A Closer Look at Women, Atherosclerosis, and Lipids: *What Is Different?*

WOMEN'S HEALTH:
Beyond the Annual Visit

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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

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Identifying Women at Risk or With Cardiovascular Disease

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Brigham and Women's Hospital
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Beyond the Annual Visit

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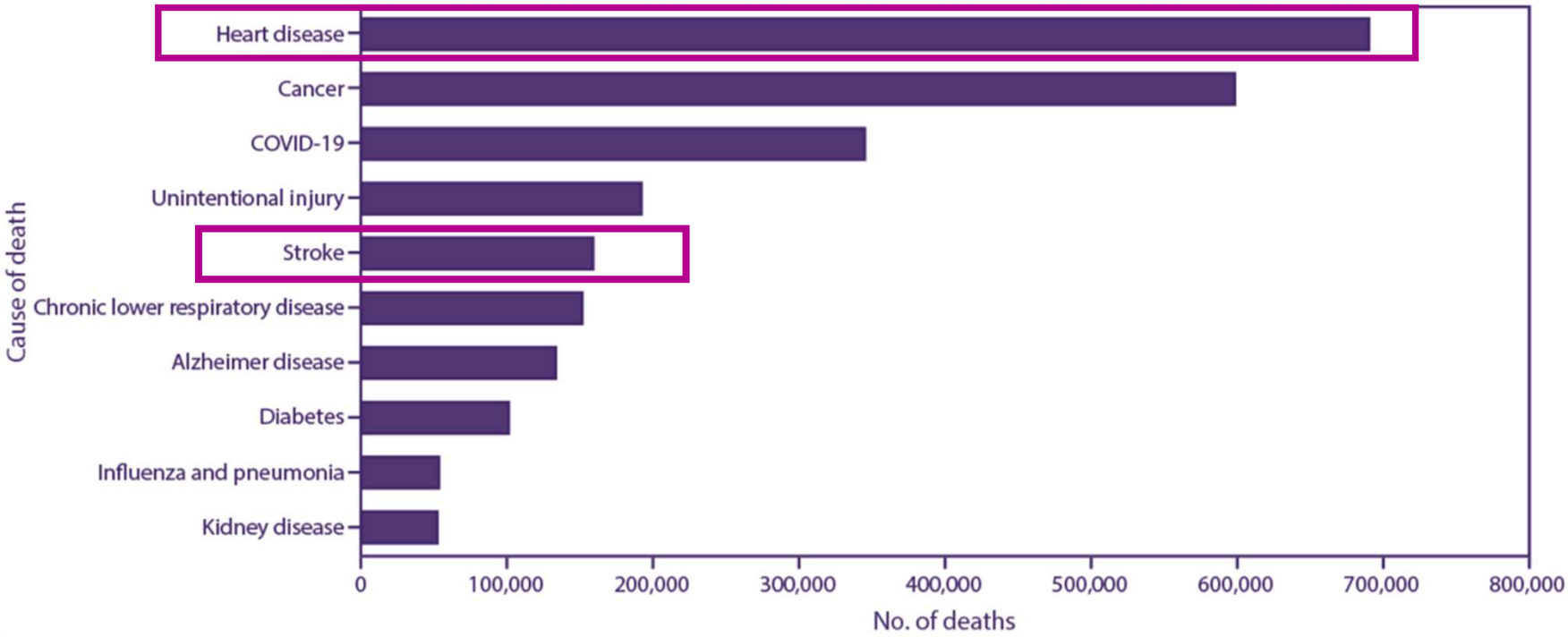
Heart Disease Remains the #1 Cause of Death

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



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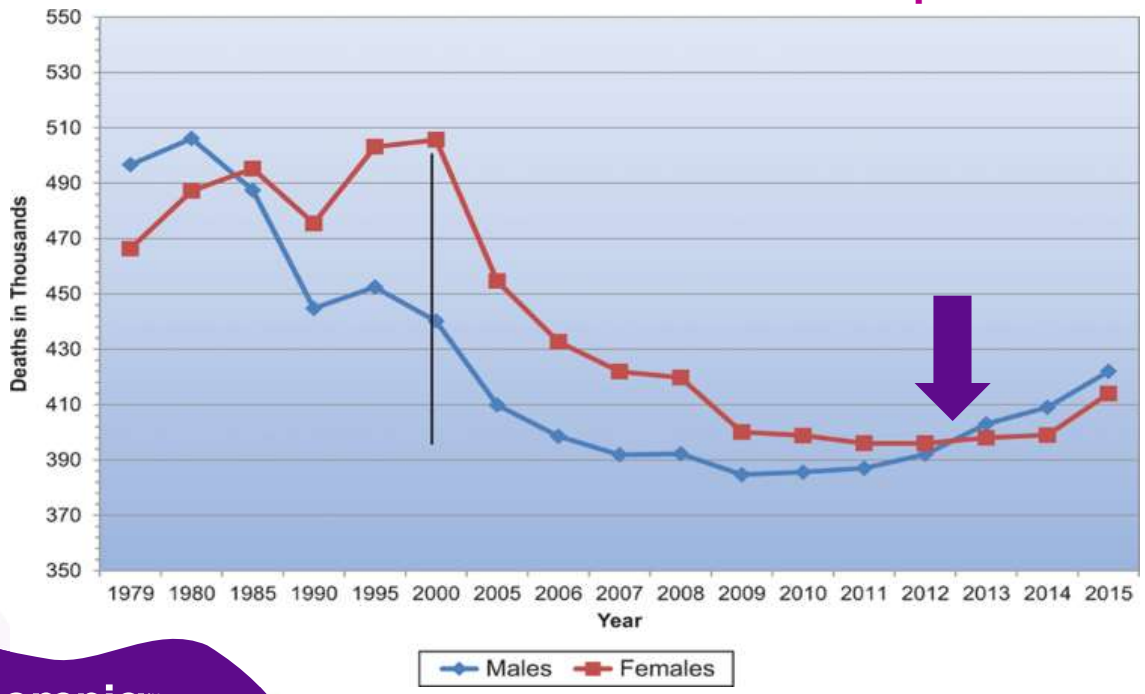
* https://www.cdc.gov/nchs/nvss/deaths.htm

† 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

US 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)

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Benjami EJ, et al. *Circulation*. 2018;137(12):e67-e492. Curtin SC. *Natl Vital Stat Rep*. 2019;68(5):1-9.

