Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L. Bhatt, MD, MPH, Michael Miller, MD, Eliot A. Brinton, MD, Terry A. Jacobson, MD, Ph. Gabriel Steg, MD, Steven B. Ketchum, PhD, Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD, Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, Brian Olshansky, MD, Mina K. Chung, MD, C. Michael Gibson, MS, MD, Robert P. Giugliano, MD, SM, Matthew J. Budoff, MD, Christie M. Ballantyne, MD, on Behalf of the REDUCE-IT Investigators
Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno, 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 Daichi 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), Medtelligence/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, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Fractyl, 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, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, 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.

All analyses independently validated by Baim Clinical Research Institute.
**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

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

### Icosapent Ethyl
- 4 g/day (n=4089)

### Placebo
- (n=4090)

### Screening Period
- Double-Blind Treatment/Follow-up Period

#### Randomization
- 0 – 4
- 5
- 6
- 7
- 8
- 9
- Every 12 months

#### End of Study
- Up to 6.2 years†
- Final 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

---

*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).

Adapted with permission from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol.* 2017;40:138-148. REDUCE-IT ClinicalTrials.gov number, NCT01492361. [https://creativecommons.org/licenses/by-nc/4.0/]
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

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Patients with an Event (%)</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>23.0%</td>
<td>28.3%</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

### First and Subsequent Events – Full Data

#### Number of Primary Composite Endpoint Events

<table>
<thead>
<tr>
<th>Event No.</th>
<th>Placebo [N=4090]</th>
<th>Icosapent Ethyl [N=4089]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Events</td>
<td>901</td>
<td>705</td>
</tr>
<tr>
<td>2nd Events</td>
<td>463</td>
<td>299</td>
</tr>
<tr>
<td>3rd Events</td>
<td>176</td>
<td>85</td>
</tr>
<tr>
<td>≥4 Events</td>
<td>184</td>
<td>96</td>
</tr>
</tbody>
</table>

**Placebo**

- **1st Events**: HR 0.75 (95% CI, 0.68-0.83), P=0.000000001
- **2nd Events**: HR 0.68 (95% CI, 0.60-0.77)
- **3rd Events**: HR 0.70 (95% CI, 0.59-0.83)
- **≥4 Events**: RR 0.46 (95% CI, 0.36-0.60)

**Icosapent Ethyl**

- **1st Events**: HR 0.75 (95% CI, 0.68-0.83)
- **2nd Events**: HR 0.68 (95% CI, 0.60-0.77)
- **3rd Events**: HR 0.70 (95% CI, 0.59-0.83)
- **≥4 Events**: RR 0.69 (95% CI, 0.61-0.77)

**No. of Fewer Cases**

- 1st Events: -99
- 2nd Events: -80
- 3rd Events: -164
- ≥4 Events: -196

**31% Reduction in Total Events**

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

reduce-it USA
Early Discontinuation from Study
N=267 (17.2%)†
Withdrawal of consent 184 (11.9%)
Investigator judgement 9 (0.6%)
Incomplete final visit 48 (3.1%)
Other 26 (1.7%)

Early Discontinuation from Study
N=321 (20.1%)†
Withdrawal of consent 209 (13.1%)
Investigator judgement 9 (0.6%)
Incomplete final visit 70 (4.4%)
Other 33 (2.1%)

Actual vs. potential follow-up time (%) 88.7%
Known vital status 1546 (99.9%)

Completed Study
N=1281 (82.8%)
Completed final visit 1176 (76.0%)
Death before final visit 105 (6.8%)

Completed Study
N=1277 (79.9%)
Completed final visit 1130 (70.7%)
Death before final visit 147 (9.2%)

Actual vs. potential follow-up time (%) 87.1%
Known vital status 1596 (99.9%)

*3 patients presented 2 screen failure reasons.

†Early discontinuation from study (17.2% icosapent ethyl; 20.1% placebo) includes patients who discontinued after having a primary event (15 [1.0%] icosapent ethyl; 34 [2.1%] placebo) and prior to having an event (252 [16.3%] icosapent ethyl; 287 [18.0%] placebo).

