# WOMEN'S HEALTH 2020:
Beyond the Annual Visit

## Prevention of ASCVD in Women Through Lipid Management in the New Era

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omnia EDUCATION

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## Prevention of ASCVD in Women Through Lipid Management in the New Era with focus on LDL-C lowering

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## Fdvh#1, JIV1

- 58 yo G3P3 South Asian with no history of heart disease here for ASCVD risk assessment
- HTN taking HCTZ 25 mg/d
- No smoking or diabetes
- Menopause at age 40
- Mother died of MI age 60
- Takes care of her toddler grandchild but otherwise is sedentary

**RISK ENHANCERS**

- 1 birth preterm (34 weeks)
- 2 pregnancies gestational DM
- Premature menopause
- Family history premature CAD
- South Asian

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## Case 1 – G.S. (con't)

*Exam:*

- 5'3", 148lb (BMI 26 kg/m$^2$) waist 35 inches
- Normal cardiac exam
- BP 136/78 mm Hg

- Lipids:
  - TC= 210 mg/dL
  - TG 160 mg/dL
  - HDL-C 42 mg/dL
  - LDL-C 136 mg/dL
- Fasting glucose 105 mg/dL; A1c 5.7
- hsCRP= 2.8 mg/L
- *ASCVD 10-year Risk:* **5.2%** & *Lifetime Risk*: 39%

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Does she need a statin?

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## Female-Specific Risk Enhancers

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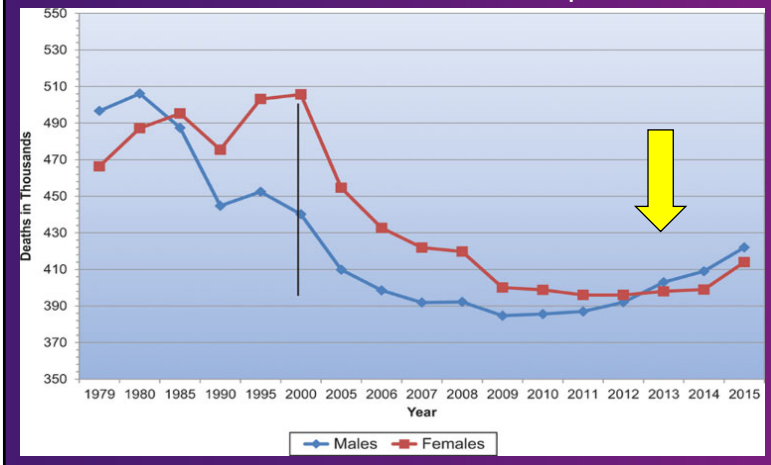
# CVD Mortality Gap Between Men and Women Has Narrowed But Plateaued

U.S. data from AHA Statistics Report




- 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)

Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association, *Circulation*. 2018;137(12):e67-e492.

Curtin SC. *National Vital Statistics Reports*. 2019;68:5.

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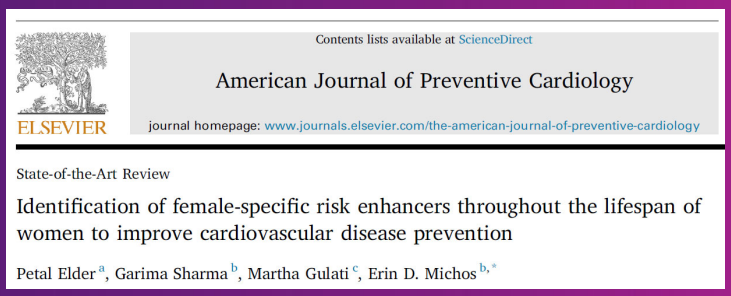
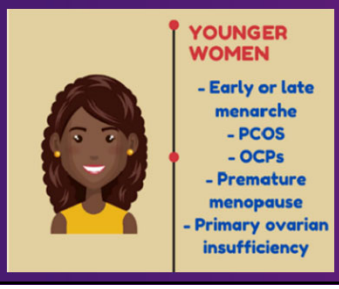
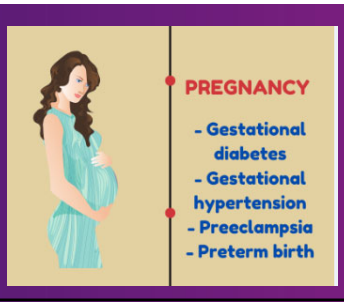
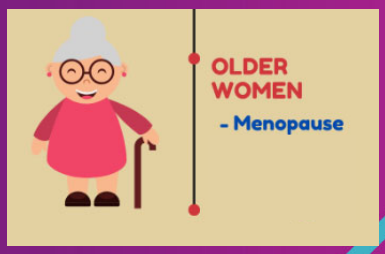
# Female-Specific Risk Enhancers Are Across the Lifespan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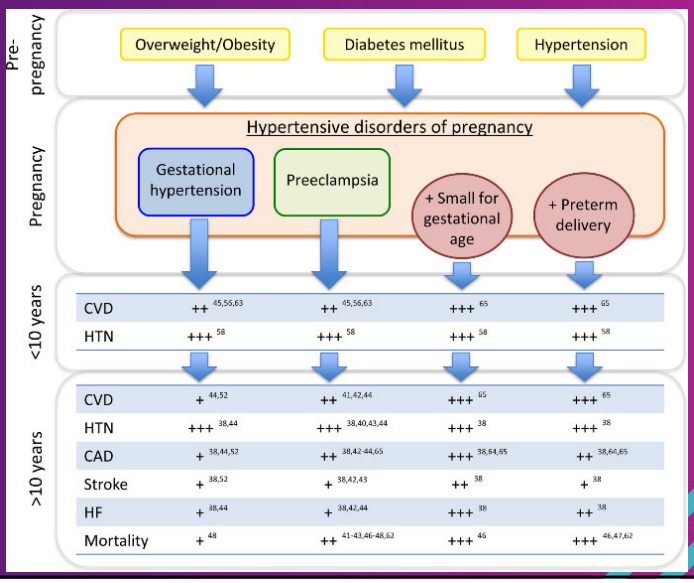
# Adverse Pregnancy Outcomes (APOs) and Future Maternal CVD Risk

