# New Options and Strategies for CV Risk Reduction in Diabetes:
**What the Data Tell Us**

**Agenda**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:30 PM</td>
<td>Registration and Buffet Dinner</td>
</tr>
<tr>
<td>7:00</td>
<td>Program Overview</td>
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<tr>
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<td>Robert H. Eckel, MD, Chair</td>
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<tr>
<td>7:15</td>
<td>New Cholesterol Guidelines: What You Should Know</td>
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<td>Robert H. Eckel, MD, Chair</td>
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<tr>
<td>7:35</td>
<td>Omega-3 FAs and their Use in Patients with ASCVD</td>
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<td>Deepak L. Bhatt, MD, MPH</td>
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<tr>
<td>7:55</td>
<td>Roundup of Recent Clinical Trial Evidence to Reduce ASCVD Events</td>
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<td>Sergio Fazio, MD, PhD</td>
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<td>8:15</td>
<td>Panel Discussion and Q&amp;A</td>
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<tr>
<td>8:35</td>
<td>Case-based Learning on Personalization of Care in Patients with</td>
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<td></td>
<td>Diabetes and High-risk ASCVD</td>
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<td>All Faculty</td>
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<tr>
<td>8:50</td>
<td>Closing Comments</td>
</tr>
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<td>Robert H. Eckel, MD, Chair</td>
</tr>
<tr>
<td>9:00 PM</td>
<td>Adjourn</td>
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</tbody>
</table>

Faculty slides are available online: medtelligence.net/june7

*Scroll to the “Related” section and click on “Syllabus”*
This syllabus is not intended to be an exact representation of the faculty presentations.

*It is being provided as a useful reference that we encourage you to use during and after the activity.*
New Options and Strategies for CV Risk Reduction in Diabetes: What the Data Tell Us

June 7, 2019
Welcome and Program Overview

Robert H. Eckel, MD, *Chair*
Robert H. Eckel, MD, *Chair*

Charles A. Boettcher II Endowed Chair in Atherosclerosis
Professor of Medicine – Division of Endocrinology, Metabolism and Diabetes, and Cardiology
Professor of Physiology and Biophysics
University of Colorado School of Medicine
Director of Lipid Clinic
University of Colorado Hospital
Aurora, CO

• Disclosures: Consulting Fees: Novo Nordisk, Sanofi; Contracted Research: ENDEC
New Cholesterol Guidelines: What You Should Know

Robert H. Eckel, MD, Chair
ACC Risk Calculator Plus to Assess Risk Category

tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate

1. 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 Cholesterol guideline algorithms to guide management

3. Also available: MESA 10-Year CHD Risk with Coronary Artery Calcification*
   - iPhone and Android app

*mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx
Clinical ASCVD

Healthy Lifestyle
Clinical ASCVD

Healthy Lifestyle
Nutrition Lifestyle Recommendations: Lipids and BP

- **Dietary patterns emphasis-based:**
  - DASH and Mediterranean-style eating plans
- Fruits, vegetables, and whole grains
- 30 – 35% fat intake
  - <6% saturated fats, no *trans* fats
- Low sodium (<2400 mg/day)
- Cut out processed or pre-prepared food
- Healthy eating for a lifetime

Advise adults to engage in aerobic physical activity

- 3 to 4 sessions a week
- lasting on average 40 min per session
- involving moderate-to-vigorous intensity physical activity.

Reconsidering the Importance of the Association of Egg Consumption and Dietary Cholesterol With Cardiovascular Disease Risk

Robert H. Eckel, MD

In contrast with randomized clinical trials that compare a drug with placebo, is more difficult for many reasons, including complexities in data gathering and changes in human behavior over time. In this issue of JAMA, Zhong and colleagues report new insights about a controversial topic, the association of egg consumption and dietary cholesterol with cardiovascular disease (CVD) incidence and all-cause mortality. Clearly, the topic of this study is important to clinicians, patients, and the public at large because the association of egg consumption and dietary cholesterol with CVD, although debated for decades, has more recently been thought to be less important. Compared with the meta-analyses and reviews previously published, this

In the report by Zhong et al, a harmonized approach was used to analyze self-reported baseline nutritional data on macronutrient intake in 29,615 adults from 6 prospective US cohorts, a group with high racial and ethnic diversity, to examine cardiovascular disease outcomes over a median of 17.5 years. The main finding was that higher consumption of eggs and dietary cholesterol (which included eggs and meats) was significantly associated with incident CVD and all-cause mortality, with a dose-response relationship. Another important finding in the study was that associations between dietary cholesterol and incident CVD and all-cause mortality were no longer significant after adjusting for consumption of eggs and processed and unprocessed red meat. Moreover, the dietary cholesterol content of eggs fully explained the association between egg consumption and inci-

ASCVD not at very high-risk*

Very high-risk ASCVD: Shown on following slides

*ACS, hx of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.
# Very High Risk of Future CVD Events

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
</tr>
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<tbody>
<tr>
<td>Recent ACS (within the past 12 mo)</td>
</tr>
<tr>
<td>History of MI (other than recent ACS event listed above)</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
</tr>
<tr>
<td>Symptomatic peripheral arterial disease (history of claudication with ABI &lt;0.85, or previous revascularization or amputation (S4.1-39))</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>CKD (eGFR 15–59 mL/min/1.73 m²) (S4.1-15, S4.1-17)</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe</td>
</tr>
<tr>
<td>History of congestive HF</td>
</tr>
</tbody>
</table>
Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk*

Very high-risk ASCVD: Shown on following slides

*ACS, hx of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.
Initiation of moderate- or high-intensity statin is reasonable

Continuation of high-intensity statin is reasonable
If on maximal statin and LDL-C ≥70 mg/dL, adding ezetimibe is reasonable

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I

Dashed arrow indicates RCT-supported efficacy, but is less cost effective

IF on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL, or non-HDL-C ≥100 mg/dL, adding PCSK9-I is reasonable

*Includes a hx of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

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

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print].
Successful Statin Add-on Trials (5–15% RRR)

CI=confidence interval; Cor Revasc=coronary revascularization; EZ=ezetimibe; HR=hazard ratio; MACE=major adverse cardiovascular events; MI=myocardial infarction; NNT=number needed to treat; Simva=simvastatin; UA unstable angina.

Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Health Lifestyle

**Age 0–19 y**
- Lifestyle to prevent or reduce ASCVD risk
- Diagnosis of Familial Hypercholesterolemia → statin

**Age 20–39 y**
- Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
- Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL

**Age 40–75 y &**
**LDL-C ≥70 mg/dL**
- Risk assessment to start

**Age 40–75 y &**
**LDL-C ≥190 mg/dL**
- No risk assessment; High-intensity statin

**Age 40–75 y &**
**LDL-C ≥70 to <190 mg/dL without diabetes mellitus**
- Moderate-intensity statin

**Age >75 y**
- Clinical assessment, Risk discussion

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Class IIb (Weak). Benefit ≥ Risk.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print]. Although high TG was noted as a CVD risk factor, treatment of HTG was covered only briefly and prescription omega-3 was not mentioned. (Published simultaneously with REDUCE-IT.)

Risk discussion:
*If risk estimate + risk enhancers favor statin,* initiate moderate-intensity statin to reduce LDL-C by 30% – 49%

Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy

Risk discussion:
Emphasize lifestyle to reduce risk factors

Risk discussion:
Initiate statin to reduce LDL-C ≥50%

Risk discussion:
If risk decision is uncertain: Consider measuring CAC in selected adults:
- CAC = zero (lower risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC = 1–99 favors statin (especially after age 55)
- CAC = 100+ and/or ≥75th percentile, initiate statin therapy

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (eg, preeclampsia, premature menopause)
- Inflammatory disease (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asia ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- Apo B ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

Grundy SM et al. *Circulation.* 2018;Nov. 10 [Epub ahead of print]. Although high TG was noted as a CVD risk factor, treatment of HTG was covered only briefly and prescription omega-3 was not mentioned. (Published simultaneously with REDUCE-IT.)

