</i>	For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with diabetes mellitus requiring medication and ≥ 1 additional risk factor, with fasting TG 135-499 mg/dL
American Heart Association (AHA)	<i>AHA Science Advisory: Omega-3 Fatty Acids for the Management of Hypertriglyceridemia</i>	The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT

***1. All 4 guidelines include TG 135-500, per REDUCE-IT design, but the FDA indication is TG>150
 2. Three of four guidelines/statements mention "LDL-C control" on a statin, per REDUCE-IT design, but the NLA and FDA mention a "maximally tolerated" statin, NOT used in REDUCE-IT**

Statin Therapy Adjuncts *Proven* to Reduce ASCVD



*Major inclusion criteria for respective CVOTs.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia.
After Orringer CE. *Trends in Cardiovasc Med.* 2019;30(3):151-157.



Case Presentation

WOMEN'S HEALTH: **Beyond the Annual Visit**



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Case 1 – C.R.

- A 68-year-old Hispanic woman with a 20-year history of T2DM, HTN, and dyslipidemia, but no history of clinical CVD
- A prior chest CT (done 2 years ago for evaluation of pneumonia) incidentally noted severe coronary artery calcifications
 - She is a nonsmoker with family history of T2DM and HTN; her mother died at 75 of CHF
- Physical exam:
 - Unremarkable; BP 148/80 mm Hg bilaterally, heart rate 90 bpm; height 5'5", weight 174 lbs, BMI 29 kg/m², waist 37 inches

Case 1 – C.R. (con't)

- TC: 206 mg/dL
- TG: 300 mg/dL
- HDL-C: 42 mg/dL
- LDL-C: 104 mg/dL
- Non-HDL-C: 164 mg/dL
- Glucose: 150 mg/dL
- A1C: 7.3%

Current medications:

- lisinopril 20 mg & HCTZ 12.5 mg/day
- metformin 1000 mg bid
- pravastatin 10 mg daily

Does she need any change to lipid-lowering therapy?

Case 1 – C.R. (con't)

- ✓ Lifestyle changes were encouraged
- ✓ Pravastatin 10 mg/d was changed to rosuvastatin 20 mg/d
- ✓ She returns for repeat labs
 - TC: 163 mg/dL
 - TG: 225 mg/dL
 - HDL-C: 44 mg/dL
 - LDL-C: 74 mg/dL
 - Non-HDL-C: 119 mg/dL
 - A1C: 6.9%

Does she need any change to lipid-lowering therapy?



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