Residual Cardiovascular Risk in 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
Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, LevelEx, Medscape Cardiology, PhaseBio, PLx Pharma, 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; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, 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), NCADR-ACTION Registry Steering Committee (Chair), VACART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, 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, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

This presentation may include off-label and/or investigational uses of drugs. REDUCE-IT was sponsored by Amarin Pharma, Inc.
Primordial, Primary, Secondary Prevention

Health Behaviors
- Fetal and infant health
- Smoking
- High-caloric diets
- Physical inactivity
- Non-ideal body weights
- Environmental pollution

Risk Factors
- Dyslipidemia
- Hypertension
- Diabetes
- Metabolic syndrome

Cardiovascular Disease
- Coronary heart disease
- Cerebrovascular disease
- Peripheral vascular disease
- Heart failure

Primordial prevention
Primary prevention
Secondary prevention

Vaduganathan M, Venkataramini AS, Bhatt DL. JACC. 2015.
“Cholesterol-Years” for CV Risk Prediction and Treatment

- Severe hypercholesterolemia from birth (FH)
- Moderate hypercholesterolemia starting in teens (genetics, lifestyle)
- Modest hypercholesterolemia from adulthood (lifestyle)
- Threshold for onset of ASCVD
- Lifelong low LDL-C (genetics, excellent lifestyle, initiation of LDL-lowering therapy at an early age)
Triglycerides a Causal Risk Factor?

Adapted with permission from Libby P. Triglycerides on the rise: should we swap seats on the seesaw? Eur Heart J. 2015;36:774-776.
A naturally randomized trial evaluating the potential clinical benefit of triglyceride lowering therapies on the risk of coronary heart disease

Brian A. Ference MD, MPhil, MSc, John J. P. Kastelein MD, PhD, Kausik K. Ray MD, MPhil, Henry N. Ginsberg MD, M. John Chapman PhD, DSc, Chris J. Packard DSc, Ulrich Laufs MD, PhD, Adam S. Butterworth PhD, Emanuele Di Angelantonio, MD, John Danesh FRCP, DPhil, Stephen J. Nicholls MBBS, PhD, Deepak L. Bhatt, MD, MPH, Marc S. Sabatine MD, MPH, and Alberico L. Catapano PhD
TGVLDL-C Variants: Same CHD Risk per Unit ApoB

<table>
<thead>
<tr>
<th>2x2 Group</th>
<th>OR\textsubscript{CHD} (95% CI) per 10 mg/dL lower ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both scores &gt; median</td>
<td>0.765 (0.717 - 0.816)</td>
</tr>
<tr>
<td>N = 104,694</td>
<td></td>
</tr>
<tr>
<td>LDLR score &gt; median</td>
<td>0.784 (0.690 - 0.892)</td>
</tr>
<tr>
<td>N = 112,018</td>
<td></td>
</tr>
<tr>
<td>LPL score &gt; median</td>
<td>0.770 (0.670 - 0.886)</td>
</tr>
<tr>
<td>N = 122,599</td>
<td></td>
</tr>
<tr>
<td>Both scores ≤ median</td>
<td>Reference</td>
</tr>
<tr>
<td>N = 131,167</td>
<td></td>
</tr>
</tbody>
</table>

## Combined Effect of LPL and LDLR Scores on Lipids & CHD: 2 x 2 factorial analysis

<table>
<thead>
<tr>
<th>2x2 Group</th>
<th>Δ Triglycerides, mg/dL (95% CI)</th>
<th>Δ LDL-C, mg/dL (95% CI)</th>
<th>Δ apoB, mg/dL (95% CI)</th>
<th>OR_{CHD} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both scores &gt; median</td>
<td>-24.3 (-16.2, -32.4)</td>
<td>-4.9 (-2.1, -7.7)</td>
<td>-6.4 (-4.4, -8.5)</td>
<td>0.842 (0.811 - 0.874)</td>
</tr>
<tr>
<td>N = 104,694</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLR score &gt; median</td>
<td>-3.8 (-15.1, -7.5)</td>
<td>-4.8 (-2.0, -7.6)</td>
<td>-3.4 (-1.5, -5.2)</td>
<td>0.921 (0.885 - 0.958)</td>
</tr>
<tr>
<td>N = 112,018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPL score &gt; median</td>
<td>-20.1 (-13.3, -28.8)</td>
<td>-0.1 (-0.5, 0.3)</td>
<td>-3.0 (-1.2, -4.9)</td>
<td>0.924 (0.889 - 0.960)</td>
</tr>
<tr>
<td>N = 122,599</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Both scores ≤ median</td>
<td>Reference</td>
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<tr>
<td>N = 131,167</td>
<td></td>
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</tr>
</tbody>
</table>

- Δ = change
- mg/dL = milligrams per deciliter
- CI = confidence interval
- OR_{CHD} = odds ratio for coronary heart disease

apoB=apolipoprotein B; CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; LDLR=low-density lipoprotein receptor; LPL=lipoprotein lipase; OR_{CHD}=odds ratio for coronary heart disease.