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Class IIa (Moderate). Benefit >> Risk.
Class IIb (Weak). Benefit ≥ Risk.
## Recommendations for Hypertriglyceridemia

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.</td>
</tr>
<tr>
<td>Ila</td>
<td>B-R</td>
<td>In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.).</td>
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Severe Hypertriglyceridemia

Review

The Chylomicronemia Syndrome Is Most Often Multifactorial
A Narrative Review of Causes and Treatment
Alan Chait, MD, and Robert H. Eckel, MD

The chylomicronemia syndrome occurs when triglyceride levels are severely elevated (usually >16.95 mmol/L [1500 mg/dL]) and is characterized by such clinical features as abdominal pain, acute pancreatitis, eruptive xanthomas, and lipemia retinalis. It may result from 1 of 3 conditions: the presence of secondary forms of hypertriglyceridemia concurrent with genetic causes of hypertriglyceridemia, termed multifactorial chylomicronemia syndrome (MFC); a deficiency in the enzyme lipoprotein lipase and some associated proteins, termed familial chylomicronemia syndrome (FCS); or familial partial lipodystrophy. Most chylomicronemia syndrome cases are the result of MFC; FCS is very rare. In all these conditions, triglyceride-rich lipoproteins accumulate because of impaired plasma clearance. This review describes the 3 major causes of the chylomicronemia syndrome; their consequences; and the approaches to treatment, which differ considerably by group.

The term chylomicronemia syndrome first appeared in the scientific literature in 1981 to describe clinical features attributed to marked elevations in plasma triglyceride levels in a small number of patients (1). Features included abdominal pain, acute pancreatitis, eruptive xanthomas, lipemia retinalis, mental confusion, memory loss, and flushing with minimal alcohol intake (1). Several of these characteristics resembled those chylomicronemia syndrome, with an emphasis on acute pancreatitis; and an approach to therapy.

Methods

This update used PubMed Central. Search terms included chylomicronemia; chylomicronemia syndrome; chylomicronemia treatment; chylomicronemia genetics;

Major Secondary Causes of Hypertriglyceridemia

- Diabetes Mellitus, Insulin Resistance
- Obesity
- Alcohol
- Chronic Kidney Disease
- Nephrotic syndrome
- Hypothyroidism
- HIV
- Hepatocellular disease
- Inflammatory diseases
Medications that Cause of Hypertriglycerideridemia

- Oral estrogens
- Bile-acid sequestrants
- Antiretroviral regimens
  - especially for HIV disease
- Phenothiazine's - 2nd-generation
- Nonselective beta-blockers
- Diuretics
- Glucocorticoids
- Immunosuppressants
- Tamoxifen
- Isotretinoin
## Recommendations for Hypertriglyceridemia

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</table>
1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.

In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print].
Top 10 Take Home Messages

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction.

Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print].
3. In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy.

- Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL.
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost-effectiveness is low at mid-2018 list prices.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print].
4. In patients with severe primary hypercholesterolemia (LDL-C level $\geq 190$ mg/dL) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.

- If the LDL-C level remains $\geq 100$ mg/dL, adding ezetimibe is reasonable
- If the LDL-C level on statin plus ezetimibe remains $\geq 100$ mg/dL & the patient has multiple factors that increase subsequent risk of ASCVD events, PCSK9 inhibitor may be considered.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print].
5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C $\geq 70$ mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk.

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by $\geq 50\%$.

Grundy SM et al. *Circulation.* 2018;Nov. 10 [Epub ahead of print].
Top 10 Take Home Messages

6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Risk discussion should include a review of
- major risk factors (eg, cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD);
- the presence of risk-enhancing factors (see No. 8);
- the potential benefits of lifestyle and statin therapies;
- the potential for adverse effects and drug–drug interactions;
- the consideration of costs of statin therapy; and
- the patient preferences & values in shared decision-making.

Grundy SM et al. Circulation. 2018;Nov. 10 [Epub ahead of print].
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL, at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.

Risk-enhancing factors favor statin therapy (see No. 8).

If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

Grundy SM et al. *Circulation*. 2018;Nov. 10 [Epub ahead of print].
Top 10 Take Home Messages

8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).

Risk-enhancing factors include
• family history of premature ASCVD;
• persistently elevated LDL-C levels ≥160 mg/dL;
• metabolic syndrome;
• chronic kidney disease;
• history of preeclampsia or premature menopause (age <40 yrs);
• chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV);
• high-risk ethnic groups (eg, South Asian);
• persistent elevations of triglycerides ≥175 mg/dL

Grundy SM et al. Circulation. 2018;Nov. 10 [Epub ahead of print].
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Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL; metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (eg, South Asian); persistent elevations of triglycerides ≥175 mg/dL; and, if measured in selected individuals

- apolipoprotein B ≥130 mg/dL;
- high-sensitivity C-reactive protein ≥2.0 mg/L;
- ankle-brachial index <0.9 and Lp(a) ≥50 mg/dL, especially at higher values of Lp(a).

Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5–7.5% (borderline risk)

Grundy SM et al. Circulation. 2018;Nov. 10 [Epub ahead of print].
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL – 189 mg/dL, at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

- If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician-patient risk discussion.

Grundy SM et al. Circulation. 2018;Nov. 10 [Epub ahead of print].
10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.
- In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).
Residual Cardiovascular Risk in Statin-Treated Patients with Elevated Triglycerides: Now We Can REDUCE-IT

Deepak L. Bhatt, MD, MPH

Executive Director of Interventional Cardiovascular Programs, Brigham and Women’s Hospital Heart and Vascular Center
Professor of Medicine, Harvard Medical School
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medintelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda.

This presentation includes off-label and/or investigational uses of drugs.

**REDUCE-IT** was sponsored by Amarin Pharma, Inc.
Triglycerides a Causal Risk Factor?

Triglyceride-rich lipoproteins ApoC3, ApoA5, AngPTL4

Causal risk factors?

Adapted with permission from Libby P. Triglycerides on the rise: should we swap seats on the seesaw? *Eur Heart J.* 2015;36:774-776.
Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

Adapted with permission from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. JAMA Cardiol. 2018;3:225-234. [https://creativecommons.org/licenses.org/by-nc/4.0/]

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
<th>No. of Events (%)</th>
<th>P</th>
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<tbody>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
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<tr>
<td>Nonfatal myocardial infarction</td>
<td>1121 (2.9)</td>
<td>1155 (3.0)</td>
<td>0.97 (0.87–1.08)</td>
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<tr>
<td>Coronary heart disease</td>
<td>1301 (3.3)</td>
<td>1394 (3.6)</td>
<td>0.93 (0.83–1.03)</td>
<td></td>
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<tr>
<td>Any</td>
<td>3085 (7.9)</td>
<td>3188 (8.2)</td>
<td>0.96 (0.90–1.01)</td>
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<td></td>
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<td></td>
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<td>.12</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Ischemic</td>
<td>574 (1.9)</td>
<td>554 (1.8)</td>
<td>1.03 (0.88–1.21)</td>
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<td>Hemorrhagic</td>
<td>117 (0.4)</td>
<td>109 (0.4)</td>
<td>1.07 (0.76–1.51)</td>
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<td>Unclassified/other</td>
<td>142 (0.4)</td>
<td>135 (0.3)</td>
<td>1.05 (0.77–1.43)</td>
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<tr>
<td>Any</td>
<td>870 (2.2)</td>
<td>843 (2.2)</td>
<td>1.03 (0.93–1.13)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.60</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>3044 (9.3)</td>
<td>3040 (9.3)</td>
<td>1.00 (0.93–1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncoronary</td>
<td>305 (2.7)</td>
<td>330 (2.9)</td>
<td>0.92 (0.75–1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3290 (10.0)</td>
<td>3313 (10.2)</td>
<td>0.99 (0.94–1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.60</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>5930 (15.2)</td>
<td>6071 (15.6)</td>
<td>0.97 (0.93–1.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = .10
Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group®
ASCEND
A randomized trial of omega-3 fatty acids (fish oil) versus placebo for primary cardiovascular prevention in 15,480 patients with diabetes