Female-Specific Risk Enhancers Are Across the Lifespan

ELSEVIER

Contents lists available at ScienceDirect

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,*]

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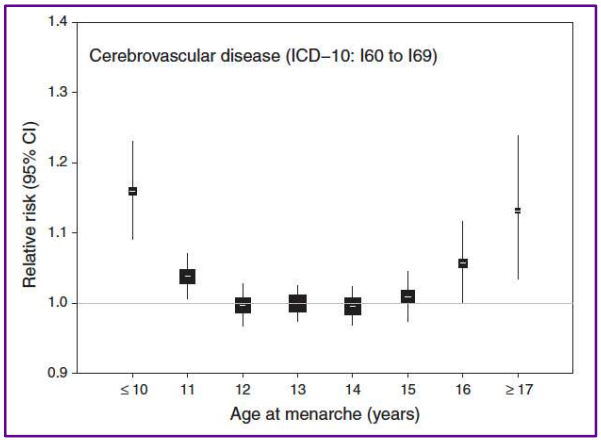
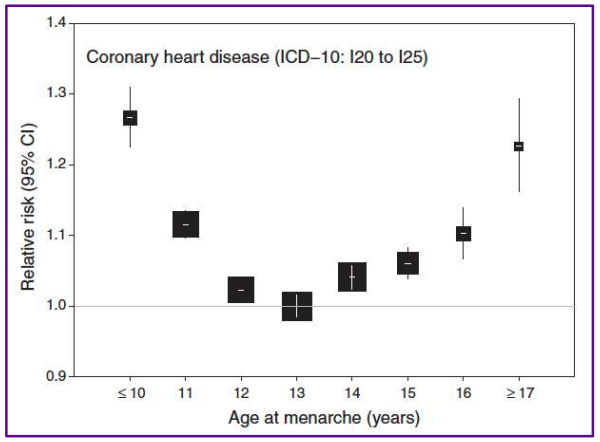
Early and Late Menarche: Important Risk Enhancers in Women





1.2 million women living in the UK
73,378 CHD events
25,426 stroke events

- The average age of menarche in US women is 13 years
- Drivers of excess risk are unknown
- **Early menarche** linked to psychological stress and overnutrition
- **Late menarche** linked to PCOS, excessive exercise, and undernutrition

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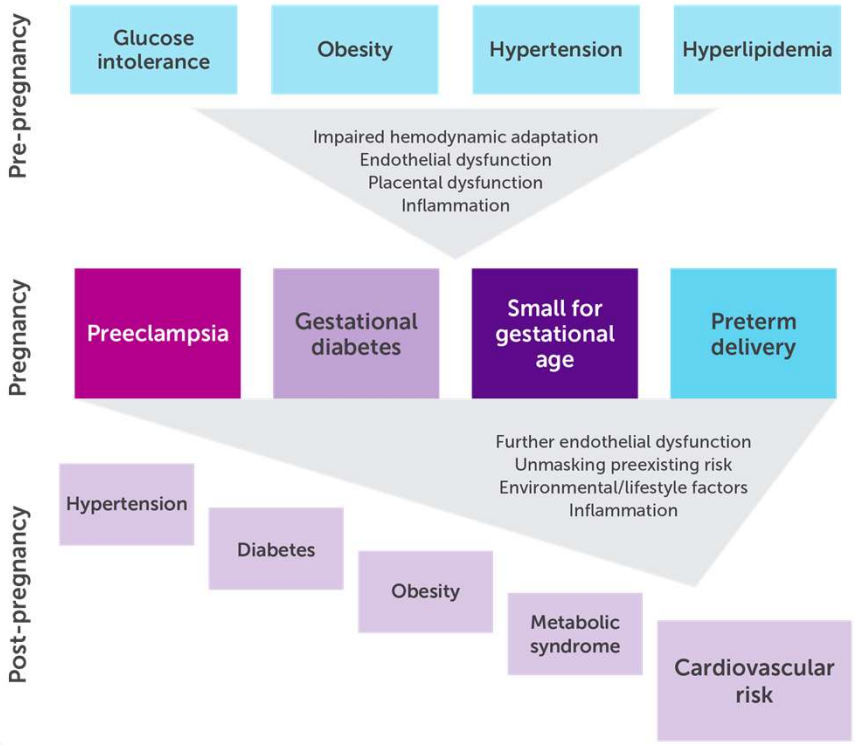
Canoy D, et al. *Circulation*. 2015;131(3):237-244.

Adverse Pregnancy Outcomes Impact Future CV Risk



	Rates	Future Risk of Hypertension	Future Risk of Diabetes	Future Risk of ASCVD
Gestational HTN/ Preeclampsia	3%-14% of pregnancies Preeclampsia: 25% of preterm births, and 2%-5% of all births	✓	✓	✓
Gestational DM	5% of all pregnancies		✓	✓
Preterm Delivery	6%-12% of all births			✓
Fetal Growth Restriction	8% of all births			✓

Gestational window "natural" stress test: increased cardiac output, increased renal blood flow, insulin resistance to facilitate transfer of glucose to the fetus, increased TG, increased plasma volume and hypercoagulable state.

Hauspurg A, et al. *Clin Cardiol*. 2018;41(2):239-246.

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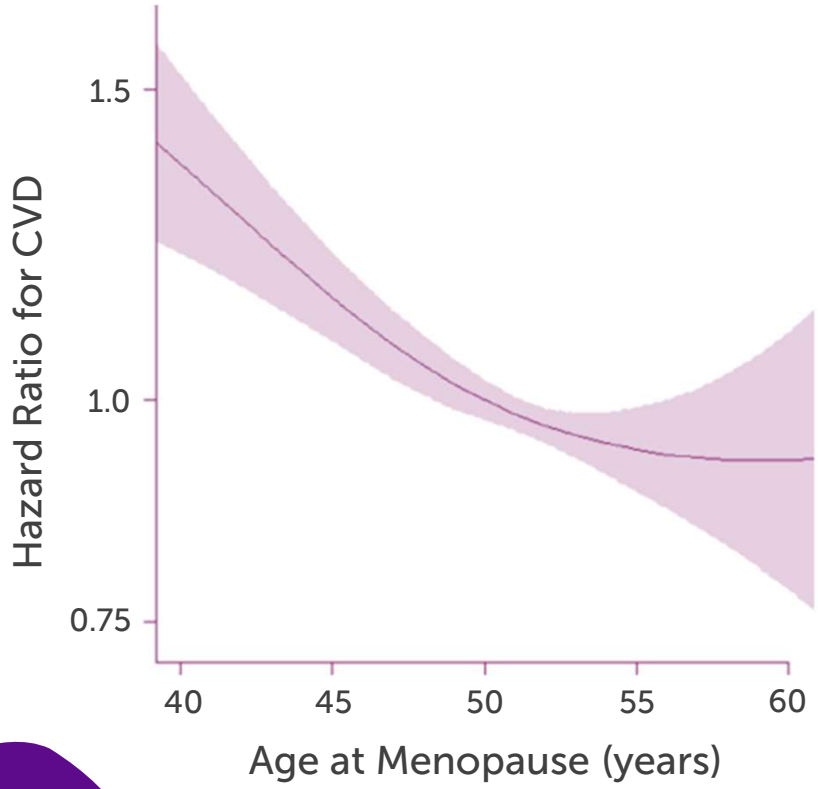
Premature Menopause and Incident CVD in UK Biobank



- >250,000 women living in the UK
- >5,700 cases of CAD
- >3,000 cases of stroke
- In these data, risk increases at <47 years
- Other cohorts, **<40-45 years**
- Average age at menopause = 51 years