Promising Therapies for Hypertriglyceridemia

Targeting RNA to Lower Triglycerides: Long Strides from Short Molecules

Treatment with w-3 fatty acids reduces serum C-reactive protein concentration

Kamran Muhammad, Thomas Morledge, Ravish Sachar, Annette Zeldin, Kathy Wolski & Deepak L. Bhatt

Low Dose (and High Dose) Omega-3 Mixtures Show No Significant Cardiovascular Benefit

STRENGTH Trial Design, Details, and Primary Endpoint

• Event-driven design: minimum 1,600 Major Adverse Cardiac Events (MACE) with 90% power to detect a 15% reduction

• 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

• Vital status obtained in 99.8% and complete MACE outcomes in 96.6% of patients, despite pandemic

• Median follow-up time 42.0 months, and study drug 38.4 months

Primary Endpoint: MACE (CV death, MI, Stroke, Coronary revascularization, or hospitalization for Unstable angina)

OMega-3 fatty acids in Elderly with Myocardial Infarction (OMEMI) Trial

• Investigator-initiated, multi-center randomized placebo-controlled double-blind clinical trial studying 1.8 g n-3 PUFA (930 mg EPA, 660 mg DHA) vs. corn oil placebo

• Inclusion criteria
  – Age 70-82 years
  – Myocardial infarction (MI) 2-8 weeks prior to inclusion

• Exclusion criteria
  – Intolerance for the study drug
  – Additional disease state thought to be incompatible with adherence to the study drugs, or low survival prognosis in the study period

• 1,027 patients were randomized. Follow-up data were available for 1,014 patients and included in the intention-to-treat analysis.

• Mean age was 75 years, 29% were female, and mean triglycerides were 111.4 mg/dL.

Primary endpoint: non-fatal AMI, unscheduled revascularization, stroke, all-cause death, or heart failure hospitalization after two years

AMI=acute myocardial infarction; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; PUFA=polyunsaturated fatty acid.

A Revolution in Omega-3 Fatty Acid Research

Icosapent Ethyl (IPE) and Eicosapentaenoic (EPA)

Benefits of IPE
- Highly purified and stable
- Long shelf-life for storage
- FDA approved prescription drug shown to reduce CV events

**JELIS** Showed CV Risk Reduction with Icosapent Ethyl (EPA)

Japanese patients with elevated TC randomized to statin alone or statin + Ethyl-EPA (1.8 g/day Epadel) in PROBE Study Design (open label; blinded endpoint adjudication)

Total Cohort (N=18,645)
No pre-specified minimum TG level

- 80% primary prevention
- 69% women
- Median statin-naïve baseline TG ≈1.7 mmol/L (IQR 1.2-2.5)
- LDL-C ≈3.5 mmol/L with statin; managed per Japanese guidelines
- Stable form of EPA (protected from degradation)

**JELIS** Showed CV Risk Reduction with Icosapent Ethyl (EPA)

Japanese patients with elevated TC randomized to statin alone or statin + Ethyl-EPA (1.8 g/day Epadel) in PROBE Study Design (open label; blinded endpoint adjudication)

Total Cohort (N=18,645)  
No pre-specified minimum TG level

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**Secondary Prevention Cohort**

- Control
- EPA  
  Hazard ratio: 0.81 (0.657–0.998)  
  p=0.048

**Primary Prevention Cohort**

- Control
- EPA  
  Hazard ratio: 0.82 (0.63–1.06)  
  p=0.132

P-value adjusted for age, gender, smoking, diabetes, and hypertension

PROBE = Prospective Randomized Open-label Blinded Endpoint evaluation

Potential Benefit of EPA in Secondary Prevention of CV Events

Design
• 241 post-PCI Japanese patients randomized within 24 hours to pitavastatin ± 1.8 g EPA for 1 year

Results
• 58% reduction in CV death, nonfatal MI, nonfatal stroke, coronary revascularization for new lesions (HR 0.42; 95% CI 0.21-0.87; P = 0.02)
• Notably, CV death at 1 year was significantly lower in the EPA group than in the control group (0.8% vs. 4.2%, P = 0.04)

PCI = percutaneous coronary intervention
CHERRY Supports That Prescription Ethyl-EPA Reduced Coronary Plaque

**Design**
- 193 post-PCI patients randomized to:
  - 4 mg/day pitavastatin alone; or
  - 1.8 g/day EPA plus 4 mg/day pitavastatin
- Followed 6-8 months
- Plaque characteristics and volume measured by integrated backscatter intravascular ultrasound (IB-IVUS)

**Results**
- EPA added to pitavastatin treatment significantly reduced coronary plaque and lipid volume at about 2X the prevalence rate
- Results in agreement with prior studies suggesting benefits of EPA in atherosclerosis

![Plaque Regression in Each Group]

- **Statin Monotherapy**: 61%
- **EPA + Statin**: 81%

*P* = 0.002

The EPA prescription product studied in CHERRY is comparable to icosapent ethyl and is not available in the USA.

