Icosapent Ethyl Provides Consistent Cardiovascular Benefit in Patients with Diabetes in REDUCE-IT

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on Behalf of the REDUCE-IT Investigators
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This presentation may include off-label and/or investigational uses of drugs. REDUCE-IT was sponsored by Amarin Pharma, Inc.
**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**
- Every 12 months

**Double-Blind Treatment/Follow-up Period**
- 4 months, 12 months, annually

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

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- Statin stabilization
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**Screening Period**
- Every 12 months

**Double-Blind Treatment/Follow-up Period**
- 4 months, 12 months, annually

**End of Study**
- Up to 6.2 years†

**Year**
- 0
- 1

**Months**
- 0 – 4
- 5
- 6
- 7
- 8
- 9

**Visit**
- 0
- 1

**Lab values**
- Screening
- Baseline

**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).


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Primary and Key Secondary Composite Endpoints

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

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Patients with an Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>30</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

Icosapent Ethyl

Placebo

Key Secondary Composite Endpoint:
CV Death, MI, Stroke

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Patients with an Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
</tr>
</tbody>
</table>

Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.00000006

Icosapent Ethyl

Placebo

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</td>
<td>901</td>
<td>705</td>
</tr>
<tr>
<td>2nd</td>
<td>463</td>
<td>299</td>
</tr>
<tr>
<td>3rd</td>
<td>176</td>
<td>85</td>
</tr>
<tr>
<td>≥4 Events</td>
<td>1,724</td>
<td>1,185</td>
</tr>
</tbody>
</table>

- **1st Events**
  - HR 0.75 (95% CI, 0.68-0.83)
  - RR 0.69 (95% CI, 0.61-0.77)
  - P = 0.0000000004

- **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)

**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.

# Key Baseline Characteristics: Diabetes Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=2394)</th>
<th>Placebo (N=2393)</th>
<th>Overall (N=4787)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (Q1-Q3)</td>
<td>64.0 (58.0-70.0)</td>
<td>64.0 (58.0-70.0)</td>
<td>64.0 (58.0-70.0)</td>
<td>0.64</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>852 (35.6%)</td>
<td>877 (36.6%)</td>
<td>1729 (36.1%)</td>
<td>0.45</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>2109 (88.1%)</td>
<td>2086 (87.2%)</td>
<td>4195 (87.6%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Westernized Region, n (%)</td>
<td>1747 (73.0%)</td>
<td>1749 (73.1%)</td>
<td>3496 (73.0%)</td>
<td>0.93</td>
</tr>
<tr>
<td>CV Risk Category, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>Established Cardiovascular Disease</td>
<td>1202 (50.2%)</td>
<td>1199 (50.1%)</td>
<td>2401 (50.2%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes + Risk Factors</td>
<td>1192 (49.8%)</td>
<td>1194 (49.9%)</td>
<td>2386 (49.8%)</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe Use, n (%)</td>
<td>124 (5.2%)</td>
<td>127 (5.3%)</td>
<td>251 (5.2%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Statin Intensity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Low</td>
<td>205 (8.6%)</td>
<td>203 (8.5%)</td>
<td>408 (8.5%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1494 (62.4%)</td>
<td>1531 (64.0%)</td>
<td>3025 (63.2%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>686 (28.7%)</td>
<td>645 (27.0%)</td>
<td>1331 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>9 (0.4%)</td>
<td>14 (0.6%)</td>
<td>23 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²), Median (Q1-Q3)</td>
<td>32.0 (28.5-35.8)</td>
<td>31.9 (28.6-36.0)</td>
<td>32.0 (28.6-36.0)</td>
<td>0.82</td>
</tr>
<tr>
<td>Triglycerides (mg/dL), Median (Q1-Q3)</td>
<td>217.0 (177.0-271.5)</td>
<td>217.0 (176.0-275.5)</td>
<td>217.0 (176.5-274.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>HDL-C (mg/dL), Median (Q1-Q3)</td>
<td>39.5 (34.5-45.3)</td>
<td>40.0 (34.5-46.0)</td>
<td>39.6 (34.5-45.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>LDL-C (mg/dL), Median (Q1-Q3)</td>
<td>73.0 (60.0-87.0)</td>
<td>75.0 (62.0-89.0)</td>
<td>74.0 (61.0-88.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides Category, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>&lt;150 mg/dL</td>
<td>249 (10.4%)</td>
<td>234 (9.8%)</td>
<td>483 (10.1%)</td>
<td></td>
</tr>
<tr>
<td>150 to &lt;200 mg/dL</td>
<td>693 (28.9%)</td>
<td>696 (29.1%)</td>
<td>1389 (29.0%)</td>
<td></td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>1449 (60.5%)</td>
<td>1462 (61.1%)</td>
<td>2911 (60.8%)</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL), Median (Q1-Q3)</td>
<td>139.0 (117.0-169.0)</td>
<td>138.0 (115.0-171.0)</td>
<td>139.0 (116.0-170.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>HbA1c (%), Median (Q1-Q3)</td>
<td>7.0 (6.3-7.8)</td>
<td>7.0 (6.3-7.9)</td>
<td>7.0 (6.3-7.9)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

