EPA Levels and Cardiovascular Outcomes in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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Disclosures

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REDUCE-IT was sponsored by Amarin Pharma, Inc.
**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 Randomization 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**
- Year
- Months: -1 Month
- Visit: 1
- Lab values: Screening

**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

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*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

Key Secondary Composite Endpoint:
CV Death, MI, Stroke

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Icosapent Ethyl</strong></td>
<td>0.75</td>
<td>24.8%</td>
<td>4.8%</td>
<td>21</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>0.75</td>
<td>28.3%</td>
<td>4.8%</td>
<td>28</td>
</tr>
</tbody>
</table>

P=0.00000001

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

P=0.0000006

RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
### First and Subsequent Events – Full Data

<table>
<thead>
<tr>
<th>Event Type</th>
<th>No. of Events</th>
<th>Placebo [N=4090]</th>
<th>Icosapent Ethyl [N=4089]</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Events</td>
<td>901</td>
<td></td>
<td>705</td>
<td>-196</td>
</tr>
<tr>
<td>2nd Events</td>
<td>463</td>
<td></td>
<td>299</td>
<td>-164</td>
</tr>
<tr>
<td>3rd Events</td>
<td>176</td>
<td></td>
<td>85</td>
<td>-99</td>
</tr>
<tr>
<td>≥4 Events</td>
<td>184</td>
<td></td>
<td>96</td>
<td>-80</td>
</tr>
</tbody>
</table>

**Full Dataset Event No.**

- **Placebo [N=4090]**
  - 1st Events: 901
  - 2nd Events: 463
  - 3rd Events: 176
  - ≥4 Events: 184

- **Icosapent Ethyl [N=4089]**
  - 1st Events: 705
  - 2nd Events: 299
  - 3rd Events: 85
  - ≥4 Events: 96

**RR 0.69** (95% CI, 0.61-0.77)  
P=0.0000000004

**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.
# Primary and Key Secondary Composite Endpoints by Baseline Serum EPA Tertiles

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Composite Endpoint (ITT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline EPA Tertiles (median) µg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 µg/mL</td>
<td>230/1199 (19.2%)</td>
<td>283/1161 (24.4%)</td>
<td>0.75 (0.63-0.90)</td>
<td>0.91</td>
</tr>
<tr>
<td>&gt;20–34 µg/mL</td>
<td>203/1135 (17.9%)</td>
<td>263/1217 (21.6%)</td>
<td>0.79 (0.66-0.95)</td>
<td></td>
</tr>
<tr>
<td>&gt;34 µg/mL</td>
<td>203/1195 (17.0%)</td>
<td>255/1155 (22.1%)</td>
<td>0.75 (0.63-0.91)</td>
<td></td>
</tr>
</tbody>
</table>

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Primary and Key Secondary Composite Endpoints by Baseline Serum EPA Tertiles

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 µg/mL</td>
<td>705/4089 (17.2%)</td>
<td>901/4090 (22.0%)</td>
<td>0.75 (0.68-0.83)</td>
<td>0.91</td>
</tr>
<tr>
<td>&gt;20–34 µg/mL</td>
<td>14</td>
<td>230/1199 (19.2%)</td>
<td>0.75 (0.63-0.90)</td>
<td></td>
</tr>
<tr>
<td>&gt;34 µg/mL</td>
<td>48</td>
<td>203/1195 (17.0%)</td>
<td>0.79 (0.66-0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Key Secondary Composite Endpoint (ITT)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline EPA Tertiles (median) µg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 µg/mL</td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65-0.83)</td>
<td>0.90</td>
</tr>
<tr>
<td>&gt;20–34 µg/mL</td>
<td>14</td>
<td>157/1199 (13.1%)</td>
<td>0.76 (0.61-0.93)</td>
<td></td>
</tr>
<tr>
<td>&gt;34 µg/mL</td>
<td>48</td>
<td>125/1135 (11.0%)</td>
<td>0.74 (0.59-0.94)</td>
<td></td>
</tr>
<tr>
<td>Icosapent Ethyl Better</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo Better</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
## Levels of Eicosapentaenoic Acid (EPA) in Serum

<table>
<thead>
<tr>
<th>Visit</th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>Between Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median Observed Values (µg/mL)</td>
<td>Median Absolute Change from Baseline</td>
<td>Median % Change from Baseline</td>
</tr>
<tr>
<td>Baseline</td>
<td>26.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>144</td>
<td>112.6</td>
<td>393.5</td>
</tr>
<tr>
<td>Year 2</td>
<td>169</td>
<td>137.3</td>
<td>478.6</td>
</tr>
<tr>
<td>Year 3</td>
<td>168</td>
<td>137.4</td>
<td>464.5</td>
</tr>
<tr>
<td>Year 4</td>
<td>162</td>
<td>132.6</td>
<td>452.1</td>
</tr>
<tr>
<td>Year 5</td>
<td>158</td>
<td>130.5</td>
<td>463.6</td>
</tr>
<tr>
<td>Last Visit</td>
<td>150</td>
<td>117.9</td>
<td>395.2</td>
</tr>
<tr>
<td>On-Treatment EPA Daily Average (derived)</td>
<td>135.2</td>
<td>103.9</td>
<td>363.9</td>
</tr>
</tbody>
</table>

Year 6 values are not included as the number of patients = 9.

