Patients with cardiovascular disease and elevated triglyceride levels face an increased risk of ischemic events and chronic kidney disease. This risk remains high despite the use of pharmacological treatment with statins or surgical interventions, including coronary artery bypass grafting (CABG) surgery.

Subanalyses of the ODYSSEY OUTCOMES and EMPA-REG OUTCOME trials demonstrate a significant residual ischemic risk in patients with a history of CABG despite intensive lipid-lowering (with PCSK9 inhibition) or SGLT2-inhibition therapy, respectively. This necessitates novel approaches to reduce ongoing ischemic risk in patients with CABG.

The multicenter, placebo-controlled, double-blind trial REDUCE-IT assesses the therapeutic effects of icosapent ethyl, a stable eicosapentaenoic acid ethyl ester, in such patients.

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Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)

8,179 statin treated patients

- Controlled low-density lipoprotein cholesterol (41-100 mg/dL)
- Mild to moderate hypertriglyceridemia (135-500 mg/dL)
- Diabetes or additional risk factors

Randomized to

Icosapent ethyl (4 g daily) Placebo

Assessment of major adverse cardiovascular events (MACE)

Primary efficacy endpoint composite

- Cardiovascular death
- Myocardial infarction
- Stroke
- Coronary revascularization
- Hospitalization for unstable angina

Secondary efficacy endpoint composite

Icosapent ethyl treatment versus placebo

- 25% risk reduction in primary endpoints
- 26% risk reduction in secondary endpoints

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Compared with placebo, randomization to icosapent ethyl was associated with a significant reduction in:

- **Primary endpoint**
- **Key secondary endpoint**
- **Total (first plus subsequent or recurrent) ischemic events**

This translated to an absolute risk reduction of **6.2%** in first events.

**Number needed to treat:** Over a median follow-up time of 4.8 years, 16 patients required treatment.

**Occurrences of adverse events** were comparable between groups.

For patients with a history of CABG, treatment with icosapent ethyl was associated with significant reductions in first and recurrent ischemic events.

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Further study to explore the effects of icosapent ethyl versus placebo across the range of kidney function among patients enrolled in the REDUCE-IT trial: REDUCE-IT RENAL

Among 8,179 statin treated patients

Estimated glomerular filtration rate (eGFR) categories

- <60 mL/min/1.73 m²: 23.3%
- 60 to <90 mL/min/1.73 m²: 22%
- ≥90 mL/min/1.73 m²: 54.5%

Patients treated with icosapent ethyl in this subgroup had the largest absolute and similar relative risk reduction for:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Icosapent ethyl</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>21.8%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Key secondary composite endpoints</td>
<td>16.8%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>7.6%</td>
<td>10.6%</td>
</tr>
</tbody>
</table>

Hazard risk of atrial fibrillation/flutter and serious bleeding was similar across all eGFR groups

Icosapent ethyl reduced fatal and nonfatal ischemic events across the broad range of baseline eGFR categories

Icosapent ethyl treatment in statin-treated patients with CVD and associated risk factors significantly decreases the risk of primary and recurrent ischemic events, regardless of their kidney function status

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