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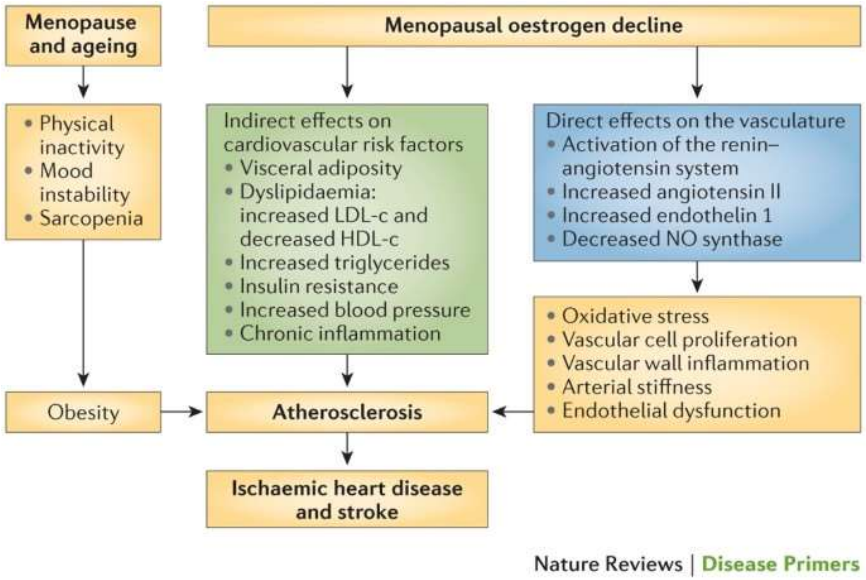
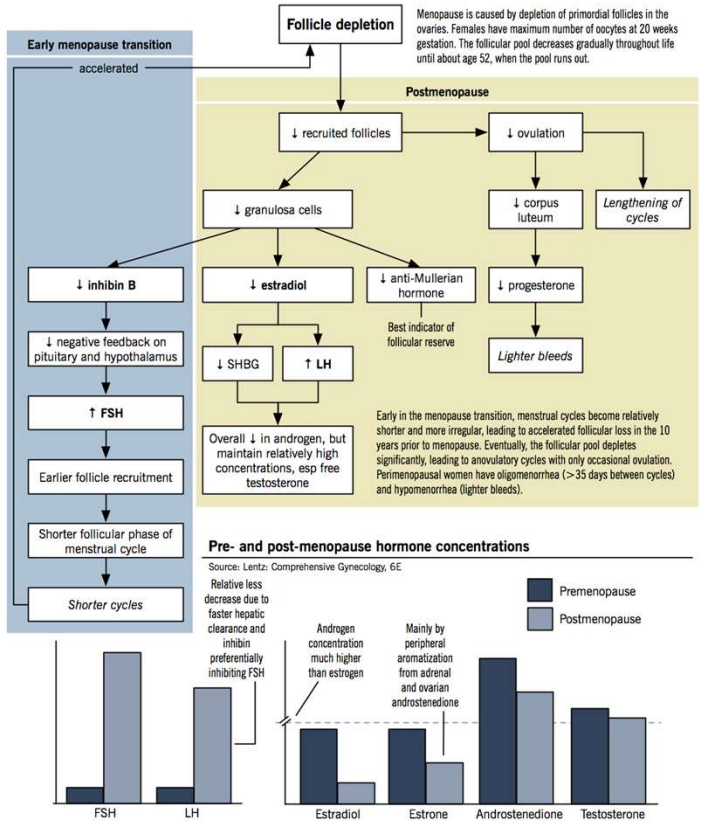
Peters SA, Woodward M. *Heart*. 2018;104(13):1069-1075.

Lipid Changes Associated with Menopause



Physiology of Menopausal Transition



Davis S, et al. *Nat Rev Dis Primers*. 2015;1:15004.

Menopausal Hormone Therapy: What Lipid Effects to Expect?

Formulation	Duration	LDL-C (mg/dL)	HDL (mg/dL)	TG (mg/dL)
Walsh Oral Estradiol Transdermal Estradiol 0.1 mg	6 weeks	-14 -4	+26 +10	+24 +0.1
Walsh CEE 0.625 mg CEE 1.25 mg	12 weeks	-15 -19	+16 +18	+24 +38
WHI CEE 0.625 mg CEE + MPA 2.5 continuous	1 year	-23 -20	+7 +4	+18 +14
KEEPS CEE 0.45 mg Transdermal Estradiol 50 ug	4 years	-4.86 -2.87	+3 -1	+13 -0.1

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Shufelt CL, Manson JE. *J Clin Endocrinol Metab*. 2021;106(5):1245-1254.

2018 Multisociety Cholesterol Guidelines and 2019 ACC/AHA Guidelines on Primary Prevention

- 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

Introduced the Concept of Risk-Enhancing Factors Some Unique to Women

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Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.
Arnett DK, et al. *Circulation.* 2019;140(11):e596-e646.

2018 Multisociety Cholesterol and 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
- **History of premature menopause (before age 40 y) *or* pregnancy-associated conditions that ↑ASCVD risk (eg, preeclampsia)**

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Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.
Arnett DK, et al. *Circulation.* 2019;140(11):e596-e646.

2018 Multisociety Cholesterol and 2019 ACC/AHA Primary Prevention Guidelines: Risk-Enhancing Factors

Additional Risk-Enhancing Factors

- High-risk race/ethnicity (eg, South Asian, East Asian, Native American, Middle Eastern)
- High-risk levels of lipids or other biomarkers
- **Persistently elevated triglycerides (≥ 175 mg/dL)**
- If measured:
  - ↑high-sensitivity C-reactive protein ≥ 2 mg/L
  - ↑Lp(a) > 50 mg/dL or 125 nmol/L
  - ↑apoB ≥ 130 mg/dL
  - ↓Ankle-brachial index < 0.9

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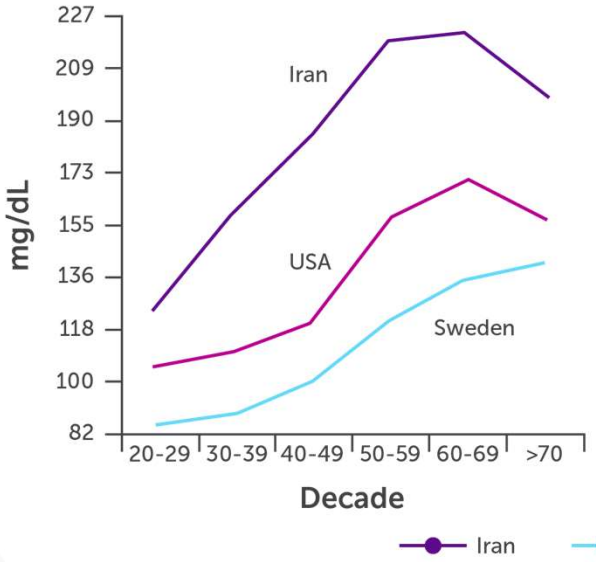
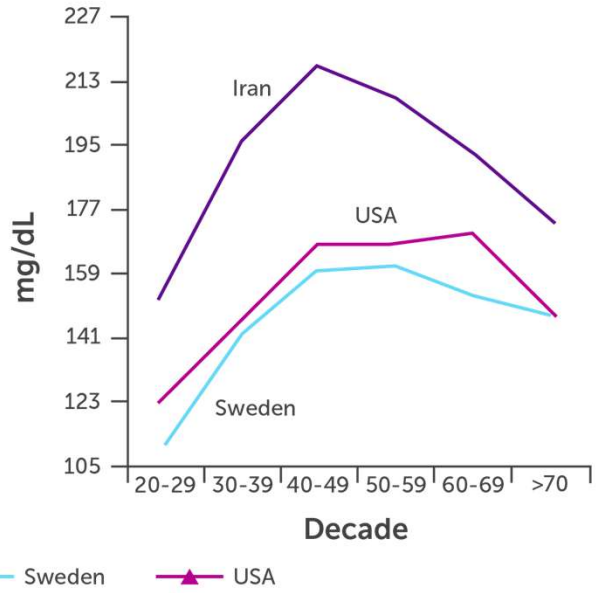
Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.
Arnett DK, et al. *Circulation.* 2019;140(11):e596-e646.