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
## Impact on the HR of Between-group Biomarker Differences (Icosapent Ethyl vs Placebo)

<table>
<thead>
<tr>
<th>Overall Trial</th>
<th>Primary Composite Endpoint</th>
<th>Key Secondary Composite Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td><strong>Significance P-value</strong></td>
<td><strong>HR (95% CI)</strong></td>
</tr>
<tr>
<td>Overall Trial</td>
<td>0.75 (0.68–0.83)</td>
<td>0.74 (0.65–0.83)</td>
</tr>
<tr>
<td>Lipid/Biomarker Covariate</td>
<td>HR (95% CI) for Treatment Comparison (Adjusting Covariate)</td>
<td>Significance P-value</td>
</tr>
<tr>
<td>EPA (µg/mL)</td>
<td>1.03 (0.91–1.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>0.77 (0.70–0.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C derived (mg/dL)</td>
<td>0.75 (0.68–0.83)</td>
<td>0.80</td>
</tr>
<tr>
<td>HDL Cholesterol-CDC (mg/dL)</td>
<td>0.73 (0.66–0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-HDL Cholesterol (mg/dL)</td>
<td>0.78 (0.71–0.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>0.76 (0.69–0.84)</td>
<td>0.03</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>0.76 (0.69–0.84)</td>
<td>0.004</td>
</tr>
<tr>
<td>RLP-C (mg/dL)</td>
<td>0.78 (0.71–0.87)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
## Stratified Analysis of Time to Primary Endpoint by Adjusting Time-Varying Covariates of Post-Baseline Biomarkers

<table>
<thead>
<tr>
<th>Lipid/Biomarker Covariate</th>
<th>Overall Trial</th>
<th>Primary Composite Endpoint</th>
<th>Key Secondary Composite Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>Significance P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Overall Trial</td>
<td>0.75 (0.68–0.83)</td>
<td>0.000000001</td>
<td>0.74 (0.65–0.83)</td>
</tr>
<tr>
<td>Lipid/Biomarker Covariate</td>
<td>HR (95% CI) for Treatment Comparison (Adjusting Covariate)</td>
<td>Significance P-value</td>
<td>HR (95% CI) for Treatment Comparison (Adjusting Covariate)</td>
</tr>
<tr>
<td>EPA (µg/mL)</td>
<td>1.03 (0.91–1.16)</td>
<td>&lt;0.0001</td>
<td>0.98 (0.84–1.14)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>0.77 (0.70–0.85)</td>
<td>&lt;0.0001</td>
<td>0.75 (0.66–0.85)</td>
</tr>
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<td>LDL-C derived (mg/dL)</td>
<td>0.75 (0.68–0.83)</td>
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Primary and Key Secondary CompositeEndpoints, Cardiovascular Death, andTotal Mortality by On-Treatment Serum EPA

Primary Endpoint\footnote{1-5}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{primary_endpoint_graph.png}
\caption{Dose-response hazard ratio and 95% CI for AUC-derived daily average serum EPA (µg/mL) vs. primary endpoint.}
\end{figure}

| No. of Patients | 5196 | 2400 | 756 | 87 | 10 |

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
AUC-Derived Daily Average EPA (µg/mL) & 26 & 100 & 200 & 300 & 400 \\
\hline
Hazard Ratio & Reference to EPA = 26 µg/mL & 2.0 & 0.2 & 0.4 & 0.6 & 0.8 & 1.0 & 1.2 & 1.4 & 1.6 & 1.8 & 2.0 \\
\hline
95% CI & 1.0 & 2.0 & 0.2 & 0.4 & 0.6 & 0.8 & 1.0 & 1.2 & 1.4 & 1.6 & 1.8 & 2.0 \\
\hline
\end{tabular}
\caption{Dose-response hazard ratio and 95% CI for AUC-derived daily average serum EPA (µg/mL) vs. primary endpoint.}
\end{table}

\textbf{P*<0.001}

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\footnote{1}, age\footnote{2}, sex\footnote{3}, baseline diabetes\footnote{4}, hsCRP\footnote{5}, treatment compliance\footnote{6}.

\footnote{P value is <0.001 for both non-linear trend and for regression slope.}

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA

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.