Interim EVAPORATE Results Show Substantial, Early Effects of Icosapent Ethyl on Plaque Volume

- First study using MDCT to evaluate the effects of IPE 4g/day vs placebo as an adjunct to statin on plaque volume/characteristics in a REDUCE-IT like population
- Already demonstrated significant, early changes in most plaque measurements by 9 months in a prespecified, interim analysis

Fully adjusted median plaque progression at 9 months (median percent change in plaque volume)

- Low Attenuation Plaque: Placebo 74%, Icosapent Ethyl 94%, No Effect
- Fibro-Fatty: Placebo 25%, Icosapent Ethyl 87%, No Effect
- Fibrous: Placebo 17%, Icosapent Ethyl 40%, P=0.011
- Calcification: Placebo 9%, Icosapent Ethyl 0%, P=0.001
- Total Non-Calcified Plaque: Placebo 43%, Icosapent Ethyl 35%, P=0.010
- Total Plaque: Placebo 26%, Icosapent Ethyl 15%, P=0.0004

Final EVAPORATE Results Show Effects of Icosapent Ethyl on Plaque Volume and Composition

### Comparison of Percent Changes in Plaque Measures

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomized Group</th>
<th>Baseline Statin Use</th>
<th>Follow-up Scan</th>
<th>Percent Changes in Plaque Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPV</td>
</tr>
<tr>
<td><strong>EVAPORATE</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Icosapent ethyl</td>
<td>100.0%</td>
<td>18 months</td>
<td>+11% (mean)</td>
</tr>
<tr>
<td>Control</td>
<td>Mineral oil placebo</td>
<td>100.0%</td>
<td>18 months</td>
<td>+11% (mean)</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>0.0019</td>
</tr>
<tr>
<td><strong>HEARTS</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Intervention</td>
<td>Lovaza</td>
<td>96.0%</td>
<td>30 months</td>
<td>+6.5% (median)</td>
</tr>
<tr>
<td>Control</td>
<td>No treatment</td>
<td>93.9%</td>
<td>30 months</td>
<td>+10.0% (median)</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td><strong>AGE</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Intervention</td>
<td>Aged garlic extract</td>
<td>29.0%</td>
<td>≈12 months</td>
<td>+19% (median)</td>
</tr>
<tr>
<td>Control</td>
<td>Cellulose placebo</td>
<td>28.0%</td>
<td>≈12 months</td>
<td>+55% (median)</td>
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<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>TTRIALS</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Intervention</td>
<td>Testosterone</td>
<td>61.6%</td>
<td>12 months</td>
<td>+16.9% (median)</td>
</tr>
<tr>
<td>Control</td>
<td>Placebo gel</td>
<td>61.5%</td>
<td>12 months</td>
<td>+8.4% (median)</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>0.006*</td>
</tr>
</tbody>
</table>

LAP, low-attenuation plaque; N/A, not available; NCP, noncalcified plaque; TPV, total plaque volume. * P-value is for adjusted treatment group mean of the change from baseline to month 12 in mm³.

Can EPA evaporate plaques?

Lale Tokgozoglu 1* and Alberico L. Catapano 2

1Department of Cardiology, Hacettepe University, Ankara, Turkey; and 2Department of Pharmacological and Biomolecular Sciences and IRCCS Multimedica, Milano, Italy
## Potential Benefits of EPA

<table>
<thead>
<tr>
<th>Effects of EPA on Plaque Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endothelial Dysfunction/Oxidative Stress</strong></td>
</tr>
<tr>
<td>Increase</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Decrease</td>
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</tbody>
</table>

Contrasting Effects of EPA and DHA

EPA incorporated in phospholipid at sn-2 position

EPA

- Preserves membrane structure and normal distribution of cholesterol
- Inhibits lipid oxidation and related cholesterol crystal formation
- Influences signal transduction pathways related to inflammation and vasodilation

Contrasting Effects of EPA and DHA

**Pure EPA Icosapent Ethyl Clinical Clinical Program**

**Efficacy and Safety**

**MARINE**¹ (N=229)
Patients with severe hypertriglyceridemia (TG ≥5.6 to ≤22.6 mmol/L, No LDL-C entry criteria)

**ANCHOR**² (N=702)
Patients on statins with mixed dyslipidemia at high risk for CHD event (TG ≥2.3 to <5.6 mmol/L, LDL-C ≥1.0 to <2.5 mmol/L)

**CV Outcomes**

**REDUCE-IT**³ (N=8179)
Patients on statins with mixed dyslipidemia at high risk for CHD event (TG ≥1.7 to <5.6 mmol/L,* LDL-C >1.0 to ≤2.5 mmol/L)

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CHD=coronary heart disease; CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride.

*Original protocol criteria specified a TG level of 1.7 to <5.6 mmol/L. A 2013 protocol amendment modified qualifying TG levels to ≥2.3 to <5.6 mmol/L.

**REDUCE-IT Design**

### Key Inclusion Criteria
- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TG ≥1.7 mmol/L and < 5.6 mmol/L
- LDL-C >1.0 mmol/L and ≤2.5 mmol/L

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

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

### Icosapent Ethyl
- 4 g/day (n=4089)
- 4 months, 12 months, annually

### Placebo
- (n=4090)
- 4 months, 12 months, annually

### End of Study
- 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
- Year
- Months: -1 Month
- Visit: 1
- Lab values: Screening

### Double-Blind Treatment/Follow-up Period
- Randomization:
  - 0
  - 0 – 4
  - 12
  - Every 12 months
  - 2 – 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
- End of Study:
  - Up to 6.2 years
  - Final Visit

* 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 1.7 mmol/L to 2.3 mmol/L, with no variability allowance.