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




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

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# Pre-Eclampsia, Pre-term Delivery and Subsequent Maternal CVD: Meta-analysis

- >20 studies, with ~6 million women including >25,800 with preeclampsia & 338, 000 with previous preterm delivery
- 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 occurred before 32 weeks' gestation or were medically indicated

Wu P et al. Circ CQO 2017;10:e003497. DOI: 10.1161/CIRCOUTCOMES.116.003497
Wu P et al. J Am Heart Assoc. 2018;7:e007809. DOI: 10.1161/JAHA.117.007809

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# Gestational Diabetes Mellitus (GDM) and Risk of Maternal CVD

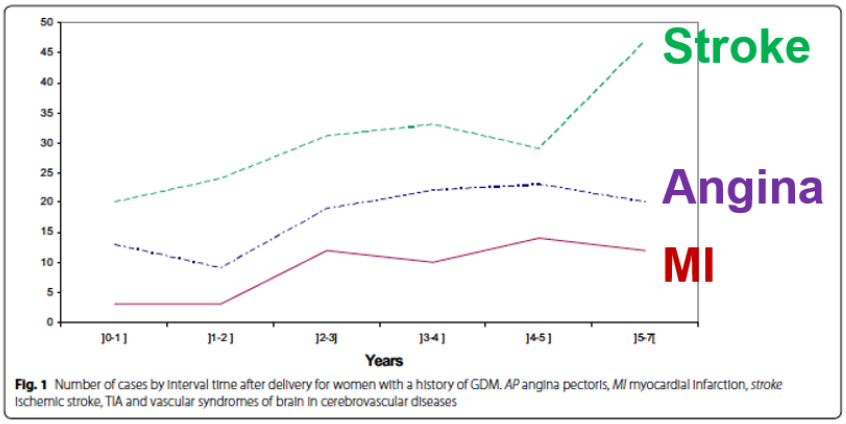


**Fig. 1** Number of cases by interval time after delivery for women with a history of GDM. *AP* angina pectoris, *MI* myocardial infarction, *stroke* ischemic stroke, TIA and vascular syndromes of brain in cerebrovascular diseases

Nationwide: All births 2007-2008 in France: 7-year follow-up; 1,518,990 deliveries with 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]**)

Goueslard et al. *Cardiovasc Diabetol* (2016) 15:15.

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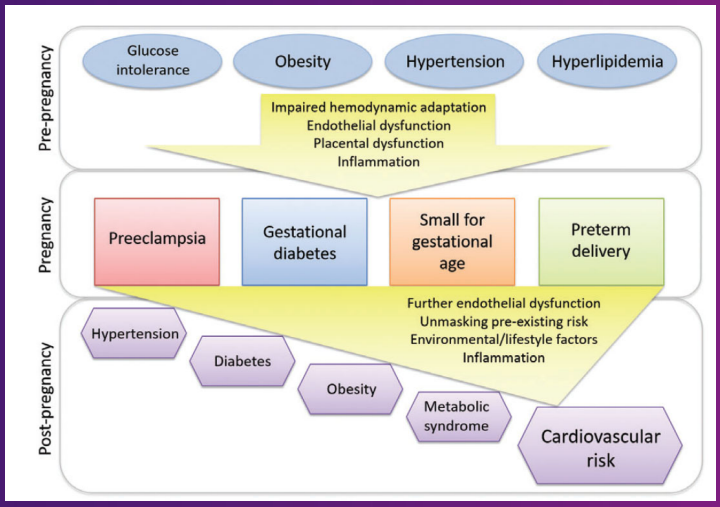
# APOs and Future Maternal CVD Risk




**APO= Adverse Pregnancy Outcome**

**Pregnancy as Nature's Free Stress Test**

Hauspurg A, Ying W, Hubel CA, Michos ED, Ouyang P. *Clin Cardiol*. 2018;41(2):239-246.

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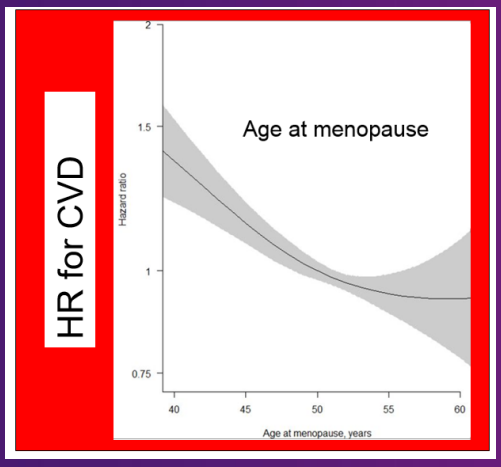
# Premature Menopause and Incident CVD in UK Biobank




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.

Peters SA and Woodward M. *Heart* 2018;104:1069-1075.

Honigberg M et al. JAMA. 2019;322(24):2411-2421. doi:10.1001/jama.2019.19191

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# CVD Risk Reduction Through LDL-C lowering Therapy for PRIMARY PREVENTION

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# 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*




*After* Eckel RH et al, *Circulation* 129 (25 Suppl 2):S76-99, 2014.

**Best evidence for ↓MI risk is with the Mediterranean diet**

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# 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 for is brisk walking ~30 min/day ~5 days/week**

*After* Eckel RH, et al. *Circulation*. 2014;129(25 Suppl 2):S76-99.

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# 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

Arnett DK, et al. *Circulation.* 2019;140(11):e563-e595.