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Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA

Primary Endpoint$^{1-5}$

Key Secondary Endpoint$^{1-5}$

Cardiovascular Death$^{1,2,4-6}$

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>5196</th>
<th>2400</th>
<th>756</th>
<th>87</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC-Derived Daily Average EPA (µg/mL)</td>
<td>26</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>Hazard Ratio: Reference to EPA = 26 µg/mL</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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$^1$, age$^2$, sex$^3$, baseline diabetes$^4$, hsCRP$^5$, treatment compliance$^6$.

$^*$P value is $<0.001$ for both non-linear trend and for regression slope.

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Primary and Key Secondary Composite Endpoints, Cardiovascular Death, and Total Mortality by On-Treatment Serum EPA

Primary Endpoint

Key Secondary Endpoint

Cardiovascular Death

Total Mortality

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<tr>
<th>No. of Patients</th>
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<th>87</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td>AUC-Derived Daily Average EPA (µg/mL)</td>
<td>5212</td>
<td>2442</td>
<td>771</td>
<td>89</td>
<td>11</td>
</tr>
</tbody>
</table>

Hazard Ratio: Reference to EPA = 26 µg/mL

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, treatment compliance.

*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

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, baseline diabetes, hsCRP, statin compliance, age. *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

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 sex¹, baseline diabetes², hsCRP², statin compliance³, age⁵. *P value is <0.001 for both non-linear trend and for regression slope.

P<0.001 for all

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

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.

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Dose-Response of Hazard Ratio (95% CI)

Any Myocardial Infarction, Any Stroke, Coronary Revascularization, Unstable Angina by On-Treatment Serum EPA

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, baseline diabetes, hsCRP, statin compliance, age. *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

P*<0.001

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. *P value is <0.001 for both non-linear trend and for regression slope.

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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

No. of Patients

26 100 200 300 400

Hazard Ratio: Reference to EPA = 26 µg/mL

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.

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Dose-Response of Hazard Ratio (95% CI) Sudden Cardiac Death, Cardiac Arrest, New Heart Failure Requiring Hospitalization, New Heart Failure by On-Treatment Serum EPA

**Note:** On-treatment post baseline 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, baseline diabetes, and hsCRP, treatment compliance and age.

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Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Dose-Response of Hazard Ratio (95% CI) on Sudden Cardiac Death, Cardiac Arrest, New Heart Failure Requiring Hospitalization, New Heart Failure by On-Treatment Serum EPA

<table>
<thead>
<tr>
<th>AUC-Derived Daily Average EPA (µg/mL)</th>
<th>Sudden Cardiac Death 1-4</th>
<th>Cardiac Arrest 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>5226</td>
<td>5225</td>
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<tr>
<td>200</td>
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<td>2471</td>
</tr>
<tr>
<td>300</td>
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<td>94</td>
<td>93</td>
</tr>
<tr>
<td>26</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Hazard Ratio: Reference to EPA = 26 µg/mL

Dose-response hazard ratio and 95% CI estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance, baseline diabetes, and hsCRP, treatment compliance, age.

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Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Dose-Response of Hazard Ratio (95% CI)
Sudden Cardiac Death, Cardiac Arrest,
New Heart Failure Requiring Hospitalization,
New Heart Failure by On-Treatment Serum EPA

Note: On-treatment post baseline 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, baseline diabetes², and hsCRP³, treatment compliance⁴ age⁵.

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Bhatt DL. ACC/WCC 2020, Chicago (virtual).
Dose-Response of Hazard Ratio (95% CI)  
Sudden Cardiac Death, Cardiac Arrest, New Heart Failure Requiring Hospitalization, New Heart Failure by On-Treatment Serum EPA

**Note:** On-treatment post baseline 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, baseline diabetes, and hsCRP, treatment compliance, and age.

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Omega-3 fatty acid mixtures do not just contain EPA
  • EPA and DHA appear to have many differing biological effects in clinical studies and experimental models
  • Might explain lack of benefit of other omega-3 trials

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Contrasting Effects of **EPA** and **DHA**

**EPA**
- Preserves membrane structure and normal distribution of cholesterol
- Inhibits lipid oxidation and related cholesterol crystal formation
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**DHA**
- Increases membrane fluidity and promotes lipid domain changes
- Has reduced antioxidant activity due to lipid disordering effects
- Is concentrated in brain and retinal membranes

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced first and total cardiovascular events by 25% and 30%, respectively.
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On-treatment EPA levels via icosapent ethyl correlate strongly with the primary endpoint, the key secondary endpoint, CV death, MI, stroke, coronary revascularization, unstable angina, sudden cardiac death, cardiac arrest, new heart failure, and all-cause mortality.
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These data provide a mechanistic underpinning for the large risk reductions seen in multiple endpoints with icosapent ethyl in REDUCE-IT.

Bhatt DL. ACC/WCC 2020, Chicago (virtual).
We thank the investigators, the study coordinators, and especially the 8,179 patients in REDUCE-IT!
reduce-it
EPA

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