# Key Baseline Medical Therapy

<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>

Primary and Key Secondary Composite Endpoints

Primary Composite Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Key Secondary Composite Endpoint:
CV Death, MI, Stroke

Hazard Ratio, 0.75

(Icosapent Ethyl)

Years since Randomization

Patients with an Event (%)

0 1 2 3 4 5

(95% CI, 0.68–0.83)

### Primary End Point in Subgroups

#### End Point/Subgroup

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>Int P Val</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Composite End Point (ITT)</strong></td>
<td>7254089 (17.2%)</td>
<td>5014691 (22.0%)</td>
<td>0.75 (0.68-0.82)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Subgroup</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Risk Category</strong></td>
<td></td>
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</tr>
<tr>
<td>Primary Prevention Cohort</td>
<td>59/3993 (6.9%)</td>
<td>7363850 (28.5%)</td>
<td>0.72 (0.65-0.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Secondary Prevention Cohort</td>
<td>146/1197 (12.2%)</td>
<td>163/1197 (13.6%)</td>
<td>0.88 (0.75-1.01)</td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Eastern</td>
<td>55/12090 (6.8%)</td>
<td>713/2650 (26.8%)</td>
<td>0.74 (0.66-0.83)</td>
<td>0.20</td>
</tr>
<tr>
<td>Western</td>
<td>131/1053 (12.5%)</td>
<td>167/1053 (15.9%)</td>
<td>0.84 (0.71-1.00)</td>
<td></td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>11/130 (8.5%)</td>
<td>21/132 (15.9%)</td>
<td>0.66 (0.24-1.3)</td>
<td></td>
</tr>
<tr>
<td><strong>East Asian Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>646/8327 (77.9%)</td>
<td>634/8252 (21.6%)</td>
<td>0.75 (0.67-0.83)</td>
<td>0.04</td>
</tr>
<tr>
<td>Yes</td>
<td>56/922 (21.4%)</td>
<td>67/922 (33.8%)</td>
<td>0.82 (0.67-1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>351/3967 (8.8%)</td>
<td>715/3895 (24.7%)</td>
<td>0.73 (0.65-0.82)</td>
<td>0.33</td>
</tr>
<tr>
<td>Female</td>
<td>154/1162 (13.3%)</td>
<td>186/1195 (15.5%)</td>
<td>0.82 (0.68-1.01)</td>
<td></td>
</tr>
<tr>
<td><strong>White vs Non-White</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>643/8359 (71%)</td>
<td>813/8698 (22.0%)</td>
<td>0.77 (0.69-0.85)</td>
<td>0.18</td>
</tr>
<tr>
<td>Non-White</td>
<td>59/388 (14.5%)</td>
<td>80/401 (22.2%)</td>
<td>0.80 (0.63-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 Years</td>
<td>322/4323 (4.4%)</td>
<td>460/1846 (21.6%)</td>
<td>0.63 (0.56-0.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>≥65 Years</td>
<td>363/1837 (20.3%)</td>
<td>441/1906 (22.5%)</td>
<td>0.87 (0.79-1.00)</td>
<td></td>
</tr>
<tr>
<td><strong>US vs Non-US</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>281/1154 (8.9%)</td>
<td>394/1356 (28.6%)</td>
<td>0.85 (0.69-0.98)</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-US</td>
<td>424/3541 (16.7%)</td>
<td>572/4092 (22.3%)</td>
<td>0.83 (0.71-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Diabetess</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetess</td>
<td>433/2394 (18.1%)</td>
<td>520/2393 (21.4%)</td>
<td>0.77 (0.64-0.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>No Diabetess</td>
<td>272/1695 (16.0%)</td>
<td>260/1694 (15.9%)</td>
<td>0.73 (0.62-0.86)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline rGFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60mL/min/1.73m²</td>
<td>107/505 (21.8%)</td>
<td>228/2111 (29%)</td>
<td>0.71 (0.58-0.85)</td>
<td>0.41</td>
</tr>
<tr>
<td>60-90mL/min/1.73m²</td>
<td>383/2071 (17.1%)</td>
<td>469/2236 (21%)</td>
<td>0.80 (0.72-0.89)</td>
<td></td>
</tr>
<tr>
<td>&lt;60mL/min/1.73m²</td>
<td>138/963 (13.4%)</td>
<td>175/936 (18.1%)</td>
<td>0.75 (0.68-0.82)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Triglycerides ≥200 vs &lt;200 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides ≥200 mg/dL</td>
<td>430/469 (17.3%)</td>
<td>550/469 (28.6%)</td>
<td>0.73 (0.68-0.83)</td>
<td>0.45</td>
</tr>
<tr>
<td>Triglycerides &lt;200 mg/dL</td>
<td>275/1025 (17.4%)</td>
<td>342/1020 (21.1%)</td>
<td>0.79 (0.67-0.93)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Triglycerides ≥350 vs &lt;350 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides ≥350 mg/dL</td>
<td>46/370 (12.1%)</td>
<td>81/1298 (22.2%)</td>
<td>0.75 (0.68-0.83)</td>
<td>0.83</td>
</tr>
<tr>
<td>Triglycerides &lt;350 mg/dL</td>
<td>654/121 (15.0%)</td>
<td>504/129 (20.1%)</td>
<td>0.79 (0.57-1.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Triglycerides ≥200 and HDL-C ≥35 mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>149/623 (18.1%)</td>
<td>214/793 (27.0%)</td>
<td>0.62 (0.51-0.77)</td>
<td>0.04</td>
</tr>
<tr>
<td>No</td>
<td>554/3039 (7.0%)</td>
<td>887/3395 (20.8%)</td>
<td>0.79 (0.71-0.88)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Statin Intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>232/1296 (18.4%)</td>
<td>310/1286 (25.3%)</td>
<td>0.69 (0.58-0.82)</td>
<td>0.12</td>
</tr>
<tr>
<td>Moderate</td>
<td>454/3533 (6.7%)</td>
<td>543/3375 (21.1%)</td>
<td>0.76 (0.67-0.86)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>452/284 (16.9%)</td>
<td>535/284 (18.9%)</td>
<td>1.12 (0.71-1.69)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline DL-C (Delivered by Textile)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥57 mg/dL</td>
<td>241/491 (48.5%)</td>
<td>322/1385 (23.8%)</td>
<td>0.72 (0.61-0.85)</td>
<td>0.62</td>
</tr>
<tr>
<td>47-64 mg/dL</td>
<td>249/1347 (18.4%)</td>
<td>307/1344 (22.2%)</td>
<td>0.61 (0.58-0.66)</td>
<td></td>
</tr>
<tr>
<td>&lt;47 mg/dL</td>
<td>213/1358 (15.9%)</td>
<td>252/1339 (18.8%)</td>
<td>0.74 (0.62-0.89)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline hCRP ≥2 vs &lt;2 mg/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 mg/L</td>
<td>288/1915 (6.0%)</td>
<td>407/1462 (28.0%)</td>
<td>0.66 (0.59-0.76)</td>
<td>0.07</td>
</tr>
<tr>
<td>&lt;2 mg/L</td>
<td>417/715 (82.9%)</td>
<td>696/714 (83.9%)</td>
<td>0.81 (0.71-0.92)</td>
<td></td>
</tr>
</tbody>
</table>