Hypertriglyceridemia in Women: Who Has It?

TG/Female
Mean values – different age groups



TG/Male
Mean values – different age groups



Peak in US Women at around **60 years**.

Risk Factors in Women:

- Insulin resistance
- Obesity
- PCOS
- Hypothyroidism
- Alcohol use
- Prescription drugs: antipsychotics (clozapine, olanzapine), b-blockers (atenolol, metoprolol)
- Menopause and MHT

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Solhpour A, et al. *Atherosclerosis*. 2009;207(1):200-207.

Stepped Approach to Reducing CVD Risk in Women

STEP 1

Screen for Sex-Specific Risk Factors

- Prematurity
- Age at menarche
- PCOS
- Hormone-based contraceptive use
- Recurrent spontaneous pregnancy loss
- Gestational diabetes
- Preeclampsia
- Preterm delivery
- Delivery of small-for-gestational-age infant
- Early menopause or premature ovarian failure

STEP 2

If Sex-Specific Risk Factors Present:

1) Assess for traditional CVD risk factors early and more frequently
2) Screen for, prevent, and treat intermediate phenotypes

Hypertension
Diabetes
Dyslipidemia
Metabolic Syndrome

STEP 3

Begin Aggressive Risk Factor Management

Implement Lifestyle Modification with AHA's Life's Simple 7:

1) Manage blood pressure
2) Control cholesterol
3) Reduce blood sugar
4) Stay active
5) Eat healthy
6) Lose weight
7) Stop smoking

STEP 4

Estimate Risk and Treat Accordingly with Consideration of Sex-Specific Risk Factors

1) Assess 10-year ASCVD risk and lifetime risk (if young)
2) Treat early if borderline or intermediate risk and if sex-specific risk factors are present

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Agarwala A, et al. *Circulation*. 2020;141(7):592-599.

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"

- Estimates 10-year hard ASCVD risk (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. Present lifetime risk because age is a primary driver in estimates; lower estimates in younger ages may delay prevention therapies
3. Then use the new ACC/AHA Cholesterol/Primary Prevention guideline algorithms to guide management with selective use of CAC scoring in borderline and intermediate groups

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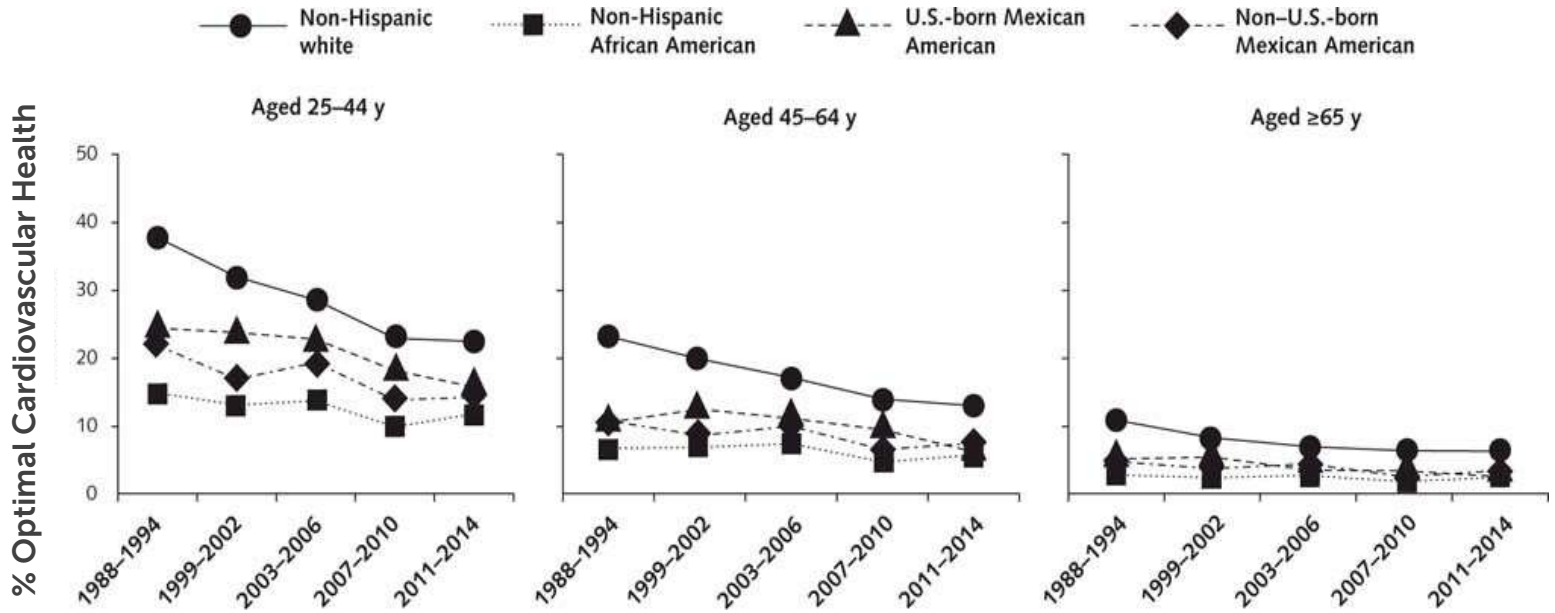
ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease.
tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate

How Are We Doing With Optimizing US Cardiovascular Health?



Ideal Score (Life's Simple 7): SBP <120 and DBP <80 and not receiving BP Meds; TC <200 mg/dL and not receiving LL meds; HbA1c <4.9%; BMI <25 kg/m^2; physical activity ≥150 min/wk moderate, ≥75 min/wk vigorous, or ≥150 min/wk moderate + vigorous intensity; health diet score >80 (4-5 dietary components of ≥4.5 cups/day fruits/vegetables, ≥2 servings [3.5 oz] fish per week, ≥3 servings [1 oz] whole grains per day, <1500 mg/d of sodium, and <450 kcal/wk sugar-sweetened beverages), never smoked or quit >12 months ago

Brown AF, et al. *Ann Intern Med*. 2018;168(8):541-549.