Jane Armitage and Louise Bowman
on behalf of the ASCEND Study Collaborative Group

Funded by British Heart Foundation, UK Medical Research Council and support from Abbott, Bayer, Mylan and Solvay
Designed, conducted and analysed independently of the funders
University of Oxford is the trial sponsor
ASCEND trial design

Eligibility: Age ≥ 40 years; any DIABETES; no prior cardiovascular disease

Participants: 15,480 UK patients

Randomization: Omega-3 fatty acids 1 g capsule/day vs placebo (and aspirin 100 mg daily vs placebo)

Follow-up: Mean 7.4 years; >99% complete for morbidity & mortality

Adherence: Average adherence to omega-3 capsules 77%

Streamlined methods: mail-based (questionnaires & study treatment); no study clinics; 2x2 factorial design; highly cost-effective

ASCEND Study Collaborative Group. Trials 2016;17:286 / Am Heart J 2018;198:135-144
Effect of omega-3 FA supplements on serious vascular events

Rate ratio 0.97 (0.87-1.08)

P=0.55

Participants with Event (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Omega-3 FA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>712 (9.2%)</td>
<td>689 (8.9%)</td>
</tr>
</tbody>
</table>

Years of Follow-up

0 1 2 3 4 5 6 7 8 9
Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

The **VITamin D and OmegaA-3 Trial (VITAL)**: Design

- **25,871 Initially Healthy Men and Women**
  - *Primary Prevention*
  - (Men ≥ 50 yrs; Women ≥ 55 yrs)

  - **Vitamin D$_3$** (2000 IU/d); N=12,927
  - **Placebo** N=12,944

    - **EPA + DHA** (1 gm/d [1.3:1 ratio]); N=6463
    - **Placebo** N=6464
    - **EPA + DHA** (1 gm/d [1.3:1 ratio]); N=6470
    - **Placebo** N=6474

**Median Treatment Period = 5.3 years.**

**5106 African Americans.**

**Blood collection in ~16, 953 at baseline, follow-up bloods in ~6000.**

Cumulative Incidence Rates of Major CVD Events by Year of Follow-up: Omega-3s vs. Placebo

Hazard ratio, 0.92 (95% CI, 0.80-1.06)

p-value = 0.24
JELIS Suggests CV Risk Reduction with EPA in Japanese Hypercholesterolemic Patients

Kaplan-Meier Estimates of Incidence of Coronary Events

Total Population

Primary Prevention Cohort

Secondary Prevention Cohort

Hazard ratio: 0.81 (0.69–0.95) p=0.011
Hazard ratio: 0.82 (0.63–1.06) p=0.132
Hazard ratio: 0.81 (0.657–0.998) p=0.048

Numbers at risk

Control group 9319 8931 8671 8433 8192 7958
Treatment group 9326 8929 8658 8389 8153 7924

*1.8 g/day

EPA and DHA Have Differing Effects on Cellular Membranes

Eicosapentaenoic acid and docosahexaenoic acid have distinct membrane locations and lipid interactions as determined by X-ray diffraction. Chem Phys Lipids. 2018;212:73-79. [*https://creativecommons.org/licenses/by-nc/4.0/]
**REDUCE-IT Design**

**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

**Lead-in**
- Statin stabilization
- Medication washout
- Lipid qualification

**1:1 Randomization**
with continuation of stable statin therapy (N=8179)

**Icosapent Ethyl**
4 g/day (n=4089)

**Placebo**
(n=4090)

4 months, 12 months, annually
End-of-study follow-up visit

4 months, 12 months, annually
End-of-study follow-up visit

**Primary Endpoint**
Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina requiring hospitalization

**Screening Period**

**Double-Blind Treatment/Follow-up Period**

**Randomization**

<table>
<thead>
<tr>
<th>Year</th>
<th>Months</th>
<th>Visit</th>
<th>Lab values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1</td>
<td>1</td>
<td>Screening</td>
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</table>

<table>
<thead>
<tr>
<th>Randomization</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.9 years†</td>
</tr>
<tr>
<td>0 – 4</td>
<td>12</td>
</tr>
<tr>
<td>2 – 3</td>
<td>Every 12 months</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Final Visit</td>
<td></td>
</tr>
</tbody>
</table>

* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL.

Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).


[*https://creativecommons.org/licenses/by-nc/4.0/]
Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Key Exclusion Criteria

1. Severe (NYHA class IV) heart failure
2. Severe liver disease
3. History of pancreatitis
4. Hypersensitivity to fish and/or shellfish
CONSORT Diagram

**Screened**
N=19,212

11 countries, 473 sites

- Incl./Excl. criteria not met: 10,429
- Withdrawal of consent: 340
- Adverse event: 13
- Primary Prevention category closed: 4
- Death: 5
- Lost to follow-up: 108
- Enrollment closed: 3
- Other: 135

*4 patients presented 2 screen failure reasons.

**Randomized**
N=8179 (43% of screened)

- Icosapent Ethyl
  N=4089 (100%)
  Completed Study
  N=3684 (90.1%)
  Early Discontinuation from Study
  N=405 (9.9%)
  Known vital status
  4083 (99.9%)
- Placebo
  N=4090 (100%)
  Completed Study
  N=3630 (88.8%)
  Early Discontinuation from Study
  N=460 (11.2%)
  Known vital status
  4077 (99.7%)


**Actual vs. potential total follow-up time (%)**
- Icosapent Ethyl
  Median: 93.6%
- Placebo
  Median: 92.9%

**Known vital status**
- Icosapent Ethyl
  Known: 4083 (99.9%)
- Placebo
  Known: 4077 (99.7%)

Median trial follow up duration was 4.9 years.
### Key Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (Q1-Q3)</td>
<td>64.0 (57.0 - 69.0)</td>
<td>64.0 (57.0 - 69.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1162 (28.4%)</td>
<td>1195 (29.2%)</td>
</tr>
<tr>
<td>Non-White, n (%)</td>
<td>398 (9.7%)</td>
<td>401 (9.8%)</td>
</tr>
<tr>
<td>Westernized Region, n (%)</td>
<td>2906 (71.1%)</td>
<td>2905 (71.0%)</td>
</tr>
<tr>
<td>CV Risk Category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Prevention Cohort</td>
<td>2892 (70.7%)</td>
<td>2893 (70.7%)</td>
</tr>
<tr>
<td>Primary Prevention Cohort</td>
<td>1197 (29.3%)</td>
<td>1197 (29.3%)</td>
</tr>
<tr>
<td>Ezetimibe Use, n (%)</td>
<td>262 (6.4%)</td>
<td>262 (6.4%)</td>
</tr>
<tr>
<td>Statin Intensity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>254 (6.2%)</td>
<td>267 (6.5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2533 (61.9%)</td>
<td>2575 (63.0%)</td>
</tr>
<tr>
<td>High</td>
<td>1290 (31.5%)</td>
<td>1226 (30.0%)</td>
</tr>
<tr>
<td>Type 2 Diabetes, n (%)</td>
<td>2367 (57.9%)</td>
<td>2363 (57.8%)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL), Median (Q1-Q3)</td>
<td>216.5 (176.5 - 272.0)</td>
<td>216.0 (175.5 - 274.0)</td>
</tr>
<tr>
<td>HDL-C (mg/dL), Median (Q1-Q3)</td>
<td>40.0 (34.5 - 46.0)</td>
<td>40.0 (35.0 - 46.0)</td>
</tr>
<tr>
<td>LDL-C (mg/dL), Median (Q1-Q3)</td>
<td>74.0 (61.5 - 88.0)</td>
<td>76.0 (63.0 - 89.0)</td>
</tr>
<tr>
<td>Triglycerides Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 mg/dL</td>
<td>412 (10.1%)</td>
<td>429 (10.5%)</td>
</tr>
<tr>
<td>150 to &lt;200 mg/dL</td>
<td>1193 (29.2%)</td>
<td>1191 (29.1%)</td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>2481 (60.7%)</td>
<td>2469 (60.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>3257 (79.7%)</td>
<td>3236 (79.1%)</td>
</tr>
<tr>
<td>One Antiplatelet</td>
<td>2416 (59.1%)</td>
<td>2408 (58.9%)</td>
</tr>
<tr>
<td>Two or More Antiplatelets</td>
<td>841 (20.6%)</td>
<td>828 (20.2%)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>385 (9.4%)</td>
<td>390 (9.5%)</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>3164 (77.4%)</td>
<td>3176 (77.7%)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>2902 (71.0%)</td>
<td>2880 (70.4%)</td>
</tr>
<tr>
<td>Statin</td>
<td>4077 (99.7%)</td>
<td>4068 (99.5%)</td>
</tr>
</tbody>
</table>