# ACC Risk Calculator *Plus* to Assess Risk Categor

**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" |
|---|---|---|---|

- 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**

ACC=American College of Cardiology; AHA=American Heart Association; ASCVD=atherosclerotic cardiovascular disease; tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate

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

**Risk-Enhancing Factors**

- Family history of premature ASCVD (men, age <55y; 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**

Grundy SM et al. Circulation. 2019;139:e1082-e1143.

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# 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 (e.g. 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

*After* Grundy SM et al. Circulation. 2019;139:e1082-e1143.

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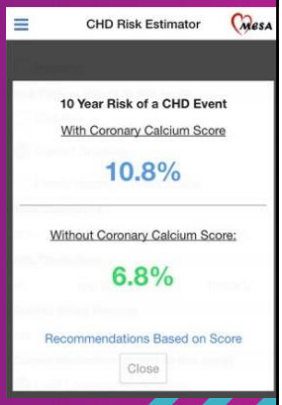
# Using The CAC Score to Guide Statin Therapy

- A CAC score predicts ASCVD events in a graded fashion
  - 0; 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."

MESA Risk Score




Grundy SM et al. *Circulation*. 2019;139:e1082-e1143. *Atherosclerosis* 2019;290:140-205.

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# Case 1 – G.S. (con't)

- Borderline 10-year risk – 5.2%
- Has multiple risk enhancing factors
- Lifestyle: encourage healthy diet, increase activity, weight loss
- BP control
- Moderate intensity statin recommended to reduce LDL-C by ≥30%
- Engaged in shared decision making
- Patient was reluctant to start statin, worried about side effects of statins based on some posts she has seen in her Facebook group
- After further discussion, CAC score was obtained
  - CAC score 24, which is 81$^{st}$ percentile for age/sex/race
  - Images reviewed with patient; she agreed to initiate statin

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## 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 ≈0.001%
  - The risk of statin-induced newly diagnosed diabetes mellitus is ≈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

Toth PP, et al. *Am J Cardiovasc Drugs* (2018) 18:157–173.
Newman CB, et al. *Arterioscler Thromb Vasc Biol*. 2019 Feb;39(2):e38-e81.

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## Case 2 – C.R.

- A 68-year-old Hispanic woman with a 20-year history of T2DM, also history of HTN and dyslipidemia, but no history of clinical CVD
- A prior chest CT 2 yrs 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 lb, BMI 29 kg/m2, waist 37 inches

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## Case 2 – 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?

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## Statin Treatment in Patients with Diabetes

- For patients of all ages with **diabetes *and* ASCVD or 10-year ASCVD risk >20%, high-intensity statin therapy** should be added to lifestyle therapy. (A)
- In patients with **diabetes *without* ASCVD but *with multiple* ASCVD risk factors**, it is reasonable to consider **high-intensity statin therapy**. (C)
- For patients with **diabetes *without* ASCVD, aged 40–75 years** (A), **and >75 years** (B), use **moderate-intensity statin** in addition to lifestyle therapy.
- For patients with **diabetes aged <40 years with additional ASCVD risk factors**, the patient and provider should *consider* using **moderate-intensity statin** in addition to lifestyle therapy. (C)
- For patients who do not tolerate the intended intensity, **the maximum tolerated statin dose should be used**. (E)

(A)= High quality evidence; (B)= Moderate quality evidence; (C)= Limited data; (E)= Consensus of expert opinion based on clinical experience.
*After* Grundy SM et al. Circulation. 2019;139:e1082-e1143.

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## Diabetes-Specific Risk Enhancers
*Independent of Other Risk Factors in Diabetes Mellitus*

- Long duration
  - ≥10 years for T2DM
  - ≥20 years for type 1 DM
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 mL/min/1.73 m2
- Retinopathy
- Neuropathy
- ABI <0.9

Arnett DK et al. *J Am Coll Cardiol*. 2019 Mar 17. [Epub ahead of print]

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## Selecting the Appropriate Statin

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

Grundy SM, et al. *J Am Coll Cardiol.* 2019;73(24): e285-e350.

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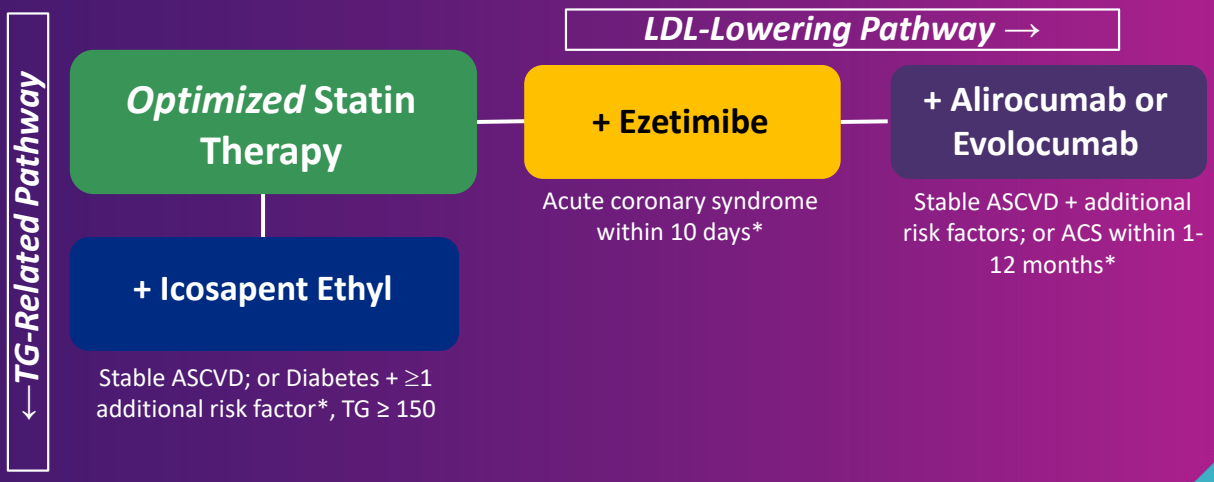
## Statin Therapy Adjuncts *Proven* to Reduce ASCVD




*Major inclusion criteria for respective CVOTs.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CVOTs, cardiovascular outcomes trials;.
*After* Orringer CE. *Trends Cardiovasc Med*. 2020;30(3):151-157.