**USA Subgroup**

**Randomized**
N=3146 (45% of Screened)

**Icosapent Ethyl**
N=1548 (100%)

**Placebo**
N=1598 (100%)

**CONSORT Diagram:**

**Screened**
N=6962

**Screen Fails**
N=3816*

**Randomized**
N=3146 (45% of Screened)

**Screened**
N=6962

**Screen Fails**
N=3816*

Incl./Excl. criteria not met 3541
Withdrawal of consent 164
Adverse event 8
Primary prevention category closed 4
Death 2
Lost to follow-up 44
Enrollment closed 3
Other 53

**Randomized**
N=3146 (45% of Screened)

**Icosapent Ethyl**
N=1548 (100%)

**Placebo**
N=1598 (100%)

**Completed Study**
N=1281 (82.8%)
Completed final visit 1176 (76.0%)
Death before final visit 105 (6.8%)

**Completed Study**
N=1277 (79.9%)
Completed final visit 1130 (70.7%)
Death before final visit 147 (9.2%)

**Actual vs. potential follow-up time (%)**
88.7%

**Known vital status**
1546 (99.9%)

**Completed Study**
N=1277 (79.9%)
Completed final visit 1130 (70.7%)
Death before final visit 147 (9.2%)

**Actual vs. potential follow-up time (%)**
87.1%

**Known vital status**
1596 (99.9%)

Primary End Point: USA Subgroup
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Hazard Ratio, 0.69
(95% CI, 0.59–0.80)
RRR = 31%
ARR = 6.5%
NNT = 15 (95% CI, 11–27)
P = 0.000001

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Key Secondary End Point: USA Subgroup
CV Death, MI, Stroke

Hazard Ratio, 0.69
(95% CI, 0.57–0.83)
RRR = 31%
ARR = 4.6%
NNT = 22 (95% CI, 14–47)
P = 0.00008

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

All-Cause Mortality: USA Subgroup

**Hazard Ratio, 0.70**
(95% CI, 0.55–0.90)

**RRR = 30%**

**ARR = 2.6%**

**NNT = 39** (95% CI, 22–154)

**P = 0.004**

**P_{interaction} = 0.02**

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>HR (95% CI)</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td></td>
<td>281/1548 (18.2%)</td>
<td>394/1598 (24.7%)</td>
<td>0.69 (0.59–0.80)</td>
<td>31%▼</td>
<td>0.000001</td>
</tr>
<tr>
<td>Key Secondary Composite (ITT)</td>
<td></td>
<td>187/1548 (12.1%)</td>
<td>266/1598 (16.6%)</td>
<td>0.69 (0.57–0.83)</td>
<td>31%▼</td>
<td>0.00008</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td></td>
<td>160/1548 (10.3%)</td>
<td>222/1598 (13.9%)</td>
<td>0.71 (0.58–0.86)</td>
<td>29%▼</td>
<td>0.0007</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td></td>
<td>103/1548 (6.7%)</td>
<td>141/1598 (8.8%)</td>
<td>0.72 (0.56–0.93)</td>
<td>28%▼</td>
<td>0.01</td>
</tr>
<tr>
<td>Urgent or Emergency Revascularization</td>
<td></td>
<td>94/1548 (6.1%)</td>
<td>144/1598 (9.0%)</td>
<td>0.64 (0.49–0.83)</td>
<td>36%▼</td>
<td>0.0006</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td></td>
<td>72/1548 (4.7%)</td>
<td>107/1598 (6.7%)</td>
<td>0.66 (0.49–0.90)</td>
<td>34%▼</td>
<td>0.007</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td></td>
<td>38/1548 (2.5%)</td>
<td>71/1598 (4.4%)</td>
<td>0.53 (0.36–0.79)</td>
<td>47%▼</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td></td>
<td>41/1548 (2.6%)</td>
<td>65/1598 (4.1%)</td>
<td>0.63 (0.43–0.93)</td>
<td>37%▼</td>
<td>0.02</td>
</tr>
<tr>
<td>Total Mortality/Nonfatal Myocardial Infarction/Nonfatal Stroke</td>
<td></td>
<td>221/1548 (14.3%)</td>
<td>309/1598 (19.3%)</td>
<td>0.70 (0.59–0.83)</td>
<td>30%▼</td>
<td>0.00005</td>
</tr>
<tr>
<td>Total Mortality</td>
<td></td>
<td>111/1548 (7.2%)</td>
<td>156/1598 (9.8%)</td>
<td>0.70 (0.55–0.90)</td>
<td>30%▼</td>
<td>0.004</td>
</tr>
</tbody>
</table>