### Number of Baseline Anti-Diabetes Medications: Diabetes Subgroup

<table>
<thead>
<tr>
<th>Anti-Diabetes Medications Taken at Baseline, n (%)</th>
<th>Icosapent Ethyl (N=2394)</th>
<th>Placebo (N=2393)</th>
<th>Overall (N=4787)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Anti-Diabetes Medications</td>
<td>221 (9.2)</td>
<td>208 (8.7)</td>
<td>429 (9.0)</td>
</tr>
<tr>
<td>Anti-Diabetes Medications</td>
<td>2173 (90.8)</td>
<td>2185 (91.3)</td>
<td>4358 (91.0)</td>
</tr>
<tr>
<td>One Anti-Diabetes Medication</td>
<td>951 (39.7)</td>
<td>1038 (43.4)</td>
<td>1989 (41.6)</td>
</tr>
<tr>
<td>Two Anti-Diabetes Medication</td>
<td>806 (33.7)</td>
<td>792 (33.1)</td>
<td>1598 (33.4)</td>
</tr>
<tr>
<td>Three Anti-Diabetes Medication</td>
<td>347 (14.5)</td>
<td>288 (12.0)</td>
<td>635 (13.3)</td>
</tr>
<tr>
<td>Four or more Anti-Diabetes Medications</td>
<td>69 (2.9)</td>
<td>67 (2.8)</td>
<td>136 (2.8)</td>
</tr>
</tbody>
</table>

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population with diabetes at baseline (N).

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

**Primary Composite Endpoint**

- **RR, 0.71**
  - (95% CI, 0.60–0.84)
  - P=0.00005

- **HR, 0.77**
  - (95% CI, 0.68–0.87)
  - P=0.000003

**Key Secondary Composite Endpoint**

- **RR, 0.71**
  - (95% CI, 0.60–0.84)
  - P=0.000005

- **HR, 0.70**
  - (95% CI, 0.60–0.81)
  - P=0.000003

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**Bhatt DL, Brinton EA, Miller M, et al. ADA 2020, Chicago (virtual).**

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.
First and Subsequent Events Full Dataset Diabetes Subgroup

Placebo (N=2393)

1st Events (N=536)

2nd Events (N=201)

≥3 Events (N=261)

Icosapent Ethyl (N=2394)

1st Events (N=433)

2nd Events (N=192)

≥3 Events (N=764)

Note: WLW method for the 1st events, 2nd events categories; Negative binomial model for ≥3 events and overall treatment comparison.
### Prespecified Hierarchical Testing: Diabetes Subgroup