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## CVD Risk Reduction Through Triglyceride-lowering Therapy

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Utah Lipid Center
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# Case 2 – 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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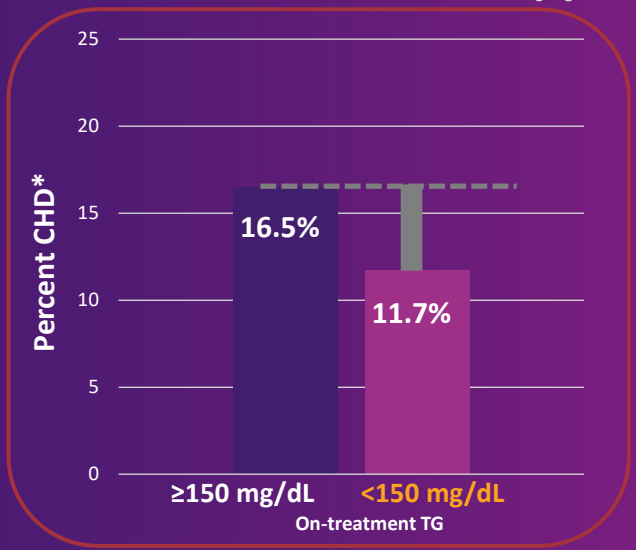
# Residual HTG Predicted Residual ASCVD Risk Despite *LDL-C at Goal* on Statin Monotherapy




**↑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.

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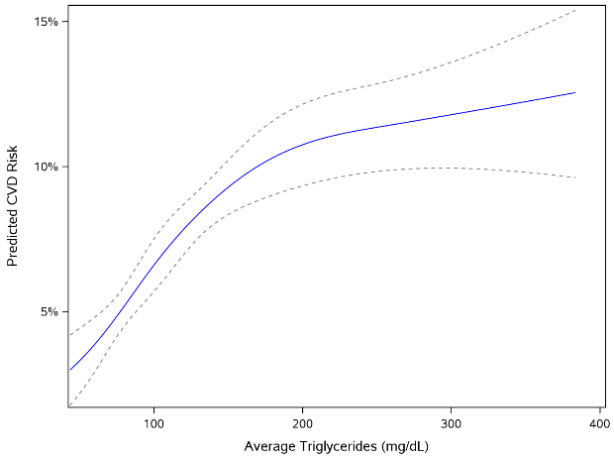
# Fasting TG Is Strongly Related to CVD Risk, Even at Very Low Levels




- 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**

95% confidence intervals shown as dotted lines
Aberra T, et al. *J Clin Lipidology*. 2020;S1933-2874(20)30079-9.

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# 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 |

Jacobson TA et al. *J Clin Lipidol*. 2014;8:473-88.
American Heart Association (AHA) Scientific Statement. Miller M et al. *Circulation*. 2011;123:2292-333.

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# Current Guidance Regarding Available Statin Adjuncts: Fibrates & Niacin

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

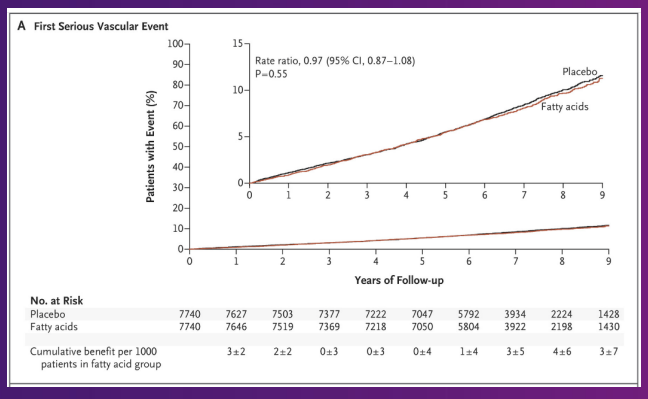
ACCORD Study Group et al. N Engl J Med. 2010;362:1563-74.
Keech A et al. Lancet. 2005;366:1849-61.
Boden WE, et al. N Engl J Med. 2011;365:2255-67.
HPS2-THRIVE Collaborative Group. N Engl J Med. 2014;371:203-12.

(A)= High evidence.
Grundy SM et al. Circulation. 2019;139:e1082-e1143.



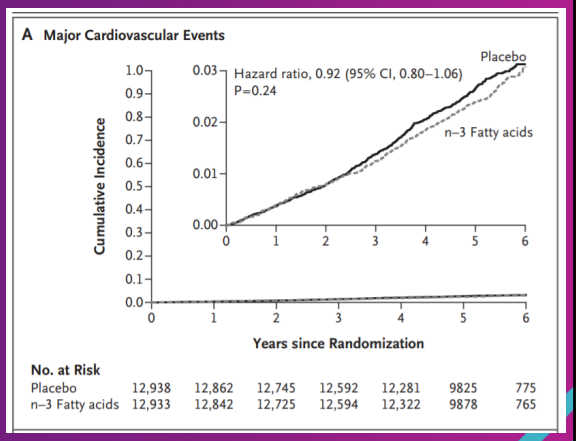
# Fatty Acids in Primary Prevention: ASCEND & VITAL (EPA+DHA 1g/d) failed to meet primary endpoint

**ASCEND Trial**



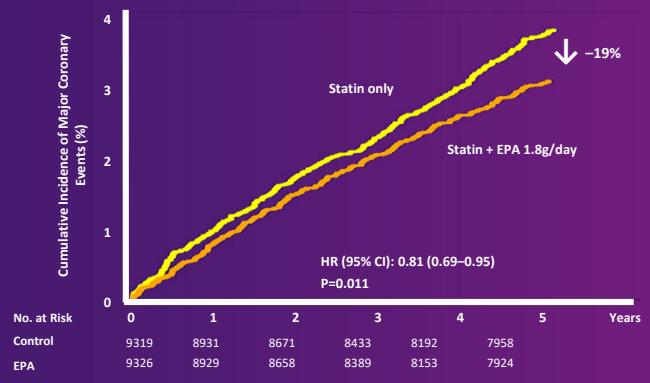

ASCEND Study Group. *N Engl J Med.* 2018;379:1540-1550.