### Key Secondary End Point in Subgroups

<table>
<thead>
<tr>
<th>End Point/Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>HR (95% CI)^*</th>
<th>Int P Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Secondary Composite Endpoint (ITT)</td>
<td>45/4839 (11.2%)</td>
<td>5/6109 (0.8%)</td>
<td>0.74 (0.55-0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subgroup</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Category</td>
<td>Secondary Prevention Cohort</td>
<td>Primary Prevention Cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>35/6290 (12.3%)</td>
<td>7/1111 (0.6%)</td>
<td>0.73 (0.54-0.94)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Eastern</td>
<td>35/6320 (12.3%)</td>
<td>7/1111 (0.6%)</td>
<td>0.75 (0.54-0.96)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>Asia/Pacific</td>
<td>35/6320 (12.3%)</td>
<td>7/1111 (0.6%)</td>
<td>0.73 (0.54-0.96)</td>
<td>0.46</td>
</tr>
<tr>
<td>East/Ind/Usa</td>
<td>No</td>
<td>Yes</td>
<td>35/6320 (12.3%)</td>
<td>7/1111 (0.6%)</td>
<td>0.73 (0.54-0.96)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>10/1111 (0.9%)</td>
<td>9/1111 (0.8%)</td>
<td>0.80 (0.59-1.09)</td>
</tr>
<tr>
<td>White vs Non-White</td>
<td>White</td>
<td>Non-White</td>
<td>11/1348 (0.8%)</td>
<td>4/1111 (0.4%)</td>
<td>0.76 (0.57-0.98)</td>
</tr>
<tr>
<td>Age Group</td>
<td>&lt;65 Years</td>
<td>≥65 Years</td>
<td>20/1111 (1.8%)</td>
<td>16/1111 (1.4%)</td>
<td>0.70 (0.55-0.87)</td>
</tr>
<tr>
<td>US vs Non-US</td>
<td>US</td>
<td>Non-US</td>
<td>16/1111 (1.5%)</td>
<td>16/1111 (1.4%)</td>
<td>0.69 (0.57-0.83)</td>
</tr>
<tr>
<td>Baseline Diabetes</td>
<td>Diabetic</td>
<td>No Diabetic</td>
<td>17/1111 (1.5%)</td>
<td>16/1111 (1.4%)</td>
<td>0.80 (0.65-0.98)</td>
</tr>
<tr>
<td>Baseline tHcy</td>
<td>≤5.0 μmol/L, ≥17.0 μmol/L</td>
<td>&gt;5.0 μmol/L, 7.0 μmol/L</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.71 (0.57-0.88)</td>
</tr>
<tr>
<td>Baseline Creatinine</td>
<td>&lt;0.70 mg/dL</td>
<td>≥0.70 mg/dL</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.77 (0.65-0.91)</td>
</tr>
<tr>
<td>Baseline Creatinine</td>
<td>&lt;0.70 mg/dL</td>
<td>≥0.70 mg/dL</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.71 (0.57-0.88)</td>
</tr>
<tr>
<td>Baseline tHcy</td>
<td>&lt;2.0 mg/dL</td>
<td>≥2.0 mg/dL</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.71 (0.57-0.88)</td>
</tr>
<tr>
<td>Baseline tHcy</td>
<td>&lt;2.0 mg/dL</td>
<td>≥2.0 mg/dL</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.71 (0.57-0.88)</td>
</tr>
<tr>
<td>Baseline Statin Intensity</td>
<td>High</td>
<td>Moderate</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.71 (0.57-0.88)</td>
</tr>
<tr>
<td>Baseline LDL-C (Derived) by Tritet</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.71 (0.57-0.88)</td>
</tr>
<tr>
<td>Baseline hCRP (in mg/dL)</td>
<td>&lt;2.0 mg/dL</td>
<td>≥2.0 mg/dL</td>
<td>15/1111 (1.4%)</td>
<td>16/1111 (1.4%)</td>
<td>0.71 (0.57-0.88)</td>
</tr>
</tbody>
</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><strong>Primary Composite (ITT)</strong></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><strong>Key Secondary Composite (ITT)</strong></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><strong>Cardiovascular Death or Nonfatal MI</strong></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><strong>Fatal or Nonfatal MI</strong></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><strong>Urgent or Emergent Revascularization</strong></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><strong>Cardiovascular Death</strong></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><strong>Hospitalization for Unstable Angina</strong></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><strong>Fatal or Nonfatal Stroke</strong></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><strong>Total Mortality, Nonfatal MI</strong></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><strong>Total Mortality</strong></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.
First and Subsequent Events – Full Data