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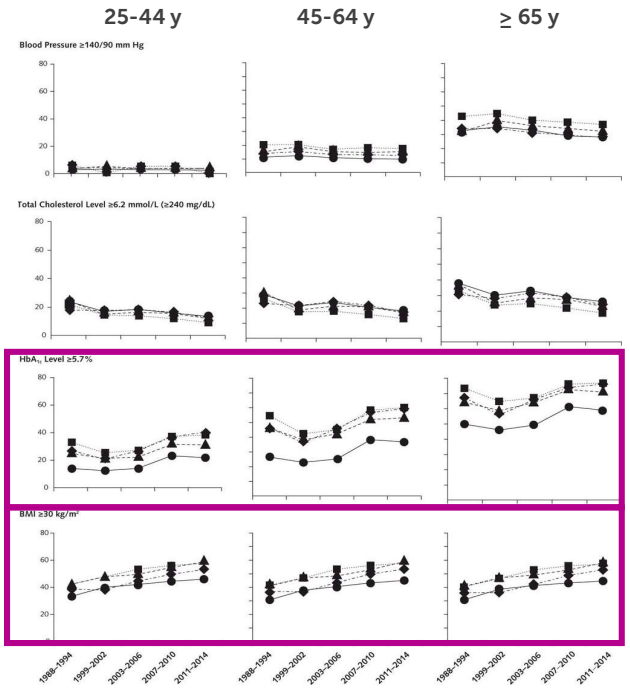
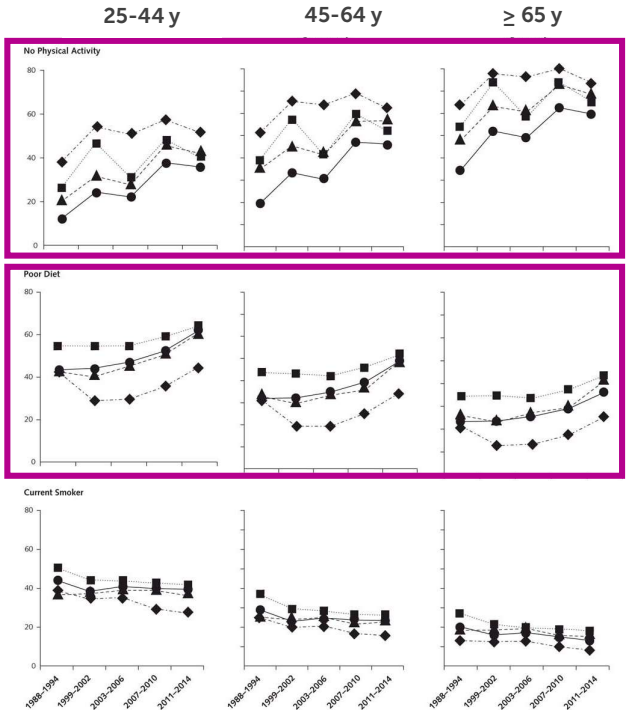
What's Driving These Trends?

↑ HbA1c

Obesity





No Leisure/ Recreational Physical Activity

Poor Diet

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Brown AF, et al. *Ann Intern Med*. 2018;168(8):541-549.

Nutrition Recommendations

American Heart Association.
Healthy for Good™

Life's Simple 7

HOW TO EAT BETTER

1 CREATE A HEALTHY DIETARY PATTERN

Make smart choices and swaps to build an overall healthy eating style. Watch calories and eat smaller portions.

ENJOY vegetables, fruits, whole grains, beans, legumes, nuts, plant-based proteins, lean animal proteins, skinless poultry, fish

LIMIT sweetened drinks, sodium, processed meats, refined carbohydrates like added sugars and processed grain foods, full-fat dairy products, eggs, highly processed foods, tropical oils like coconut and palm

AVOID trans fat and partially hydrogenated oils (found in some commercial baked goods and fried foods)

2 READ NUTRITION LABELS

Learning how to read and understand food labels can help you make healthier choices.

When you have more than one choice, compare nutrition facts. Choose products with lower amounts of sodium, saturated fat and added sugars.

LEARN MORE AT HEART.ORG/MYLIFECHECK AND HEART.ORG/EATSMART

3 TIPS FOR SUCCESS

WATCH CALORIES

Eat only as many calories as you use up through physical activity. Understand serving sizes and keep portions reasonable.

COOK AT HOME

Take control over the nutritional content of your food by learning healthy preparation methods.

LOOK FOR THE HEART-CHECK

The Heart-Check mark helps you find foods that can be part of a healthy eating plan.

LEARN THE SALTY SIX

Limit the amount of sodium you eat each day. Learn the Salty Six. These common foods can be loaded with excess sodium:

Breads & Rolls
Pizza
Sandwiches
Cold Cuts & Cured Meats
Soups
Burritos & Tacos

Physical Activity Recommendations

Moderate	Vigorous
Moderate activity means that your heart is beating faster. You can still carry on a conversation, but you'll be breathing heavier. And you'll notice that you're starting to sweat.	*Vigorous* activity is higher intensity and it feels more taxing: Your heart is beating much faster. Although you can carry on a conversation, you will find yourself pausing to take a breath.
150 minutes each week: 30 minutes a day 5 days a week	**75 minutes each week:** 15 minutes 5 days a week
Examples: Walking at a brisk pace, riding a bike on flat ground, treading water, pushing a lawnmower or stroller (with a larger child), playing tag with kids, playing a game of volleyball or badminton, doing continuous garden chores (such as weeding and mulching), inline skating at a moderate pace	**Examples:** Running/jogging, racquetball or tennis, swimming laps, biking up a hill, basketball, inline skating at a brisk pace

Every 1 minute of vigorous activity is worth 2 minutes of moderate activity

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

Pam Taub, MD, FACC, FASPC

Director of Step Family Foundation Cardiovascular Rehabilitation and Wellness Center
Professor of Medicine
UC San Diego Health System
Division of Cardiovascular Medicine
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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** **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

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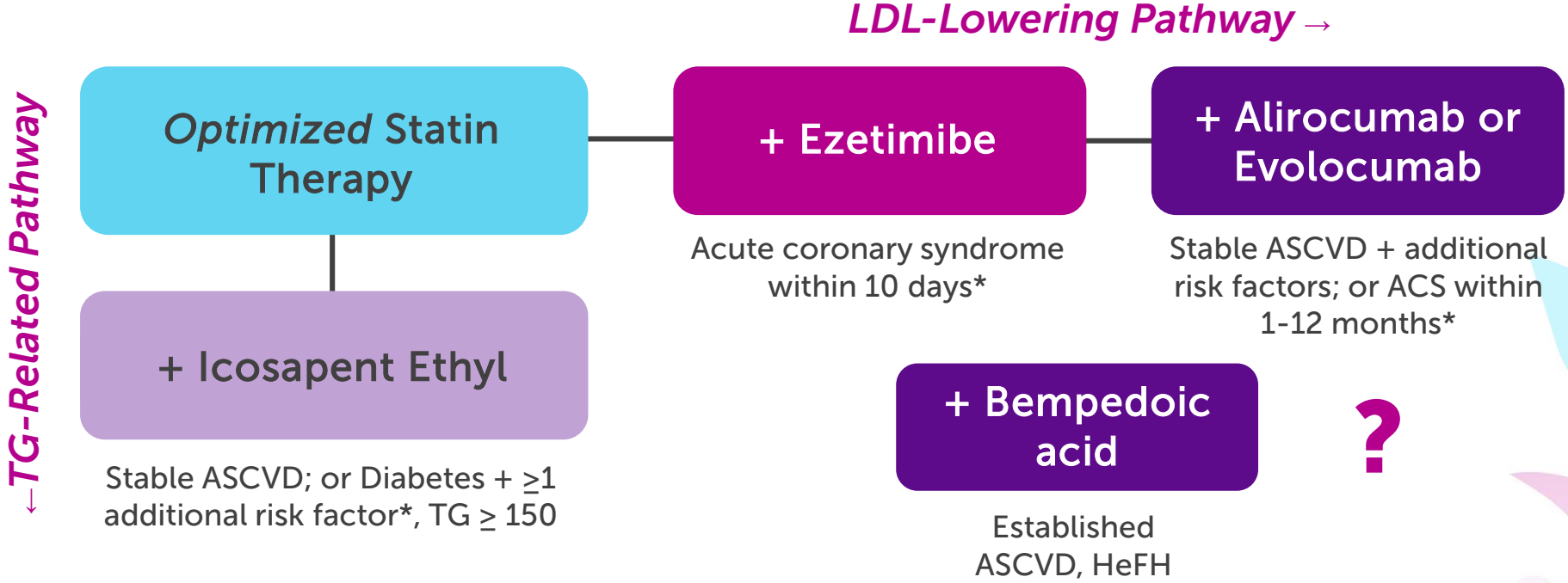
Grundy SM, et al. *J Am Coll Cardiol.* 2019;73(24):e285-e350.