RRR denotes relative risk reduction

**Primary Endpoint: USA Subgroup**

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

<table>
<thead>
<tr>
<th>Endpoint/Study</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint (ITT)</td>
<td>0.85 (0.69–1.04)</td>
<td>0.69 (0.60–0.79)</td>
<td>0.82 (0.61–1.09)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Risk Category</td>
<td>Multi-Variate Analysis of Primary Prevention - Primary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes vs No</td>
<td>201/1398 (14.5%)</td>
<td>226/1342 (16.9%)</td>
<td>0.77 (0.60–0.98)</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Non-White</td>
<td>252/1384 (18.2%)</td>
<td>264/1437 (18.4%)</td>
<td>0.91 (0.79–1.04)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>224/1398 (16.0%)</td>
<td>182/1090 (17.6%)</td>
<td>0.82 (0.70–0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 mL/min/1.73m2</td>
<td>209/1189 (17.6%)</td>
<td>206/1195 (17.1%)</td>
<td>0.98 (0.84–1.15)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>60 - &lt;90 mL/min/1.73m2</td>
<td>179/940 (19.1%)</td>
<td>196/1090 (18.0%)</td>
<td>0.95 (0.72–1.26)</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>≥90 mL/min/1.73m2</td>
<td>241/1346 (18.0%)</td>
<td>262/1384 (19.0%)</td>
<td>0.96 (0.76–1.21)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>224/1398 (16.0%)</td>
<td>182/1090 (17.6%)</td>
<td>0.82 (0.70–0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>209/1189 (17.6%)</td>
<td>206/1195 (17.1%)</td>
<td>0.98 (0.84–1.15)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Diabetes Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Diabetes</td>
<td>209/1189 (17.6%)</td>
<td>206/1195 (17.1%)</td>
<td>0.98 (0.84–1.15)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>241/1346 (18.0%)</td>
<td>262/1384 (19.0%)</td>
<td>0.96 (0.76–1.21)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>HDL-C by Tertiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;60 mL/min/1.73m2</td>
<td>209/1189 (17.6%)</td>
<td>206/1195 (17.1%)</td>
<td>0.98 (0.84–1.15)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>60 - &lt;90 mL/min/1.73m2</td>
<td>179/940 (19.1%)</td>
<td>196/1090 (18.0%)</td>
<td>0.95 (0.72–1.26)</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>≥90 mL/min/1.73m2</td>
<td>241/1346 (18.0%)</td>
<td>262/1384 (19.0%)</td>
<td>0.96 (0.76–1.21)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

### Key Secondary Endpoint: Subgroups – USA

#### CV Death, MI, Stroke

<table>
<thead>
<tr>
<th>Endpoint/Subgroup</th>
<th>Hazard ratio (95% CI)</th>
<th>IcosapentEthyl</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>let µM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Secondary Composite (ITT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Category</td>
<td>Secondary Prevention</td>
<td>Primary Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SITE</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Non-White</td>
<td>White</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Statin Intensity</strong></td>
<td>LDL-C (Derived) by Tertiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;97 mg/dL</td>
<td>68-96 mg/dL</td>
<td>≤67 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Statin Intensity</strong></td>
<td>HDL-C by Tertiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;43.5 mg/dL</td>
<td>36-43.5 mg/dL</td>
<td>≤35 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Statin Intensity</strong></td>
<td>ApoB by Tertiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;89 mg/dL</td>
<td>68-89 mg/dL</td>
<td>≤67 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Statin Intensity</strong></td>
<td>Triglycerides by Tertiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥35 mg/dL</td>
<td>22-34 mg/dL</td>
<td>≤21 mg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Icosapent Ethyl**: Better
- **Placebo**: Worse
- **HR**: Hazard Ratio
- **let µM**: 0.2 0.6 1.6 3.0

| n/N(% | | | | | |
|-------|-------|-------|-------|-------|
| HR | 0.68 (0.46–0.99) | 0.70 (0.56–1.01) | 0.66 (0.47–0.91) | 0.69 (0.50–0.94) | 0.71 (0.52–0.96) |
| 0.60 (0.44–0.81) | 0.67 (0.56–0.83) | 0.69 (0.57–0.87) |

**Image**

All-Cause Mortality: USA Subgroup by CV Risk Category

Secondary Prevention

Hazard Ratio, 0.71  
(95% CI, 0.53–0.94)  
RRR = 29%

Primary Prevention

Hazard Ratio, 0.69  
(95% CI, 0.44–1.09)  
RRR = 31%

Note: The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.
First and Subsequent Events: USA

Full Dataset

- 1st Events
  - HR 0.69
  - (95% CI, 0.59-0.80)
  - P=0.000001

- 2nd Events
  - HR 0.63
  - (95% CI, 0.49-0.80)
  - RR 0.63
  - (95% CI, 0.52-0.76)