**RR 0.69**
(95% CI, 0.61-0.77)

**P=0.0000000004**

31% Reduction in Total Events

**Full Dataset Event No.**

- **1st Events**
  - Placebo [N=4090]
    - 901
  - Icosapent Ethyl [N=4089]
    - 705
- **2nd Events**
  - Placebo [N=4090]
    - 463
  - Icosapent Ethyl [N=4089]
    - 299
- **3rd Events**
  - Placebo [N=4090]
    - 176
  - Icosapent Ethyl [N=4089]
    - 85
- **≥4 Events**
  - Placebo [N=4090]
    - 184
  - Icosapent Ethyl [N=4089]
    - 1,185

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

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

## Treatment-Emergent Adverse Events

### No Overall Treatment Difference in Adverse Event Profiles

<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>&gt;0.99</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>

TEAE event rates represent the enrolled high CV risk patients and the 4.9-year median study follow-up.

* From Fisher’s exact test.
# Treatment-Emergent Adverse Event of Interest: 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>All Bleeding TEAEs</td>
<td>482 (11.8%)</td>
<td>404 (9.9%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Bleeding SAEs</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>
<tr>
<td>Intracranial Bleeding</td>
<td>0 (0.0%)</td>
<td>1 (0.0%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>13 (0.3%)</td>
<td>10 (0.2%)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Note: Hemorrhagic stroke was an adjudicated endpoint; other bleeding events were included in safety analyses.

* From Fisher’s exact test.

Atrial Fibrillation or Flutter

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

<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>Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization</td>
<td>321 (7.9)</td>
<td>248 (6.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Afib/Aflutter TEAEs¹</td>
<td>236 (5.8)</td>
<td>183 (4.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Serious Afib/Aflutter TEAEs²</td>
<td>22 (0.5)</td>
<td>20 (0.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization³</td>
<td>127 (3.1)</td>
<td>84 (2.1)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Note: Clinical consequences, including stroke, MI, cardiac arrest, and sudden cardiac death were reduced in the overall ITT population, with consistent results in those with a history of atrial fibrillation at baseline.

* From Fisher’s exact test.

1. Includes atrial fibrillation/flutter TEAEs. 2. Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. 3. Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalization clinical events by the Clinical Endpoint Committee.
**Primary Composite Endpoint:**

**Total 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></td>
<td>Rate per 1000 Patient Years</td>
<td>Rate per 1000 Patient Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Composite Endpoint (ITT)</td>
<td>61.1</td>
<td>88.8</td>
<td>0.70 (0.62–0.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline Triglycerides by Tertiles*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.9 to ≤2.1 mmol/L</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;2.1 to ≤2.8 mmol/L</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;2.8 to ≤15.8 mmol/L</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

Key Triglyceride-Lowering Trials and Effects on CV Outcomes

A

<table>
<thead>
<tr>
<th>Trial</th>
<th>TG Level (mg/dl)</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA-HIT 1999</td>
<td>250</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>FIELD 2005</td>
<td>200</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>ACCORD-Lipid 2010</td>
<td>150</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>AIM-HIGH 2011</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPS2-THRIVE 2014</td>
<td>50</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td>GISSI-P 1999</td>
<td>0</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>JELIS 2007</td>
<td>100</td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>REDUCE-IT 2018</td>
<td>250</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint (%)</th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA-HIT 1999</td>
<td>RRR 22% p=0.006</td>
<td>HR 0.89</td>
<td>HR 0.92</td>
</tr>
<tr>
<td>FIELD 2005</td>
<td>p=0.16</td>
<td>p=0.32</td>
<td>p=0.79</td>
</tr>
<tr>
<td>ACCORD-Lipid 2010</td>
<td>HR 1.02</td>
<td>HR 0.96</td>
<td>HR 0.96</td>
</tr>
<tr>
<td>AIM-HIGH 2011</td>
<td>HR 0.89 p=0.29</td>
<td>HR 0.96</td>
<td>HR 0.96</td>
</tr>
<tr>
<td>HPS2-THRIVE 2014</td>
<td>HR 0.90</td>
<td>HR 0.90</td>
<td>HR 0.90</td>
</tr>
<tr>
<td>GISSI-P 1999</td>
<td>HR 0.81 p=0.011</td>
<td>HR 0.81</td>
<td>HR 0.81</td>
</tr>
<tr>
<td>JELIS 2007</td>
<td>HR 0.75 p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REDUCE-IT 2018</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fibrate

Omega-3 Fatty Acid

Patel PN, Patel SM, Bhatt DL. Curr Opin Cardiol. 2019;34:721–727. ** ** P<0.001; * P<0.05
reduce-it EPA
Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA

P*<0.001 for all

Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance1, age2, sex3, baseline diabetes4, hsCRP5, treatment compliance6.