## Effects on Biomarkers from Baseline to Year 1


<table>
<thead>
<tr>
<th>Biomarker*</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Median Between Group Difference at Year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Absolute Change from Baseline</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>216.5</td>
<td>175.0</td>
<td>216.0</td>
<td>221.0</td>
<td>-44.5</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>118.0</td>
<td>113.0</td>
<td>118.5</td>
<td>130.0</td>
<td>-15.5</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>74.0</td>
<td>77.0</td>
<td>76.0</td>
<td>84.0</td>
<td>-5.0</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>40.0</td>
<td>39.0</td>
<td>40.0</td>
<td>42.0</td>
<td>-2.5</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>82.0</td>
<td>80.0</td>
<td>83.0</td>
<td>89.0</td>
<td>-8.0</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>2.2</td>
<td>1.8</td>
<td>2.1</td>
<td>2.8</td>
<td>-0.9</td>
</tr>
<tr>
<td>Log hsCRP (mg/L)</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
<td>-0.4</td>
</tr>
<tr>
<td>EPA (µg/mL)</td>
<td>26.1</td>
<td>144.0</td>
<td>26.1</td>
<td>23.3</td>
<td>+114.9</td>
</tr>
</tbody>
</table>

*Apo B and hsCRP were measured at Year 2.*
Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

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

Key Secondary End Point: CV Death, MI, Stroke

Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

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

## Primary End Point in Subgroups

**End Point/Subgroup** | **Hazard Ratio (95% CI)** | **Icosapent Ethyl** | **Placebo** | **HR (95% CI)** | **Int P Val**
--- | --- | --- | --- | --- | ---
**Primary Composite End Point (ITT)** | 775/499 (17.2%) | 301/1650 (22.3%) | 0.75 (0.68–0.83) | 0.14
**Secondary Prevention Cohort** | 59/2792 (2.1%) | 796/3950 (20.0%) | 0.73 (0.65–0.82) | 0.13
**Primary Prevention Cohort** | 146/1187 (12.2%) | 163/1187 (13.6%) | 0.80 (0.75–0.85) | 0.30
**Region**
- **Western** | 551/2696 (19.9%) | 710/5505 (13.0%) | 0.74 (0.68–0.82) | 0.20
- **Eastern** | 143/1053 (13.6%) | 167/1053 (15.8%) | 0.84 (0.76–0.93) | 0.64
- **Asia Pacific** | 111/920 (9.9%) | 21/920 (2.3%) | 0.49 (0.34–0.69) | 0.04
**Ezekial Use**
- **No** | 646/3827 (17.0%) | 854/5628 (15.3%) | 0.75 (0.67–0.83) | 0.06
- **Yes** | 55/258 (21.4%) | 67/528 (12.6%) | 0.82 (0.71–0.96) | 0.20
**Sex**
- **Male** | 551/2682 (16.8%) | 715/5505 (13.4%) | 0.73 (0.65–0.82) | 0.20
- **Female** | 154/1162 (13.3%) | 186/1161 (15.8%) | 0.82 (0.74–0.91) | 0.20
**Triglycerides ≥150 mg/dL**
- **Non-White** | 82/4083 (20.2%) | 99/4081 (24.2%) | 0.77 (0.69–0.85) | 0.12
- **White** | 53/358 (14.8%) | 53/358 (15.1%) | 0.69 (0.53–0.88) | 0.20
**Age Group**
- **<65 Years** | 322/1872 (17.4%) | 460/2164 (21.1%) | 0.60 (0.53–0.67) | 0.01
- **≥65 Years** | 383/1875 (20.6%) | 444/1938 (22.9%) | 0.87 (0.78–0.98) | 0.14
**US vs Non-US**
- **US** | 261/1548 (16.2%) | 294/1558 (18.7%) | 0.69 (0.59–0.81) | 0.04
- **Non-US** | 435/2414 (16.7%) | 527/2522 (21.2%) | 0.81 (0.71–0.91) | 0.14
**Baseline Diabetes**
- **No** | 433/2394 (18.1%) | 536/2953 (18.4%) | 0.77 (0.64–0.90) | 0.36
- **Diabetes** | 372/1695 (21.6%) | 425/1924 (22.3%) | 0.73 (0.62–0.88) | 0.36
**Baseline LDL-C**
- **<100 mg/dL** | 107/905 (11.8%) | 239/1393 (17.0%) | 0.71 (0.60–0.85) | 0.14
- **≥100 mg/dL** | 380/2217 (17.2%) | 468/2208 (21.0%) | 0.80 (0.70–0.92) | 0.20
**Baseline HDL-C**
- **≥45 mg/dL** | 117/840 (13.9%) | 158/1158 (13.5%) | 0.70 (0.59–0.85) | 0.14
- **<45 mg/dL** | 140/1105 (12.7%) | 204/1170 (17.4%) | 0.72 (0.62–0.84) | 0.14
**Baseline Triglycerides ≥200 mg/dL**
- **Yes** | 432/1854 (23.3%) | 532/2522 (21.1%) | 0.73 (0.64–0.83) | 0.03
- **No** | 383/2414 (16.7%) | 410/2522 (16.7%) | 0.79 (0.70–0.83) | 0.03
**Baseline N-terminal Pro BNP**
- **≥900 pg/mL** | 149/823 (18.1%) | 140/958 (14.7%) | 0.70 (0.57–0.86) | 0.14
- **<900 pg/mL** | 170/939 (18.1%) | 263/911 (28.9%) | 0.79 (0.67–0.93) | 0.14
**Baseline eGFR**
- **≥60 mL/min/1.73m²** | 107/905 (11.8%) | 239/1393 (17.0%) | 0.71 (0.60–0.85) | 0.14
- **<60 mL/min/1.73m²** | 380/2217 (17.2%) | 468/2208 (21.0%) | 0.80 (0.70–0.92) | 0.20
**Baseline Body Mass Index**
- **<25 kg/m²** | 107/905 (11.8%) | 239/1393 (17.0%) | 0.71 (0.60–0.85) | 0.14
- **≥25 kg/m²** | 380/2217 (17.2%) | 468/2208 (21.0%) | 0.80 (0.70–0.92) | 0.20
**Baseline Randomized fat composition**
- **Non-polyunsaturated** | 162/905 (17.9%) | 227/1158 (19.4%) | 0.72 (0.61–0.86) | 0.14
- **Polyunsaturated** | 215/1019 (21.2%) | 293/1309 (22.4%) | 0.80 (0.70–0.92) | 0.20

**Key Secondary End Point in Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>HR (95% CI)*</th>
<th>Int P Val</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Prevention Cohort</td>
<td></td>
<td>361/2892 (12.5%)</td>
<td>489/2893 (16.9%)</td>
<td>0.72 (0.63–0.82)</td>
<td>0.41</td>
</tr>
<tr>
<td>Primary Prevention Cohort</td>
<td></td>
<td>98/1197 (8.2%)</td>
<td>117/1197 (9.8%)</td>
<td>0.81 (0.62–1.06)</td>
<td></td>
</tr>
</tbody>
</table>

### Key Secondary End Point in Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>HR (95% CI)*</th>
<th>Int P Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>286/2394 (11.9%)</td>
<td>391/2393 (16.3%)</td>
<td>0.70 (0.60–0.81)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>No Diabetes</td>
<td>173/1695 (10.2%)</td>
<td>215/1694 (12.7%)</td>
<td>0.80 (0.65–0.98)</td>
<td>0.97</td>
<td></td>
</tr>
</tbody>
</table>