**VITAL Trial**

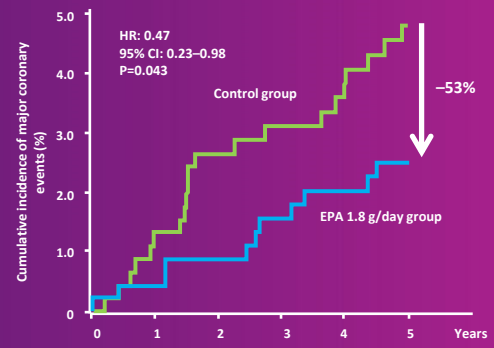



Manson JE, et al. *N Engl J Med.* 2019;380:23-32.

# 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 |
|---|---|---|---|---|---|---|
| Control | 9319 | 8931 | 8671 | 8433 | 8192 | 7958 |
| EPA | 9326 | 8929 | 8658 | 8389 | 8153 | 7924 |




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

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.

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.

Yokoyama M, et al. *Lancet*. 2007;369(9567):1090-1098.

Saito Y, et al. *Atherosclerosis*. 2008;200(1):135-140.

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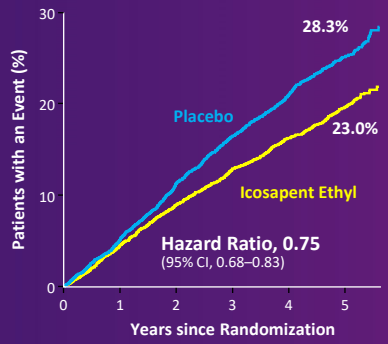
# REDUCE-IT Primary and Secondary Endpoints

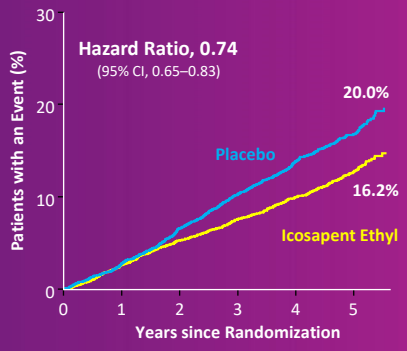
**Primary End Point:** CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina




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

**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

**Key Secondary End Point:** CV Death, MI, Stroke




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

Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22.

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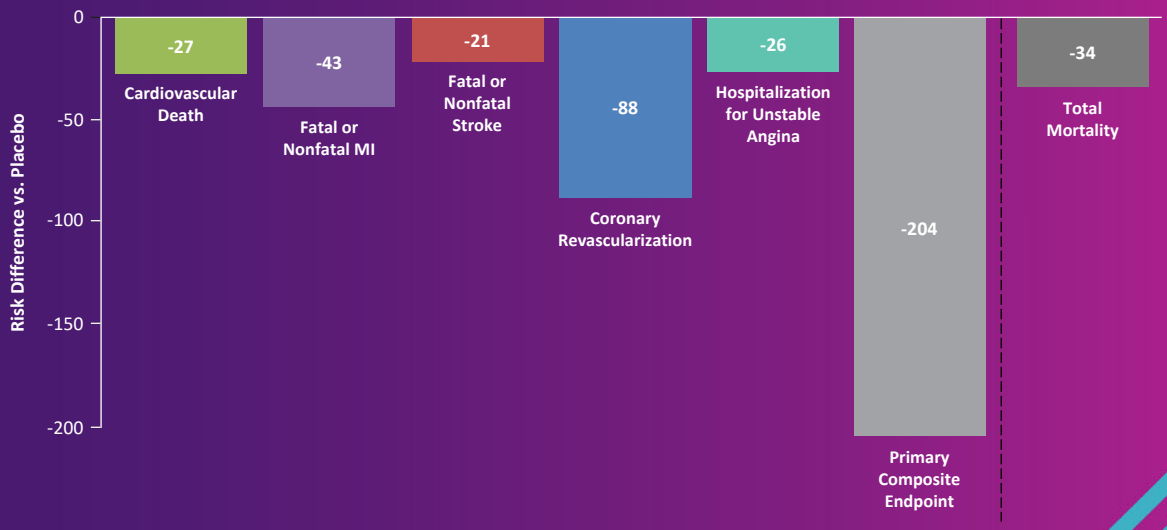
## Decrease in Total Events For Every 1000 US Patients on Icosapent Ethyl 4g/day for 5 Years




Bhatt DL et al. *N Engl J Med.* 2019;380:11-22. Bhatt DL. AHA Scientific Sessions 2019, Philadelphia, PA.