*P value is <0.001 for both non-linear trend and for regression slope.
Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Dose-Response of Hazard Ratio (95% CI)
Any Myocardial Infarction, Any Stroke, Coronary Revascularization, Unstable Angina by On-Treatment Serum EPA

Any Myocardial Infarction$^{1,3}$

Any Stroke$^{2,4,5}$

Coronary Revascularization$^{1,2}$

Unstable Angina$^2$

Note: Area under the curve (AUC) derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and sex$^1$, baseline diabetes$^2$, hsCRP$^3$, statin compliance$^4$, age$^5$. *P value is <0.001 for both non-linear trend and for regression slope.

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Dose-Response of Hazard Ratio (95% CI)
Primary Composite Endpoint by On-Treatment Serum EPA
Established Cardiovascular Disease or Diabetes with Risk Factors

Primary Endpoint: Established Cardiovascular Disease

Primary Endpoint: Diabetes with Risk Factors

P*<0.001 for all

Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance, age, sex, baseline diabetes, hsCRP.

*P value is <0.001 for both non-linear trend and for regression slope.
Baseline and Achieved EPA Levels in Omega-3 CVOTs Cross-study Comparison

**Plasma and serum EPA levels have been strongly correlated, with plasma levels being slightly higher than serum levels.**

Time to First and Total Primary and Key Secondary Endpoint Events: Diabetes Subgroup: N=4787


Total events analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event.
Hazard Ratio, 0.66
(95% CI, 0.58–0.76)
RRR = 34%
ARR = 4.1%
NNT = 24
P=0.0000000008

Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years. ARR is based on the observed rates of events of 9.2% for IPE and 13.3% for Placebo.

Time to Coronary Revascularization Benefit

Very early benefit demonstrated

Hazard Ratio (95% Confidence Interval)

Time to Coronary Revascularization Benefit

Very early benefit demonstrated, with consistent statistical significance obtained by only 11 months

Time to Elective, Urgent, and Emergent Revascularization Events

Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years. Time to Elective Revascularization ARR is based on the observed event rates of 4.7% for IPE and 6.8% for Placebo.

Time to Urgent Coronary Revascularization ARR is based on the observed rates of 4.4% for IPE and 6.6% for Placebo.

Time to Emergent Coronary Revascularization ARR is based on the observed event rates of 1.0% for IPE and 1.6% for Placebo.

Comparison of Relative Risk Reductions in Revascularization in Major Clinical Trials

- 4S: 37%
- CURE: 8%
- PROVE IT-TIMI 22: 14%
- NORSTENT: 24%
- FOURIER: 22%
- ODYSSEY OUTCOMES: 12%

Comparison of Relative Risk Reductions in Revascularization in Major Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>37%</td>
</tr>
<tr>
<td>CURE</td>
<td>8%</td>
</tr>
<tr>
<td>PROVE IT-TIMI 22</td>
<td>14%</td>
</tr>
<tr>
<td>NORSTENT</td>
<td>24%</td>
</tr>
<tr>
<td>FOURIER</td>
<td>22%</td>
</tr>
<tr>
<td>ODYSSEY OUTCOMES</td>
<td>12%</td>
</tr>
<tr>
<td>REDUCE-IT</td>
<td>34%</td>
</tr>
</tbody>
</table>

Primary Endpoint:
CV Death, Nonfatal MI, Nonfatal Stroke, Coronary Revasc, Unstable Angina: Patients With a History of PCI (N=3408)

Hazard Ratio, 0.66
(95% CI, 0.58–0.76)
RRR = 34%
ARR = 8.5%
NNT = 12
P=0.000000003

Key Secondary Endpoint:
CV Death, MI, Stroke:
Patients With a History of PCI (N=3408)

Hazard Ratio, 0.66
(95% CI, 0.56–0.79)
RRR = 34%
ARR = 5.4%
NNT = 19
P=0.000006

Primary Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina: Patients With a History of CABG; N=1837

Hazard Ratio, 0.76
(95% CI, 0.63–0.92)
RRR = 24%
ARR = 6.2%
NNT = 16
P=0.004

Key Secondary Endpoint: CV Death, MI, Stroke: Patients With a History of CABG; N=1837

Hazard Ratio, 0.69
(95% CI, 0.56–0.87)
RRR = 31%
ARR = 6.0%
NNT = 17
P=0.001

The Road to Approval

3/2019: ADA recommends icosapent ethyl in high-risk patient groups (Level A)

3/2019: 8/2019: ESC/EAS recommends icosapent ethyl if TG still elevated despite statins (Level IIa, B)