### Key Secondary End Point in Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>HR (95% CI)*</th>
<th>Int P Val</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Triglycerides ≥150 vs &lt;150 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides &lt;150 mg/dL</td>
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</table>

# Prespecified Hierarchical Testing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td></td>
<td>705/4089 (17.2%)</td>
<td>901/4090 (22.0%)</td>
<td>0.75 (0.68–0.83)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Key Secondary Composite (ITT)</td>
<td></td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65–0.83)</td>
<td>26%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td></td>
<td>392/4089 (9.6%)</td>
<td>507/4090 (12.4%)</td>
<td>0.75 (0.66–0.86)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td></td>
<td>250/4089 (6.1%)</td>
<td>355/4090 (8.7%)</td>
<td>0.69 (0.58–0.81)</td>
<td>31%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent or Emergent Revascularization</td>
<td></td>
<td>216/4089 (5.3%)</td>
<td>321/4090 (7.8%)</td>
<td>0.65 (0.55–0.78)</td>
<td>35%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td></td>
<td>174/4089 (4.3%)</td>
<td>213/4090 (5.2%)</td>
<td>0.80 (0.66–0.98)</td>
<td>20%▼</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td></td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.68 (0.53–0.87)</td>
<td>32%▼</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td></td>
<td>98/4089 (2.4%)</td>
<td>134/4090 (3.3%)</td>
<td>0.72 (0.55–0.93)</td>
<td>28%▼</td>
<td>0.01</td>
</tr>
<tr>
<td>Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke</td>
<td></td>
<td>549/4089 (13.4%)</td>
<td>690/4090 (16.9%)</td>
<td>0.77 (0.69–0.86)</td>
<td>23%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Mortality</td>
<td></td>
<td>274/4089 (6.7%)</td>
<td>310/4090 (7.6%)</td>
<td>0.87 (0.74–1.02)</td>
<td>13%▼</td>
<td>0.09</td>
</tr>
</tbody>
</table>

RRR denotes relative risk reduction.
## REDUCE-IT Tertiary Endpoints: Cardiac Arrest, Sudden Cardiac Death, Arrhythmias

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Arrest</td>
<td>22/4089 (0.5%)</td>
<td>42/4090 (1.0%)</td>
<td>0.52 (0.31, 0.86)</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>61/4089 (1.5%)</td>
<td>87/4090 (2.1%)</td>
<td>0.69 (0.50, 0.96)</td>
</tr>
<tr>
<td>Cardiac Arrhythmias Requiring Hospitalization of ≥ 24 Hours</td>
<td>188/4089 (4.6%)</td>
<td>154/4090 (3.8%)</td>
<td>1.21 (0.97, 1.49)</td>
</tr>
</tbody>
</table>

Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at Least One TEAE, n (%)</td>
<td>3343 (81.8%)</td>
<td>3326 (81.3%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>1252 (30.6%)</td>
<td>1254 (30.7%)</td>
<td>0.98</td>
</tr>
<tr>
<td>TEAE Leading to Withdrawal of Study Drug</td>
<td>321 (7.9%)</td>
<td>335 (8.2%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Serious TEAE Leading to Withdrawal of Study Drug</td>
<td>88 (2.2%)</td>
<td>88 (2.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Serious TEAE Leading to Death</td>
<td>94 (2.3%)</td>
<td>102 (2.5%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

**Treatment-Emergent Adverse Event of Interest: Serious Bleeding**

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding related disorders</td>
<td>111 (2.7%)</td>
<td>85 (2.1%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>62 (1.5%)</td>
<td>47 (1.1%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Central nervous system bleeding</td>
<td>14 (0.3%)</td>
<td>10 (0.2%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Other bleeding</td>
<td>41 (1.0%)</td>
<td>30 (0.7%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 icosapent ethyl versus 10 placebo; P=0.55)

## Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

<table>
<thead>
<tr>
<th>Primary System Organ Class Preferred Term</th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positively Adjudicated Atrial Fibrillation/Flutter[1]</td>
<td>127 (3.1%)</td>
<td>84 (2.1%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Note: Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

[1] Includes positively adjudicated Atrial Fibrillation/Flutter clinical events by the Clinical Endpoint Committee (CEC). P value was based on stratified log-rank test.

Achieved Triglyceride Levels: <150 mg/dL and ≥150 mg/dL

A Primary End Point by Achieved Triglyceride Level at 1 Year

Hazard Ratio (95% CI):
- Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL: 0.99 (0.84–1.16)
- Icosapent Ethyl Triglyceride ≥150 mg/dL vs Placebo: 0.71 (0.63–0.79)
- Icosapent Ethyl Triglyceride <150 mg/dL vs Placebo: 0.70 (0.60–0.81)

B Key Secondary End Point by Achieved Triglyceride Level at 1 Year

Hazard Ratio (95% CI):
- Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL: 1.00 (0.82–1.23)
- Icosapent Ethyl Triglyceride ≥150 mg/dL vs Placebo: 0.67 (0.56–0.80)
- Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL: 0.66 (0.57–0.77)

## Potential Benefits of EPA

### Effects of EPA on Plaque Progression

<table>
<thead>
<tr>
<th></th>
<th>Endothelial Dysfunction/Oxidative Stress</th>
<th>Inflammation/Plaque Growth</th>
<th>Unstable Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase</strong></td>
<td>Endothelial function</td>
<td>EPA/AA ratio</td>
<td>Fibrous cap thickness</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide bioavailability</td>
<td></td>
<td>Lumen diameter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plaque stability</td>
</tr>
<tr>
<td><strong>Decrease</strong></td>
<td>Cholesterol crystalline domains</td>
<td>IL-6</td>
<td>Plaque volume</td>
</tr>
<tr>
<td></td>
<td>Ox-LDL</td>
<td>ICAM-1</td>
<td>Arterial stiffness</td>
</tr>
<tr>
<td></td>
<td>RLP-C</td>
<td>IL-10</td>
<td>Plaque vulnerability</td>
</tr>
<tr>
<td></td>
<td>Adhesion of monocytes</td>
<td>hsCRP</td>
<td>Thrombosis</td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td>Lp-PLA₂</td>
<td>Platelet activation</td>
</tr>
<tr>
<td></td>
<td>Foam cells</td>
<td>MMPs</td>
<td></td>
</tr>
</tbody>
</table>

Adapted with permission* from Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol. 2018;72:330-343. [*https://creativecommons.org/licenses.org/by-nc/4.0/*]
Possible Mechanisms by which Triglyceride-Rich Lipoproteins Give Rise to Inflammation and Accentuate Atherogenesis

Triglyceride-rich lipoprotein (TGRL)

- Lipases
  - Saturated Fatty Acids
  - Apolipoprotein CIII

Cholesterol
- TGRL can deliver more cholesterol/particle to macrophages than LDL

Foam cell formation

- Putative transducers:
  - TLRs
  - PKC
- Transcriptional Activators:
  - NFκB
  - p38 MAP kinase
  - Egr-1

Leukocyte recruitment

production of:
- MCP-1
- IL-8
- others

Endothelial cell

Macrophage

n-3 Fatty acids

Vascular cell adhesion molecule-1

Leukocyte recruitment

Possible Mechanisms by which Triglyceride-Rich Lipoproteins Give Rise to Inflammation and Accentuate Atherogenesis

Courtesy of Dr. Peter Libby 2019
Antiplatelet and Anticoagulant Pathways

Placebo-corrected Reductions in Blood Pressure from Baseline with Icosapent Ethyl 4g/day

<table>
<thead>
<tr>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.3</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

(95% CI, -0.9 to -1.6) (95% CI, -0.3 to -0.7)

Prespecified exploratory analysis with no adjustment for multiple comparisons.