Statin Therapy Adjuncts *Proven* to Reduce ASCVD



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

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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

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Jacobson TA, et al. *J Clin Lipidol*. 2014;8(5):473-488.
American Heart Association (AHA) Scientific Statement. Miller M, et al. *Circulation*. 2011;123(20):2292-333.

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 <u>not</u> been shown to improve ASCVD outcomes and is generally not recommended. (A)
- Combination therapy (**statin/niacin**) has <u>not</u> 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.

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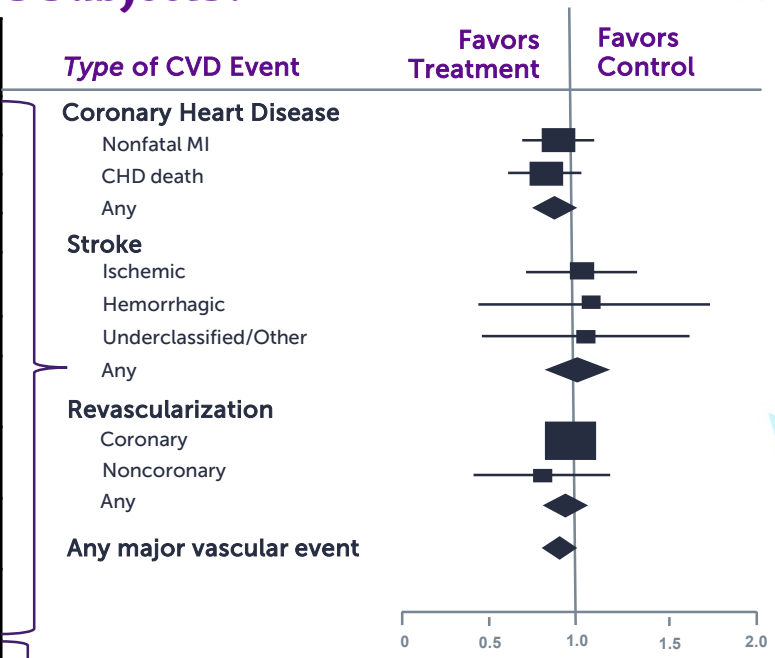
ACCORD Study Group, et al. *N Engl J Med*. 2010;362(17):1563-1574.
Keech A, et al. *Lancet*. 2005;366(9500):1849-1861.
Boden WE, et al. *N Engl J Med*. 2011;365(24):2255-2267.
HPS2-THRIVE Collaborative Group. *N Engl J Med*. 2014;371(3):203-212.

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

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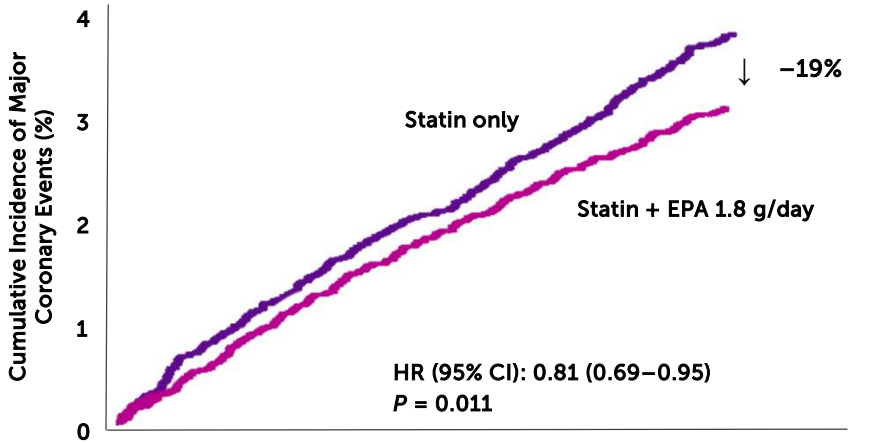
Aung T, et al. *JAMA Cardiol*. 2018;3(3):225-234. Bowman L, et al. *N Engl J Med*. 2018;379(16):1540-1550. Manson JE, et al. *N Engl J Med*. 2019;380(1):23-32. Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22.

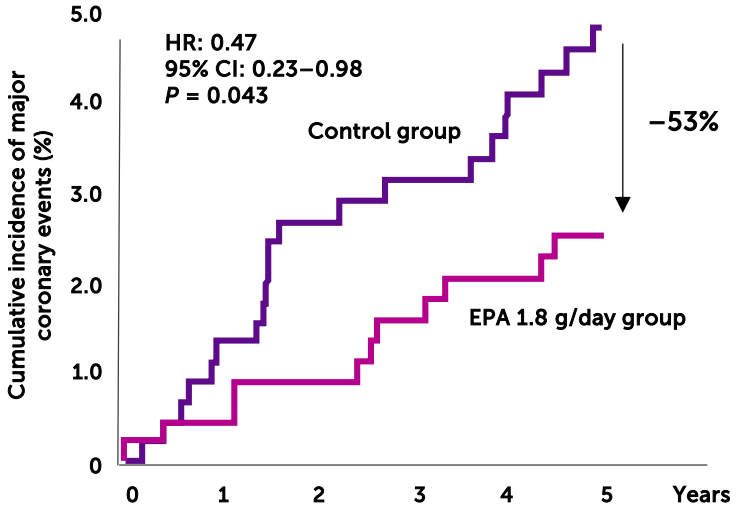
JELIS: Rx Pure EPA + Statins Led to ↓Major Coronary Events* in Hypercholesterolemic Patients on Statins and in HTG Subgroup†



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 nonfatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.



No. of patients						
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.