<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>Relative Risk Reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Endpoint</td>
<td></td>
<td>433/2394 (18.1%)</td>
<td>536/2393 (22.4%)</td>
<td>0.77 (0.68–0.87)</td>
<td>23%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Key Secondary Composite Endpoint</td>
<td></td>
<td>286/2394 (11.9%)</td>
<td>391/2393 (16.3%)</td>
<td>0.70 (0.60–0.81)</td>
<td>30%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td></td>
<td>243/2394 (10.2%)</td>
<td>324/2393 (13.5%)</td>
<td>0.72 (0.61–0.85)</td>
<td>28%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td></td>
<td>147/2394 (6.1%)</td>
<td>212/2393 (8.9%)</td>
<td>0.67 (0.54–0.83)</td>
<td>33%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Urgent or Emergent Revascularization</td>
<td></td>
<td>136/2394 (5.7%)</td>
<td>173/2393 (7.2%)</td>
<td>0.76 (0.61–0.95)</td>
<td>24%</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td></td>
<td>123/2394 (5.1%)</td>
<td>151/2393 (6.3%)</td>
<td>0.79 (0.62–1.00)</td>
<td>21%</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td></td>
<td>72/2394 (3.0%)</td>
<td>74/2393 (3.1%)</td>
<td>0.96 (0.69–1.33)</td>
<td>4%</td>
<td>0.81</td>
</tr>
<tr>
<td>Fatal or Non-Fatal Stroke</td>
<td></td>
<td>62/2394 (2.6%)</td>
<td>92/2393 (3.8%)</td>
<td>0.65 (0.47–0.90)</td>
<td>35%</td>
<td>0.009</td>
</tr>
<tr>
<td>Total Mortality/Nonfatal Myocardial Infarction, or Nonfatal Stroke</td>
<td></td>
<td>335/2394 (14.0%)</td>
<td>435/2393 (18.2%)</td>
<td>0.73 (0.64–0.84)</td>
<td>27%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total Mortality</td>
<td></td>
<td>180/2394 (7.5%)</td>
<td>202/2393 (8.4%)</td>
<td>0.86 (0.71–1.06)</td>
<td>14%</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Time to First and Total Primary Endpoint Events by CV Risk Category and Diabetes Status at Baseline

**Patients without Established CVD With Diabetes and Other Risk Factors**
- RR, 0.88 (95% CI, 0.68–1.15) P=0.35
- HR, 0.88 (95% CI, 0.70–1.10) P=0.24

**Patients with Established CVD With Diabetes**
- RR, 0.70 (95% CI, 0.59–0.84) P=0.00009
- HR, 0.72 (95% CI, 0.62–0.84) P=0.00003

**Patients with Established CVD Without Diabetes**
- RR, 0.59 (95% CI, 0.49–0.70) P=0.000000007
- HR, 0.73 (95% CI, 0.62–0.85) P=0.00006

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

Safety: Diabetes Subgroup

Safety was generally consistent with the full study, including increases in atrial fibrillation/flutter (3.5% vs 2.2%; p=0.01) and bleeding (13.1% vs 10.9%; p=0.02).

Serious bleeding was not significantly different (3.2% vs 2.5%; p=0.19).

There were no meaningful between-group differences in HbA1c or glucose control across study visits, including placebo-corrected median changes from baseline to year 1 for HbA1c (0%, p=0.19) and glucose (-0.06 mmol/L, p=0.34).
Limitations

The study was not powered for subgroup analyses.

While cardiovascular risk category (established cardiovascular disease or diabetes plus risks) were stratification factors, the presence of diabetes within the established cardiovascular disease cohort was not.

These data include both pre-specified and post hoc analyses.

The study was not designed for in-depth biomarker analyses. Glucose and HbA1c were infrequently collected, generally on an annual basis.
Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced both first and total primary endpoint events in patients with diabetes at baseline by 23% and 24%, respectively.

For the key secondary endpoint of hard MACE, reductions for first and total events were 30% and 29%, respectively.

Reductions were consistent and robust across the prespecified hierarchy of endpoints, among patients with diabetes with or without cardiovascular disease, as well as those with established CVD and no diabetes at baseline.

These data highlight the substantial impact of icosapent ethyl on the underlying atherothrombotic burden in the at-risk REDUCE-IT population, both in those with but also in those without diabetes mellitus.
We thank the investigators, the study coordinators, and especially the 8,179 patients in REDUCE-IT!