Proportions of First and Subsequent Events

Total N=2,909

First Events
- Coronary Revascularization: n=415 (26%)
- Fatal or Nonfatal MI: n=532 (33%)
- Hospitalization for Unstable Angina: n=214 (13%)
- Cardiovascular Death: n=261 (16%)

Subsequent Events
- Coronary Revascularization: n=789 (60%)
- Fatal or Nonfatal MI: n=225 (17%)
- Hospitalization for Unstable Angina: n=85 (7%)
- Cardiovascular Death: n=126 (10%)

**First and Subsequent Events**

**Placebo** [N=4090]
- 1st Events: 901 (HR 0.75, 95% CI 0.68-0.83, P=0.0000000016)
- 2nd Events: 376 (HR 0.68, 95% CI 0.60-0.78)
- 3rd Events: 143 (RR 0.52, 95% CI 0.38-0.70)
- ≥4 Events: 126 (RR 0.69, 95% CI 0.59-0.82)

**Icosapent Ethyl** [N=4089]
- 1st Events: 705 (HR 0.75, 95% CI 0.68-0.83)
- 2nd Events: 236 (HR 0.68, 95% CI 0.60-0.78)
- 3rd Events: 63 (RR 0.52, 95% CI 0.38-0.70)
- ≥4 Events: 72 (RR 0.69, 95% CI 0.59-0.82)

**Note:** WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

**RR 0.70** (95% CI, 0.62-0.78)

**P=0.00000000036**

**30% Reduction in Total Events**

**Reduced Dataset Event No.**
- No. of Fewer Cases:
  - 1st Events: -196
  - 2nd Events: -140
  - 3rd Events: -71
  - ≥4 Events: -63

Total (First and Subsequent) Events
Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Primary Composite Endpoint

Placebo: Total Events
Icosapent Ethyl: Total Events
Placebo: First Events
Icosapent Ethyl: First Events

RR, 0.70
(95% CI, 0.62–0.78)
P=0.00000000036

HR, 0.75
(95% CI, 0.68–0.83)
P=0.00000001

For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:

- Cardiovascular Death: -12
- Fatal or Nonfatal MI: -42
- Fatal or Nonfatal Stroke: -14
- Coronary Revascularization: -76
- Hospitalization for Unstable Angina: -16
- Primary Composite Endpoint: -159

# Primary Composite Endpoint:
## Total Endpoint Events by Baseline TG Tertiles

<table>
<thead>
<tr>
<th>TOTAL EVENTS – Primary Composite Endpoint/Subgroup</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Composite Endpoint (ITT)</strong></td>
<td></td>
<td></td>
<td>0.70 (0.62–0.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Baseline Triglycerides by Tertiles</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥81 to ≤190 mg/dL</td>
<td>56.4</td>
<td>74.5</td>
<td>0.74 (0.61–0.90)</td>
<td>0.0025</td>
</tr>
<tr>
<td>&gt;190 to ≤250 mg/dL</td>
<td>63.2</td>
<td>86.8</td>
<td>0.77 (0.63–0.95)</td>
<td>0.0120</td>
</tr>
<tr>
<td>&gt;250 to ≤1401 mg/dL</td>
<td>64.4</td>
<td>107.4</td>
<td>0.60 (0.50–0.73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P (interaction) = 0.17

Bhatt DL. ACC 2019, New Orleans.
Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced important CV events by 25%, including:

- 20% reduction in death due to cardiovascular causes
- 31% reduction in heart attack
- 28% reduction in stroke

Low rate of adverse effects, including:

- Small but significant increase in atrial fibrillation/flutter
- Non-statistically significant increase in serious bleeding

Consistent efficacy across multiple subgroups

- Including baseline triglycerides from 135-500 mg/dL
- Including secondary and primary prevention cohorts
Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by 30%, including:

- 25% reduction in first cardiovascular events
- 32% reduction in second cardiovascular events
- 31% reduction in third cardiovascular events
- 48% reduction in fourth or more cardiovascular events

Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides > ~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk.
Section 10 – Cardiovascular Disease and Risk Management: Lipid Management

• Treatment of Other Lipoprotein Disease Fractions or Targets
  • In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk. A

  • “It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products.”

• Other Combination Therapy
  • Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease 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

Roundup of Recent Clinical Trial Evidence to Reduce ASCVD Events

Sergio Fazio, MD, PhD
Sergio Fazio, MD, PhD

William and Sonja Connor Chair of Preventive Cardiology
Professor of Medicine, Physiology & Pharmacology
Director, Center for Preventive Cardiology
Knight Cardiovascular Institute
Oregon Health & Science University
Portland, OR

• Disclosures: Consulting Fees: Amarin, Amgen, AstraZeneca, Esperion, Novartis
A 68-year-old gentleman with 30 years of continuous exposure to statin therapy and recent finding of calcified coronaries (Agatston 2450)

“I thought the statin was supposed to protect me”
Residual CV risk may be due not only to other lipid measures that may not be controlled, but other risk factors at suboptimal control such as hypertension, diabetes, or smoking.
Additional LDL-C Lowering in Subjects on Statin Monotherapy Reduces CV Risk

Event Rate

<table>
<thead>
<tr>
<th>Time since Randomization (years)</th>
<th>Hazard ratio 0.936 (95% CI, 0.89-0.99)</th>
<th>P=0.016</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

CI=confidence interval; Cor Revasc=coronary revascularization; EZ=ezetimibe; HR=hazard ratio; MACE=major adverse cardiovascular events; MI=myocardial infarction; NNT=number needed to treat; Simva=simvastatin; UA=unstable angina.

Pharmacologic Approaches to Managing Residual CV Risk

- CAD or High-Risk Patient
  - Maximally Tolerated Statin Therapy
    - Ezetimibe: Mild/Mod Reduction in LDL
    - PCSK9i: Aggressive Reduction in LDL
    - Anticoagulation/Antiplatelet
    - Elevated Lp(a)
    - Elevated Triglycerides
      - GLP-1 RA – SGLT-2i
      - Diabetes
      - ASA
      - IL-1B inhibition?
      - EPA, N-3 FA, TG lowering?
    - Additional Thrombotic Risk
    - Niacin, PCSK9i, antisense?
### Fenofibrate Outcome Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>CV Risk Profile</th>
<th>Statin Use</th>
<th>Daily Intervention</th>
<th>Median Baseline TG Level</th>
<th>Effect on TG Level</th>
<th>Primary Outcome</th>
<th>Primary Outcome Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACCORD</strong> (N=5518)</td>
<td>• T2DM 40-79 yrs w/CVD or • 55-79 yrs w/ ≥2 CV risk factors</td>
<td>All pts: Open-label simvastatin (mean dose: 22 mg/d)</td>
<td>Fenofibrate</td>
<td>162 mg/dL</td>
<td>-26%</td>
<td>• Nonfatal MI or Stroke or CV death</td>
<td>HR=0.92* (95% CI, 0.79-1.08) P=0.32</td>
</tr>
<tr>
<td><strong>FIELD</strong> (N=9795)</td>
<td>• T2DM 50-75 yrs</td>
<td>Added during study in 2547 pts (26%)</td>
<td>Fenofibrate</td>
<td>154 mg/dL</td>
<td>-30% (at 1 yr)</td>
<td>• Nonfatal MI or CHD death Median f/u: 5 yrs</td>
<td>HR=0.89* (95% CI, 0.75-1.05) P=0.16</td>
</tr>
</tbody>
</table>

Niacin Outcome Trials

AIM-HIGH (−29% TG)

- Cumulative % with Primary Outcome
  - Time (years)
  - Cumulative % with Primary Outcome
    - 0 years: 0%
    - 1 year: 16.4%
    - 2 years: 16.2%
    - 3 years: 16.2%
    - 4 years: 16.4%

- Log-rank P = 0.79
- HR 1.02, 95% CI 0.87–1.21

N at risk
- Monotherapy: 1696
  - 1 year: 1581
  - 2 years: 1381
  - 3 years: 910
  - 4 years: 436
- Combination Therapy: 1718
  - 1 year: 1606
  - 2 years: 1366
  - 3 years: 903
  - 4 years: 428

HPS2-THRIVE (−26% TG)

- Effect of ERN / LRPT on Major Vascular Events
- Risk ratio 0.96 (95% CI 0.90–1.03)
- Log-rank P = 0.29