- 3rd Events
  - HR 0.63
  - (95% CI, 0.49-0.80)
  - RR 0.56
  - (95% CI, 0.40-0.80)

- ≥4 Events
  - RR 0.56
  - (95% CI, 0.40-0.80)

**Full Dataset Event No.**
- Placebo [N=1598]
  - 1st Events: 394
  - 2nd Events: 204
  - 3rd Events: 85
  - ≥4 Events: 87

- Icosapent Ethyl [N=1548]
  - 1st Events: 281
  - 2nd Events: 123
  - 3rd Events: 49
  - ≥4 Events: 502

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

Safety Summary: USA Subgroup
Treatment Emergent Adverse Events in the Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=1548)</th>
<th>Placebo (N=1598)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at Least One TEAE, n (%)</td>
<td>1354 (87.5)</td>
<td>1387 (86.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>436 (28.2)</td>
<td>458 (28.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Drug-Related TEAE</td>
<td>188 (12.1)</td>
<td>183 (11.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>533 (34.4)</td>
<td>571 (35.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Drug-Related Serious TEAE</td>
<td>5 (0.3)</td>
<td>2 (0.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>TEAE Leading to Withdrawal of Study Drug</td>
<td>145 (9.4)</td>
<td>170 (10.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Drug-Related TEAE Leading to Withdrawal of Study Drug</td>
<td>56 (3.6)</td>
<td>75 (4.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Serious TEAE Leading to Withdrawal of Study Drug</td>
<td>31 (2.0)</td>
<td>48 (3.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Serious TEAE Leading to Death</td>
<td>36 (2.3)</td>
<td>53 (3.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Drug-Related Serious TEAE Leading to Withdrawal of Study Drug</td>
<td>1 (0.1)</td>
<td>2 (0.1)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

- Tolerability and safety findings were consistent with the full study population
- The tolerability and safety virtually identical to placebo; no significant differences in the overall rates of TEAEs or serious TEAEs
- A significant increase in minor bleeding (16.7% vs 13.6%, p=0.02), but no significant excess in serious adverse events related to bleeding
- There was a significant increase in the overall TEAE rate of atrial fibrillation or flutter (6.6% vs 4.5%, p=0.012), but not in either the category of serious adverse events of atrial fibrillation or flutter, or the adjudicated endpoint of hospitalization ≥24 hours for atrial fibrillation or flutter

For Every 1000 Patients in the USA Treated with Icosapent Ethyl 4g/day for 5 Years

- Cardiovascular Death: -27
- Fatal or Nonfatal MI: -43
- Fatal or Nonfatal Stroke: -21
- Hospitalization for Unstable Angina: -26
- Coronary Revascularization: -88
- Primary Composite Endpoint: -204
- Total Mortality: -34

Conclusions: USA Subgroup

- Compared with placebo, in the USA patients, icosapent ethyl 4 grams per day resulted in statistically significant:
  - 31% reductions in the primary and key secondary endpoints
  - 28% to 47% reductions in all prespecified hierarchical testing endpoints
  - 36% reduction in total events, including a 37% reduction in second events, a 37% reduction in third events, and a 44% reduction in 4\textsuperscript{th} or more events
  - 30% relative risk reduction and 2.6% absolute risk reduction in all-cause mortality

We thank the investigators, the study coordinators, and the 3,146 USA patients who participated in REDUCE-IT!
REDUCE-IT USA: RESULTS FROM THE 3,146 PATIENTS RANDOMIZED IN THE UNITED STATES

DEEPAK L. BHATT, MD, MPH, FAHA; MICHAEL MILLER, MD; ELIOT A. BRINTON, MD; TERRY A. JACOBSON, MD; PH. GABRIEL STEG, MD; STEVEN B. KETCHUM, PHD; RALPH T. DOYLE, JR., BA; REBECCA A. JULIANO, PHD; LIXIA JIAO, PHD; CRAIG GRANOWITZ, MD, PHD; JEAN-CLAUDE TARDIF, MD; BRIAN OLSHANSKY, MD; MINA K. CHUNG, MD; C. MICHAEL GIBSON, MS, MD; ROBERT P. GIUGLIANO, MD, SM; MATTHEW J. BUDOFF, MD; CHRISTIE M. BALLANTYNE, MD; ON BEHALF OF THE REDUCE-IT INVESTIGATORS*

CIRCULATION

HTTPS://WWW.AHAJOURNALS.ORG/DOI/10.1161/CIRCULATIONAHA.119.044440