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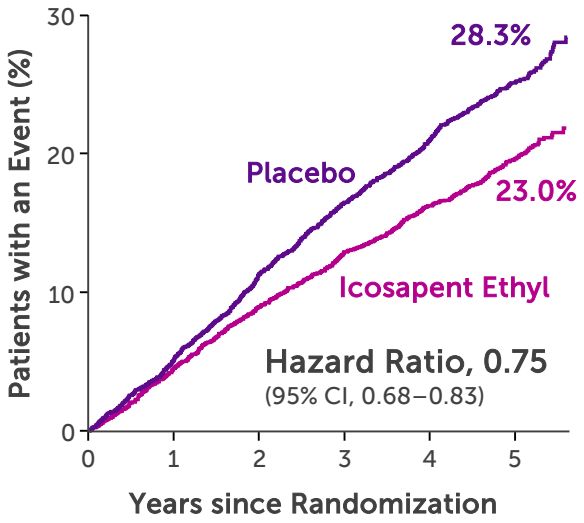
Yokoyama M, et al. *Lancet.* 2007;369(9567):1090-1098. Saito Y, et al. *Atherosclerosis*. 2008;200(1):135-140.

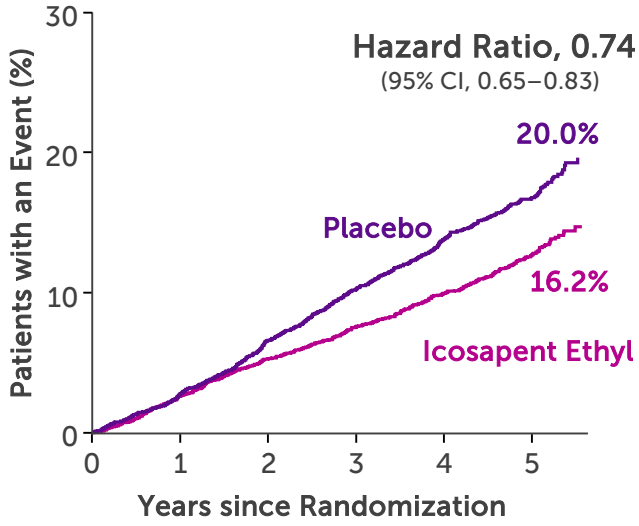
REDUCE-IT Primary and Secondary Endpoints

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



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

Key Secondary Endpoint: CV Death, MI, Stroke



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

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

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

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	800	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

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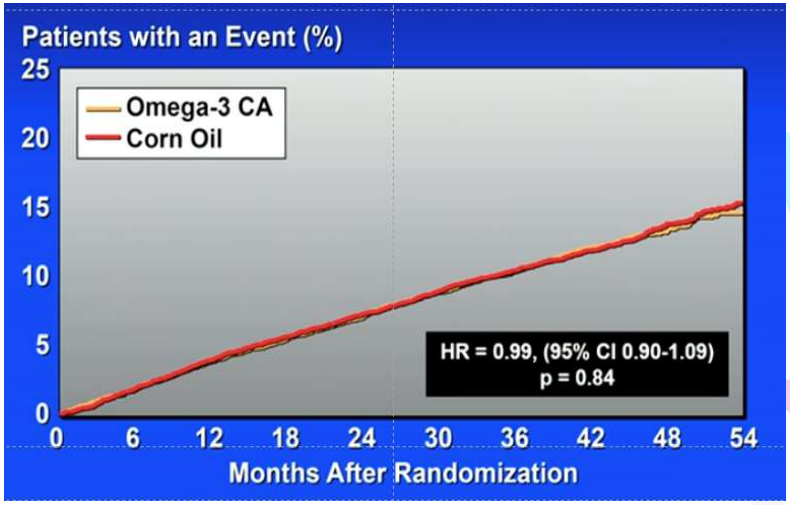
STRENGTH Trial Design, Details, and Primary Endpoint

- 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)



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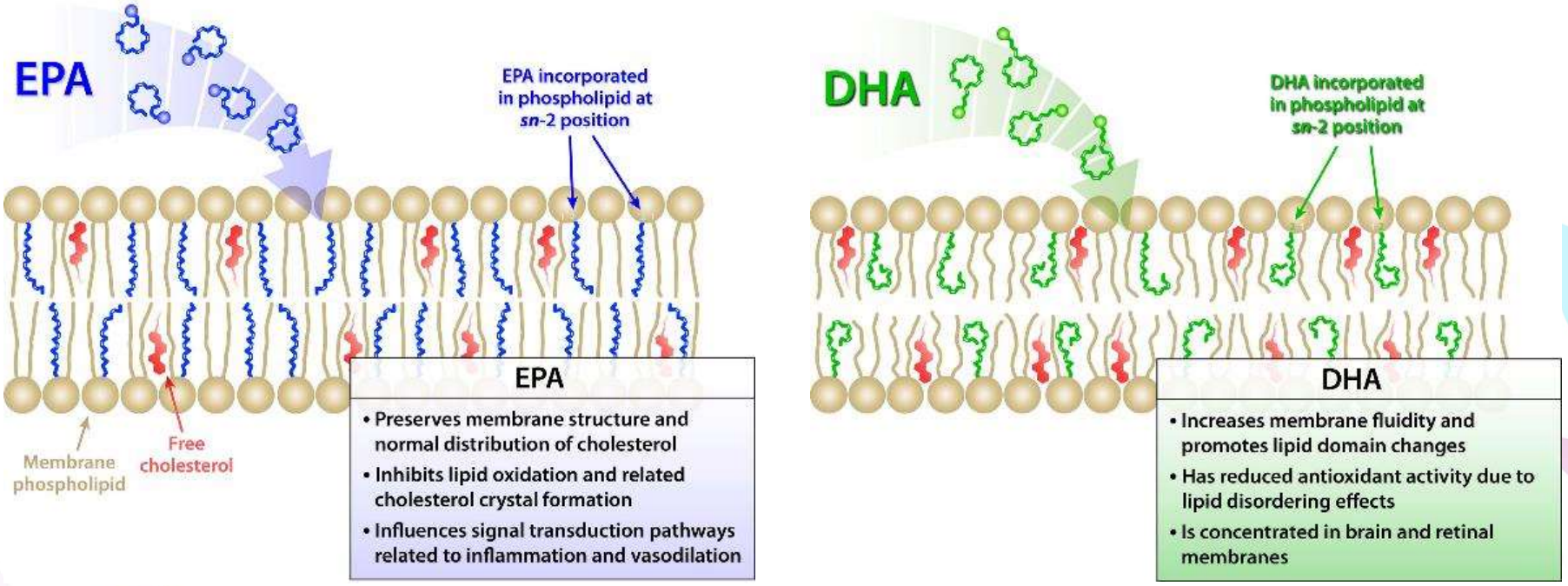
Lincoff AM. American Heart Association Virtual Scientific Sessions; November 15, 2020.
Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280.

Contrasting Effects of EPA and DHA



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Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135-1147. Reproduced with permission.

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

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Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135-1147. Sherratt SCR, Mason RP. *Chem Phys Lipids*. 2018;212:73-79. Mason RP, et al. *J Cardiovasc Pharmacol*. 2016;68(1):33-40. Kohli P, Levy BD. *Br J Pharmacol*. 2009;158(4):960-971.

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	X
VITAL	EPA/DHA	X
STRENGTH	EPA/DHA	X
OMEMI	EPA/DHA	X

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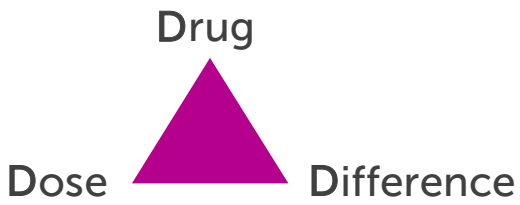
Iqbal T, Miller M. *Curr Cardiol Rep.* 2021;23(8):111.