- Patients Suffering Events (%)
  - Placebo: 15.0%
  - ERN / LRPT: 14.5%

N at risk
- Monotherapy: 1696
  - 1 year: 1581
  - 2 years: 1381
  - 3 years: 910
  - 4 years: 436
- Combination Therapy: 1718
  - 1 year: 1606
  - 2 years: 1366
  - 3 years: 903
  - 4 years: 428

CANTOS: Reducing Inflammation by Blocking IL1-beta Reduces CV Events in Subjects on Statin Therapy

CANTOS: Primary Cardiovascular Endpoint (MACE)

Stable CAD (post MI)
Residual Inflammatory Risk
(hsCRP ≥2mg/L)

N=10,061
39 Countries
2011–2017
1490 Primary Events

All pts on statins

HR 0.85 (0.76-0.96)
P=0.007

- 39% reduction in hsCRP
- No change in LDL-C
- 15% reduction in MACE
Reducing Inflammation Doesn’t Always Work

**Interleukin-1β Inhibition**
- IL-1β
- IL-6
- hsCRP
- 17% reduction in MACE+
- LDL, BP, coagulation

2011 – 2017

**Low-dose Methotrexate**
- IL-1β
- IL-6
- hsCRP
- No reduction in MACE+

2013 – 2018
Anticoagulation and CVD Risk Reduction: The COMPASS Trial


Primary Endpoint Components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R + A N=9152</th>
<th>A N=9126</th>
<th>Rivaroxaban + Aspirin vs Aspirin</th>
<th>N (%)</th>
<th>N (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>160 (1.7%)</td>
<td>203 (2.2%)</td>
<td>0.78 (0.64-0.96)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>83 (0.9%)</td>
<td>142 (1.6%)</td>
<td>0.58 (0.44-0.76)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>178 (1.9%)</td>
<td>205 (2.2%)</td>
<td>0.86 (0.70-1.05)</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Reduction of R+A vs A
Rivaroxaban plus aspirin (R+A) vs aspirin (A)

<table>
<thead>
<tr>
<th>Absolute RR</th>
<th>Relative RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>↓1.3%</td>
<td>↓24%</td>
</tr>
<tr>
<td>All-cause death</td>
<td>↓0.7%</td>
<td>↓18%</td>
</tr>
</tbody>
</table>
| Bleeding     | ↑1.2% | ↑70% | 0.01   

Rivaroxaban + Aspirin vs Aspirin
HR: 0.76, 95% CI 0.66-0.86, P=<0.0001
Rivaroxaban vs. Aspirin HR: 0.90, 95% CI 0.79-1.03, P=0.12
## COMPASS Trial: Net Clinical Benefit

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivarox+ASA (N, %)</th>
<th>ASA Alone (N, %)</th>
<th>Rivarox+ASA vs ASA Alone (HR, P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>288 (3.1)</td>
<td>170 (1.9)</td>
<td>1.70, &lt;0.001</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>15 (0.2)</td>
<td>10 (0.1)</td>
<td>1.49, 0.32</td>
</tr>
<tr>
<td>Nonfatal ICH</td>
<td>21 (0.2)</td>
<td>19 (0.2)</td>
<td>1.10, 0.77</td>
</tr>
<tr>
<td>Nonfatal Bleed Critical Organ</td>
<td>42 (0.5)</td>
<td>29 (0.3)</td>
<td>1.43, 0.14</td>
</tr>
<tr>
<td>Other Major Bleeding</td>
<td>210 (2.3)</td>
<td>112 (1.2)</td>
<td>1.88, &lt;0.001</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>838 (9.2)</td>
<td>503 (5.5)</td>
<td>1.70, &lt;0.001</td>
</tr>
<tr>
<td>Major GI Bleed</td>
<td>140 (1.5)</td>
<td>65 (0.7)</td>
<td>2.15, &lt;0.001</td>
</tr>
<tr>
<td>Net Clinical Benefit*</td>
<td>431 (4.7)</td>
<td>534 (5.9)</td>
<td>0.80, &lt;0.001</td>
</tr>
</tbody>
</table>

# CV Outcome Trials in Diabetes

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>Drug (Class)</th>
<th>Primary endpoint</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG¹ 7,020</td>
<td>Empagliflozin SGLT-2</td>
<td>CV death, non-fatal myocardial infarction, or non-fatal stroke</td>
<td>0.86, (95% CI, 0.74, 0.99)  P=0.0382</td>
</tr>
<tr>
<td>LEADER² 9,340</td>
<td>Liraglutide GLP-1 RA</td>
<td></td>
<td>0.87, (95% CI, 0.78-0.97)  P=0.001 for non-inferiority  P=0.01 for superiority</td>
</tr>
<tr>
<td>SUSTAIN-6³ 3,297</td>
<td>Semaglutide GLP-1 RA</td>
<td></td>
<td>0.74, (95% CI, 0.58–0.95)  P&lt;0.001 for noninferiority  P=0.02 for superiority</td>
</tr>
<tr>
<td>CANVAS⁴ 10,134</td>
<td>Canagliflozin SGLT-2</td>
<td></td>
<td>0.86, (95% CI, 0.75-0.97)  P&lt;0.0001 for noninferiority  P=0.0158 for superiority</td>
</tr>
<tr>
<td>HARMONY⁵ 10,793</td>
<td>Albiglutide GLP-1 RA</td>
<td></td>
<td>0.78, (95% CI, 0.68–0.90)  P&lt;0.0001 for non-inferiority  P=0.0006 for superiority</td>
</tr>
<tr>
<td>DECLARE TIMI-58⁶ 17,160</td>
<td>Dapagliflozin SGLT-2</td>
<td>CV death, non-fatal myocardial infarction, or ischemic stroke</td>
<td>0.93, (95% CI, 0.84-1.03)  P&lt;0.001 for noninferiority  P=0.17 for superiority</td>
</tr>
</tbody>
</table>

SGLT2 inhibitors: CV Outcome Studies

- Empa-Reg (Empagliflozin): 2015
- CANVAS (Canagliflozin): 2017
- DECLARE (Dapagliflozin): 2018
- VERTIS-CV (Ertugliflozin): ~2020
DECLARE TIMI-58: Dual Primary Outcomes

Dapagliflozin vs placebo  n=17,160,  60% with no prior ASCVD,  median f/u 4.2 yr.

CVD/HHF
4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005

MACE
8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17

Hospitalization for Heart Failure, HR 0.73 (0.61-0.88)

DECLARE: MACE by Prior MI

Patients with prior MI
HR (95% CI) = HR 0.84 (0.72 to 0.99)

Patients without prior MI
HR (95% CI) = HR 1.00 (0.88 to 1.13)

Absolute risk reduction
2.6% (prior MI) vs. 0% (no prior MI)

DECLARE: HHF Outcomes by EF

Verma S, McMurray JJV
_Circulation_. 2019: March 21-on line;

Kato, ET et al
_Circulation_. 2019: March 21-on line
Renal Outcomes with SGLT-2 Inhibitors
Renal Outcomes: GLP1ra vs SGLT2i
Progression to sustained doubling of creatinine, ≥40% decline in eGFR, ESRD, or death from renal disease.