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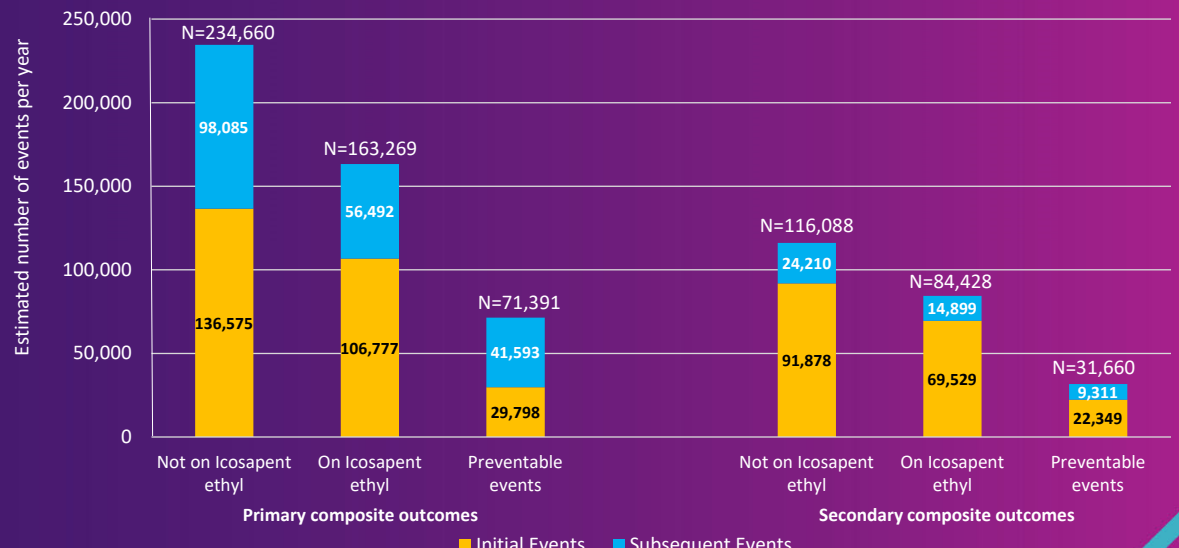
## Annual Projected Initial and Subsequent Preventable Primary and Secondary Composite Endpoint Events based on REDUCE-IT




NHANES: National Health and Nutrition Examination Survey, 1999-2016.; Wong N. *Eur Med J*. June 2020.

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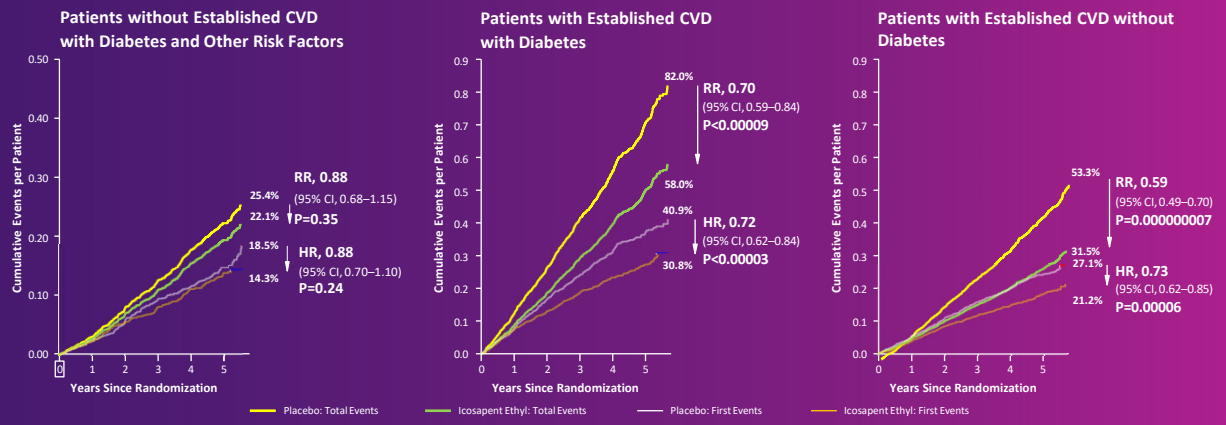
# REDUCE-IT: Time to First & Total Primary Endpoint Events by CV Risk Category & Diabetes Status at Baseline




Interaction P value between patients with established CVD with diabetes and patients with established CVD without diabetes = 0.98
Interaction P value between patients with diabetes and other risk factors, patients with established CVD with diabetes, and patients with established CVD without diabetes = 0.32

Bhatt DL, Brinton EA, Miller M, et al. *Diabetes.* 2020;69(Suppl 1):4-LB.

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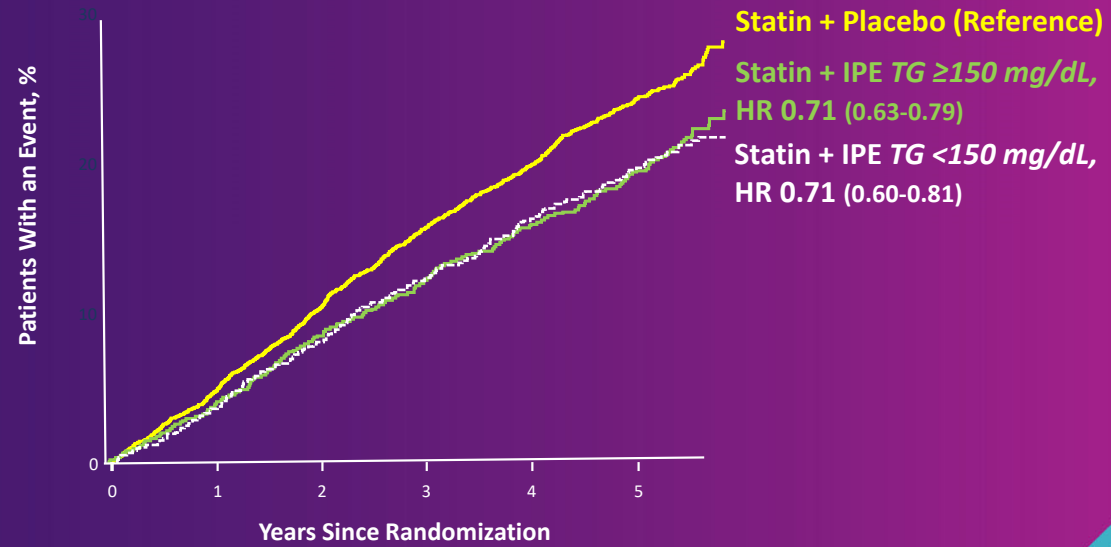
# ↓CVD with IPE Did *NOT* Vary by *TG Decrease* *(HR similar with achieved TG ≥ or < 150 mg/dL)*




Bhatt DL, *N Engl J Med*. 2019;380(1):11-22.