11/2019: Icosapent ethyl reduces recurrent ischemic events

11/2019: Icosapent ethyl shows robust results in USA subgroup

2011: MARINE

2012: ANCHOR

2018 ACC/AHA Guideline: use of statins, OM3FAs, fibrates in TG ≥500 mg/dL

12/2019: Health Canada approval

12/13/2019: FDA Approval of expanded indication

10/2019 NLA recommends icosapent ethyl in high-risk patient groups (Level 1, B-R)

11/14/2019: EMDAC votes 16-0 to recommend expanded indication

11/10/2018 REDUCE-IT

3/2019: ADA recommends icosapent ethyl in high-risk patient groups (Level A)

12/13/2019: FDA Approval of expanded indication

10/2019 NLA recommends icosapent ethyl in high-risk patient groups (Level 1, B-R)
Time to First Event Residual Risk Reduction: PROVE-IT, IMPROVE-IT, REDUCE-IT

PROVE-IT¹

<table>
<thead>
<tr>
<th>KM Event Rate (%)</th>
<th>Standard of Care/Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.3</td>
<td>22.4</td>
<td></td>
</tr>
</tbody>
</table>

IMPROVE-IT²

<table>
<thead>
<tr>
<th>KM Event Rate (%)</th>
<th>Standard of Care/Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.7</td>
<td>32.7</td>
<td></td>
</tr>
</tbody>
</table>

REDUCE-IT³

<table>
<thead>
<tr>
<th>KM Event Rate (%)</th>
<th>Standard of Care/Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.3</td>
<td>23.0</td>
<td></td>
</tr>
</tbody>
</table>

* Kaplan-Meier event rates based on the following time periods: PROVE-IT, 2 years; IMPROVE-IT, 7 years; REDUCE-IT, 5.7 years.

First events PROVE-IT: Death from any cause, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina.

First events IMPROVE-IT, REDUCE-IT: CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, hospitalization for unstable angina.

Redefining Residual Risk Post REDUCE-IT

Known Cardiovascular Disease or High Risk

Plant-Based Diet; High Intensity Statin

Biologic Issue

- Residual Cholesterol Risk
  - LDL-C ≥100 mg/dL
- Residual Inflammatory Risk
  - hsCRP ≥2 mg/L
- Residual Thrombotic Risk
- Residual Triglyceride Risk
- Residual Lp(a) Risk

Critical Biomarker

Potential Intervention

- Targeted LDL/Apo B Reduction
- Targeted Inflammation Reduction
- Targeted Antithrombotic Reduction
- Targeted Triglyceride Reduction
- Targeted Lp(a) Reduction

Randomized Trial Evidence

- IMPROVE-IT
- FOURIER, SPIRE, ODYSSEY
- CANTOS, COLCOT
- LoDoCo2
- CLEAR-Synergy
- CHARISMA, PEGASUS COMPASS, THEMIS
- THEMIS-PCI
- REDUCE-IT STRENGTH PROMINENT

REDUCE-IT?

Redefining Residual Risk Post REDUCE-IT

Known Cardiovascular Disease or High Risk

Plant-Based Diet; High Intensity Statin

Biologic Issue
- Residual Cholesterol Risk
  - LDL-C ≥100mg/dL
- Residual Inflammatory Risk
  - hsCRP ≥2mg/L
- Residual Thrombotic Risk
- Residual Triglyceride Risk
- Residual Lp(a) Risk

Critical Biomarker

Potential Intervention
- Targeted LDL / Apo B Reduction
- Targeted Inflammation Reduction
- Targeted Antithrombotic Reduction
- Targeted Triglyceride Reduction
- Targeted Lp(a) Reduction

Randomized Trial Evidence
- IMPROVE-IT
- FOURIER, SPIRE, ODISSEY
- CANTOS, COLCOT, LoDoCo2, CLEAR-Synergy
- CHARISMA, PEGASUS COMPASS, THEMIS
- THEMIS-PCI

REDUCE-IT

Planned

REDUCE-IT STRENGTH

Profound reductions in first and total cardiovascular events with icosapent ethyl in the REDUCE-IT trial: why these results usher in a new era in dyslipidaemia therapeutics


1VA New England Healthcare System, Boston University School of Medicine, 150 S. Huntington Avenue, Boston, MA 02130, USA; 2Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA, USA; 3CGH Medical Center, Sterling, IL, USA; 4Gicarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD, USA; 5Imperial Centre for Cardiovascular Disease Prevention, School of Public Health, Imperial College London, London, UK; 6Sorbonne University, Pitie-Salpetriere University Hospital, Paris, France; and 7University Heart Center, University Hospital, Zurich, Switzerland

Pyramid of Risk

Secondary and Tertiary Prevention
- CVD
- CAD
- PVD
- Heart Failure
- Cerebrovascular Disease

Primary Prevention
- Risk Factors
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - Metabolic Syndrome

Primordial Prevention
- Health Behaviors
  - Fetal and Infant Health
  - Smoking
  - Physical Activity
  - Body Weight
  - Environmental Pollution
  - Diet

Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. JACC 2017;70:2171-2185.
Thank You!

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Professor of Medicine,
Harvard Medical School
Email: DLBhattMD@post.harvard.edu
Twitter: @DLBhattMD

www.brighamandwomens.org/heart