<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients</th>
<th>Events</th>
<th>Treatment n/N</th>
<th>Placebo n/N</th>
<th>Weights</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELIXA</td>
<td>6003</td>
<td>76</td>
<td>30/3032</td>
<td>41/3031</td>
<td>9.5</td>
<td>1.16 [0.74, 1.83]</td>
</tr>
<tr>
<td>LEADER</td>
<td>9340</td>
<td>184</td>
<td>87/4668</td>
<td>97/4672</td>
<td>23.4</td>
<td>0.89 [0.67, 1.19]</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>3297</td>
<td>32</td>
<td>18/1648</td>
<td>14/1649</td>
<td>4.0</td>
<td>1.28 [0.64, 2.58]</td>
</tr>
<tr>
<td>EXCEL</td>
<td>12914</td>
<td>519</td>
<td>246/6456</td>
<td>273/6456</td>
<td>63.1</td>
<td>0.88 [0.74, 1.05]</td>
</tr>
<tr>
<td>Fixed Effects for GLP1-RA (P-value=0.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| SGLT2i       |          |        |               |             |         |             |
| EMPA-REG OUTCOME | 6968  | 152    | 81/4645       | 71/2323     | 20.9    | 0.54 [0.40, 0.75] |
| CANVAS Program | 10142 | 249    | NA            | NA          | 34.0    | 0.60 [0.47, 0.77] |
| DECLARE-TIMI 58 | 17160 | 365    | 127/8582      | 238/8578    | 45.1    | 0.53 [0.43, 0.66] |
| Fixed Effects for SGLT2i (P-value<0.001) |           |        |               |             |         |             |
SGLT2i and Renal Outcome Trials

- **CREDENCE (Canagliflozin)**
  NCT 02065791; (stopped early - July 2018)

- **DAPA-CKD (Dapagliflozin)**
  NCT 03036150 (completion date ~2020)

- **EMPA-KIDNEY (Empagliflozin)**
  NCT 03594110 (~2022)
CreDENCE: ESRD, Doubling of Serum Creatinine, Renal or CV Death

\[ n=4401, \text{eGFR} <60 \text{ mL/min in 60\%, } <45 \text{ mL/min in 31\%} \]

Hazard ratio, 0.70 (95% CI, 0.59–0.82)
P = 0.00001

T2DM and CVD: 2018 ACC/ADA Decision Pathway

Patient has T2D* and established clinical ASCVD.

Address concurrently.

Guideline-directed medical therapy (lifestyle, antiplatelet, blood pressure, lipids) and glucose-lowering therapy (metformin).

Consider addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV outcome benefit.

Initiate clinician-patient discussion.

No additional action taken at this time

SGLT2 inhibitor selected

GLP-1RA selected

*Most trials of SGLT2i and GLP-1RA required baseline A1C >7% (Example: EXSCEL Trial required HbA1c > 6.5%), and most patients were already on metformin as first-line therapy if tolerated and not contraindicated

# ASCVD Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors/10-year risk</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
</tbody>
</table>
| Extreme risk        | – Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL
|                     | – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH
|                     | – History of premature ASCVD (<55 male, <65 female)                                        | <55            | <80              | <70          |
| Very high risk      | – Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%
|                     | – DM or stage 3 or 4 CKD with 1 or more risk factor(s)                                     | <70            | <100             | <80          |
|                     | – HeFH                                                                                     |                |                  |              |
| High risk           | – ≥2 risk factors and 10-year risk 10%-20%                                                | <100           | <130             | <90          |
|                     | – DM or stage 3 or 4 CKD with no other risk factors                                        |                |                  |              |
| Moderate risk       | ≤2 risk factors and 10-year risk <10%                                                     | <100           | <130             | <90          |
| Low risk            | 0 risk factors                                                                             | <130           | <160             | NR           |

AHA/ACC  2018 Cholesterol Guidelines

Clinical ASCVD

Healthy Lifestyle

Very high-risk ASCVD

High-intensity or maximal statin (Class I)

If on maximal statin & LDL-C ≥70 mg/dL, adding ezetimibe is reasonable (Class IIa)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)

If on clinically judged maximal LDL-C-lowering therapy & LDL-C ≥70 mg/dL, or non-HDL-C ≥100 mg/dL, adding PCSK9-I is reasonable (Class IIa)

Grundy SM et al. Circulation. 2018;Nov. 10
CLEAR Harmony: 52-week Lipid Efficacy with Bempedoic Acid, an ATP Citrate Lyase inhibitor

n= 2230 patients with ASCVD or FH or both, on max tolerated statin ± other lipid Rx

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

*Death, myocardial infarction, or recurrent acute coronary syndrome; PROVE IT-TIMI 22.

## CV Outcomes Trials in Patients with HTG

<table>
<thead>
<tr>
<th></th>
<th>Reported</th>
<th>Ongoing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>REDUCE-IT</strong>*</td>
<td><strong>STRENGTH</strong>*</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>EPA (EE)</td>
<td>EPA+DHA (FFA)</td>
</tr>
<tr>
<td></td>
<td>4 g/d</td>
<td>4 g/d</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>8,179</td>
<td>Estimated 13,000</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>≥45 years</td>
<td>≥18 years</td>
</tr>
<tr>
<td><strong>Risk Profile</strong></td>
<td>CVD (70%) or ↑CVD risk (30%)</td>
<td>CVD (50%) or ↑CVD risk (50%)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>4.8 years</td>
<td>3–5 years (planned)</td>
</tr>
<tr>
<td><strong>Statin Use</strong></td>
<td>100% (at LDL-C goal)</td>
<td>100% (at LDL-C goal)</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Expanded MACE</td>
<td>Expanded MACE</td>
</tr>
<tr>
<td><strong>Entry TG</strong></td>
<td>135–499 mg/dL</td>
<td>200–499 mg/dL</td>
</tr>
<tr>
<td><strong>Entry HDL-C</strong></td>
<td>N/A</td>
<td>≤40 mg/dL</td>
</tr>
</tbody>
</table>

*Locations: International sites; Statistics: Powered for 15% RRR.
REDUCE-IT Study of EPA: Effect on the Primary Endpoint
(CV Death, MI, Stroke, Coronary Revasc, Unstable Angina)

- Hazard Ratio 0.75
  (95% CI 0.68–0.83)
- RRR=24.8%
- ARR=4.8%
- NNT=21 (95% CI 15–33)
- \( P=0.00000001 \)

ARR=absolute risk reduction; CI=confidence interval; Revasc=revascularization; RRR=relative risk reduction.
# Mechanism-based Statin-adjunct Therapy for ASCVD Prevention

## Prior ASCVD Event or High-Risk 1º Prevention: On Aggressive Statin MonoRx

### Residual Risk Factors

<table>
<thead>
<tr>
<th>↑Pro-atherogenic factor</th>
<th>Cholesterol</th>
<th>Inflammation</th>
<th>Thrombosis</th>
<th>Triglycerides</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker</strong></td>
<td>LDL-C &gt;100 mg/dL</td>
<td>hsCRP &gt;2 mg/L</td>
<td>No established Biomarker</td>
<td>TG &gt;135 mg/dL (HDL &lt;40 mg/dL)</td>
<td>Lp(a) &gt;50 mg/dL</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Ezetimibe or PCSK9i</td>
<td>Anti-Inflammatory (IL-inhibition)</td>
<td>Anti-coagulant or Anti-platelet</td>
<td>RX Omega-3 EPA (EPA+DHA, pemafibrate?)</td>
<td>Lp(a) ASO</td>
</tr>
<tr>
<td><strong>Randomized Trial Evidence</strong></td>
<td>IMPROVE-IT</td>
<td>CANTOS (CIRT negative)</td>
<td>COMPASS</td>
<td>REDUCE-IT</td>
<td>Planned</td>
</tr>
</tbody>
</table>

Statin Therapy Adjuncts Proven to Reduce ASCVD

*Major inclusion criteria for each trial.
ACS=acute coronary syndrome; ASCVD=atherosclerotic cardiovascular disease.


**Intense Statin Therapy**

- **+ Ezetimibe**
  - Acute coronary syndrome within 10 days*

- **+ Alirocumab or Evolocumab**
  - Stable ASCVD + additional risk factors; or ACS within 1-12 months*

- **+ Eicosapentaenoic Acid**
  - Stable ASCVD; or Diabetes + \( \geq 1 \) additional risk factor*

*Major inclusion criteria for each trial.
ACS=acute coronary syndrome; ASCVD=atherosclerotic cardiovascular disease.
In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk. (Grade A)
Conclusions

• After a long drought, a plethora of clinical studies has provided evidence for additional pharmacologic avenues to reduce CVD risk in statin-treated

• Cardio-protective agents should be preferred for diabetes management

• Control of coagulation and inflammation still needs to be positioned for wider scopes in CVD risk reduction

• The value of additional LDL lowering is proven, but use of EPA for subjects with elevated TG produces even larger CV benefits