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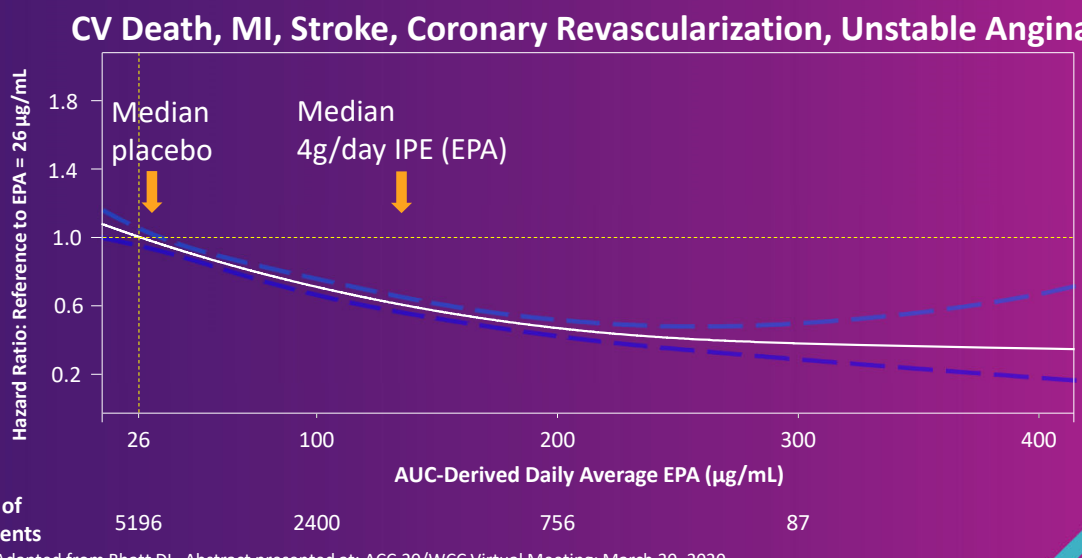
# Primary Endpoint by On-Treatment Serum EPA




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

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# Reported Clinical and Biologic Cardiovascular Benefits of Omega-3 Fatty Acids

**Arrhythmias**
- ↓Sudden death (GISSI-P and REDUCE-IT)
- ↑Atrial fibrillation *harmful* (vs apparent and beneficial ↓ventricular arrhythmias)
- Heart rate variability improvement

**Anti-atherogenic**
- ↓Non-HDL-C
- ↓TG
- ↓Chylomicrons
- ↓VLDL- and ↓Chylomicron-remnants
- ↑HDL-C (only in DHA-containing, ↓ w/ EPA-alone)
- ↑LDL and HDL particle size (DHA only)
- Plaque stabilization

**Antithrombotic**
- ↓Platelet aggregation
- ↑Blood flow (↓viscosity)

**Anti-inflammatory and endothelial-protective effects**
- ↓C-reactive protein (hsCRP)
- ↓Endothelial adhesion molecules & ↓Leukocyte adhesion receptors
- ↓Proinflammatory eicosanoids
- ↓Proinflammatory leukotrienes
- ↑NO production/vasodilation

**↓Systolic and diastolic BP**

*After* Nelson JR, et al. *Vascul Pharmacol.* 2017;91:1-9.
*After* Bays HE. Chapter 21. In: Kwiterovich PO, ed. *The John Hopkins Textbook of Dyslipidemia.* Wolters Kluwer: 2010; 245-257.

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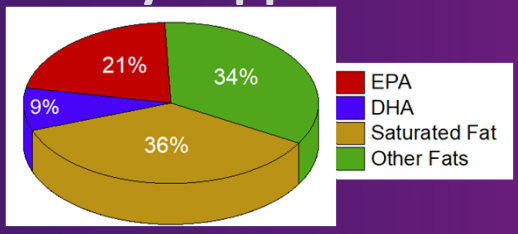
## Fish Oil Dietary Supplements: Poorly Regulated but Widely Used

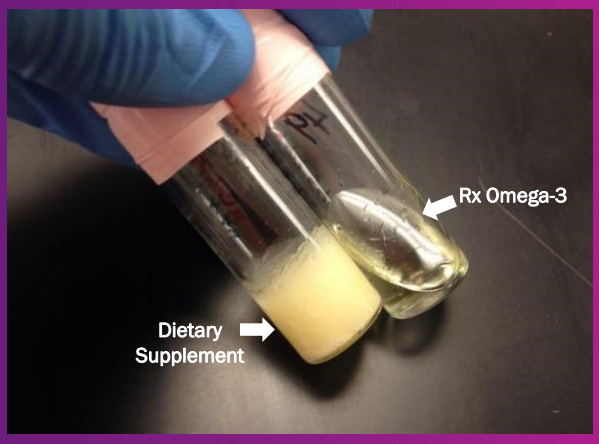
- Approximately 8% of US adults (19 million) take fish-oil dietary supplements, ***but***
- There are ***NO*** over-the-counter omega-3 products in USA (FDA-regulated and ***non***-prescription), ***and***
- ***Only*** non-Rx omega-3s in USA are ***dietary supplements***
  - Minimal FDA oversight, lots 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

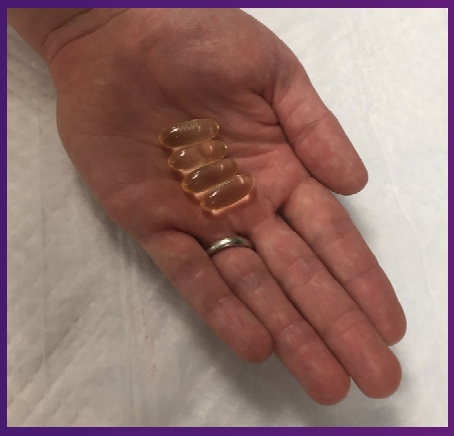



High saturated fatty acid content of common fish oil dietary supplement makes it ***solid at room temperature***