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.

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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!

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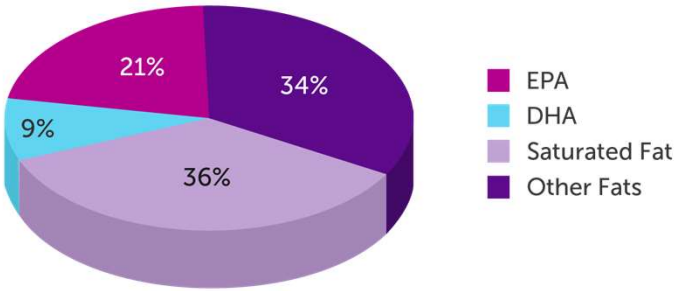
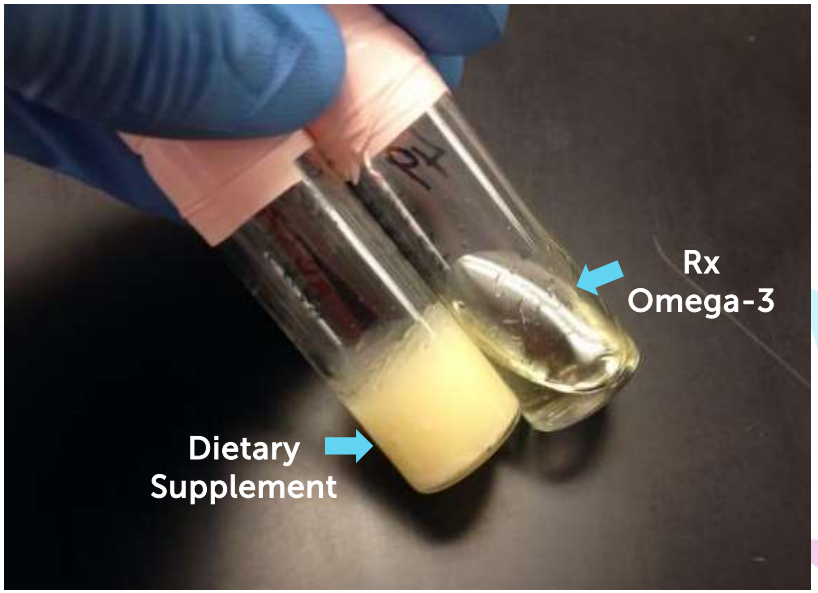
Problems w/ Content of *Leading* US Fish Oil Dietary Supplements



- 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***

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Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483(1):425-429. Hilleman D, Smer A. *Manag Care*. 2016;25(1):46-52. Albert BB, et al. *Sci Rep*. 2015;5:7928. Kleiner AC, et al. *J Sci Food Agric*. 2015;95(6):1260-1267. Ritter JC, et al. *J Sci Food Agric*. 2013:93(8):1935-1939. Jackowski SA, et al. *J Nutr Sci*. 2015;4:e30. Rundblad A, et al. *Br J Nutr*. 2017;117(9):1291-1298. European Medicines Agency, 2018: 712678.

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)

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Photos courtesy of Preston Mason, PhD.

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

Released December 13, 2019. After https://amarincorp.com/docs/Vascepa-PI.pdf

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 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

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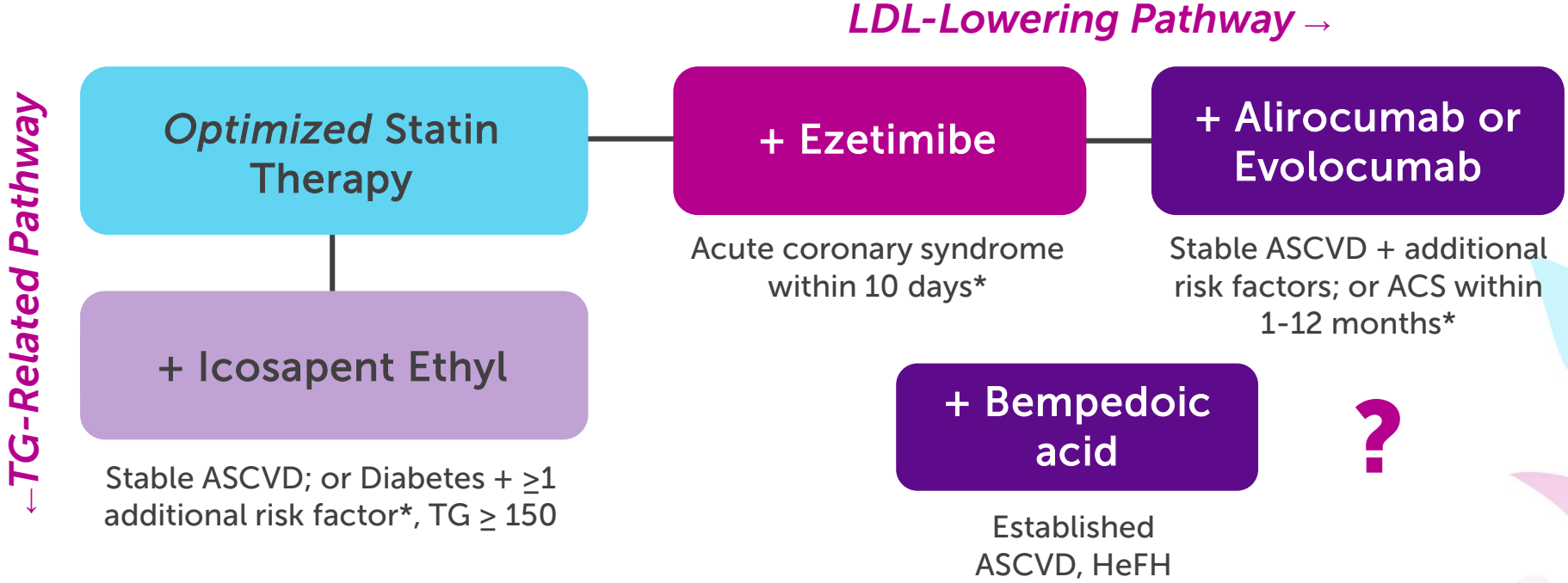
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PUFA, polyunsaturated fatty acids; TG, triglyceride.

American Diabetes Association. [web annotation]. *Diabetes Care.* 2019;42(Suppl. 1):S103–S123. Retrieved from https://hyp.is/JHhz_lCrEembFJ9LIVBZIw Mach F, et al; ESC Scientific Document Group. *Eur Heart J*. 2020 ;41(1):111-188. Orringer, CE, et al. *J Clin Lipidol.* 2019;13(6):860-872. Skulas-Ray AC, et al. *Circulation.* 2019;140(12):e673-e691. Arnold SV, et al. *Circulation.* 2020;141(19):e779-e806. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

Statin Therapy Adjuncts *Proven* to Reduce ASCVD



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

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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/m^2, 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?

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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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To Submit Questions Throughout The Activity

Type in the chat control panel on the left-hand side of the Omnia platform

OR

Type in the comment box in Facebook Live

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