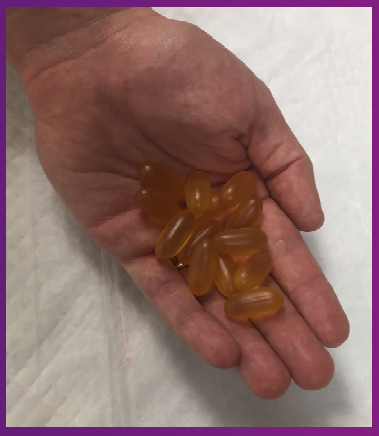
Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483:425-429. Hilleman D, Smer A. *Manag Care*. 2016;25:46-52. Albert BB, et al. *Sci Rep*. 2015;5:7928. Kleiner AC, et al. *J Sci Food Agric*. 2015;95:1260-7. Ritter JC, et al. *J Sci Food Agric*. 2013:93:1935-9. Jackowski SA, et al. *J Nutr Sci*. 2015;4:e30. Rundblad A, et al. *Br J Nutr*. 2017;117:1291-8. European Medicines Agency, 2018: 712678.

## Achieving the Recommended 4 gm/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)**

Photos courtesy of Preston Mason, PhD

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## 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 grams per day

Released December 13, 2019. After https://www.vascepa.com/assets/pdf/Vascepa_PI.pdf.

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## 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) | *#10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019* | 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) | *2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce CV Risk* | 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) | *NLA Scientific Statement on the Use of Icosapent Ethyl in Statin-treated Patients with Elevated Triglycerides and High- or Very-high ASCVD Risk* | 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) | *AHA Science Advisory: Omega-3 Fatty Acids for the Management of Hypertriglyceridemia* | 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 4 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***

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride.
American Diabetes Association. [web annotation]. Diabetes Care 2019;42(Suppl. 1):S103–S123. Retrieved from https://hyp.is/JHhz_lCrEembFJ9LIVBZIw. *Eur Heart J*. 2020 Jan 1;41(1):111-188. *Orringer, CE., et al. Journal of Clinical Lipidology, November 2019. AHA Science Advisory.* Skulas-Ray AC, et al. *Circulation*. 2019;140:e673–e691.

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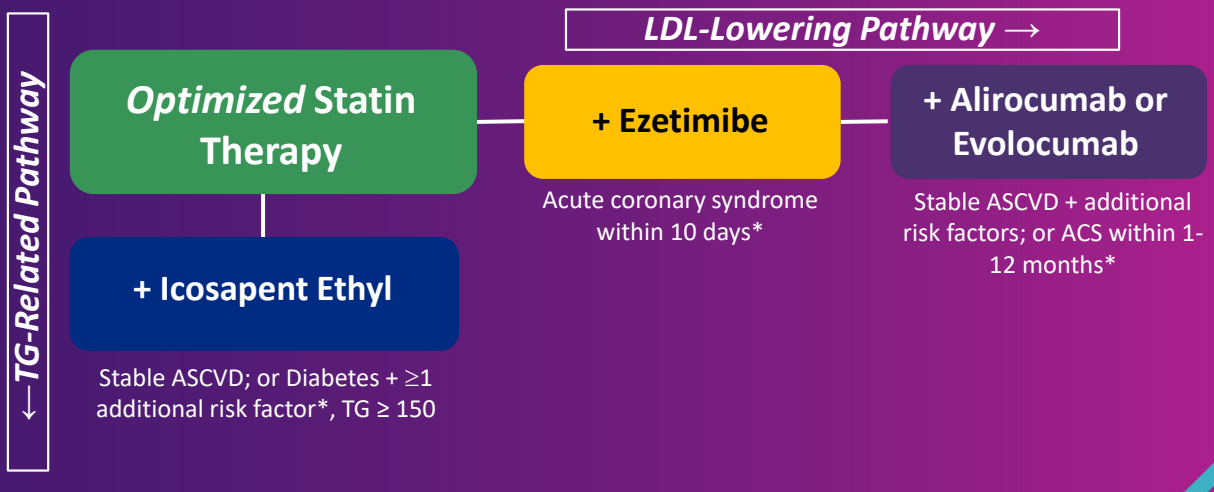
## Statin Therapy Adjuncts *Proven* to Reduce ASCVD




*Major inclusion criteria for respective CVOTs.
ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease.
*After* Orringer CE. *Trends Cardiovasc Med*. 2020;30(3):151-157.

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# Summary—*Updates* in Lipid Guidelines

- 2018 Multi-Society Cholesterol/2019 ACC/AHA 1º Prevention Guidelines
  - *Improved* risk assessment
  - *Lifelong* healthy lifestyle
  - *On-treatment* LDL-C levels emphasized (thresholds ≈ goals)
  - Ezetimibe & PCSK9i to ↓**CVD** (if LDL-C > threshold w/ max statin)

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- 2019 *Four* New Guidelines/Statements for patients w/ HTG:
  - *If* TG 135-500, despite LDL-C control with statin therapy, and
  - *If* Prior CVD, or DM2 + additional risk, then
  - IPE 4g/d recommended to ↓**CVD**
  - Non-IPE and dietary-supplement omega-3 *not* recommended

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- New FDA indication (2019) for IPE to ↓CVD (≈ to Statements)
- Implementing this new guidance:
  - Statin *rechallenge* often useful
  - Consider statin *adjuncts* to ↓**CVD**:
    - Ezetimibe and/or PCSK9i for *residual LDL-C* elevation
    - Icosapent ethyl in the case of *residual TG* elevation

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