Diabetes and Cardiovascular Risk Management
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University of Maryland School of Medicine

Disclosures

- Amarin: Steering Committee: REDUCE IT trial
Learning Objectives

• Demonstrate screening recommendations for early detection
• Identify antihypertensive treatment approaches for adults with diabetes and hypertension
• Cite ADA lipid treatment guidelines
• Summarize the CV risk reduction noted in clinical trials of certain antihyperglycemic agents

Atherosclerotic Cardiovascular Disease

• Leading cause of morbidity and mortality in diabetes.
  – Coronary heart disease
  – Cerebrovascular disease
  – Peripheral arterial disease presumed to be of atherosclerotic origin
Focus on ASCVD

- Early assessment and targeted intervention needed to treat and prevent *all* ASCVD and diabetes risk factors
- Common conditions coexisting with type 2 diabetes are clear risk factors for ASCVD
  - Hypertension and dyslipidemia
  - Diabetes itself confers independent risk


Hypertension

Goals for most people with diabetes and hypertension

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>&lt;140 mmHg</td>
</tr>
<tr>
<td>Diastolic</td>
<td>&lt;90 mmHg</td>
</tr>
</tbody>
</table>

Lower targets (<130 mmHg, <80 mmHg) may be appropriate for certain individuals if it can be achieved without undue treatment burden.

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Population</th>
<th>Intensive</th>
<th>Standard</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD BP (16)</td>
<td>4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors</td>
<td>Systolic blood pressure target: &lt;120 mmHg</td>
<td>Systolic blood pressure target: 130–140 mmHg</td>
<td>• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death</td>
</tr>
<tr>
<td>ADVANCE BP (17)</td>
<td>11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors</td>
<td>Intervention: a single-pill, fixed-dose combination of perindopril and indapamide</td>
<td>Control: placebo</td>
<td>• Intervention reduced risk of primary composite and point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)</td>
</tr>
<tr>
<td>HOT (143)</td>
<td>18,790 participants, including 1,501 with diabetes</td>
<td>Diastolic blood pressure target: ≤80 mmHg</td>
<td>Diastolic blood pressure target: ≤90 mmHg</td>
<td>• In the overall trial, there was no cardiovascular benefit with more intensive targets</td>
</tr>
<tr>
<td>SPRING (144)</td>
<td>9,361 participants without diabetes</td>
<td>Systolic blood pressure target: &lt;120 mmHg</td>
<td>Systolic blood pressure target: &lt;140 mmHg</td>
<td>Intensive systolic blood pressure target lowered risk of the primary composite outcome 35% (MI, ACS, stroke, heart failure, and death due to CVD)</td>
</tr>
</tbody>
</table>

### Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

- **Initial BP between 140/90 mmHg and 160/100 mmHg**
  - Start one agent
  - **Lifestyle management**
  - **Start two agents**

- **Initial BP ≥ 160/100 mmHg**
  - Start one drug:
    - ACEI
    - ARB
    - CCB
    - Diuretic

- **Albuminuria**
  - **Start:**
    - ACEI or ARB
    - CCB
    - Diuretic

- **Assess BP Control and Adverse Effects**
  - Treatment tolerated and target achieved
  - Continue therapy
  - Not meeting target
  - Consider change to alternative medication:
    - ACEI or ARB
    - CCB
    - Diuretic

- **Add agent from complementary drug class**
  - Not meeting target or adverse effects using a drug from each of three classes
  - Continue therapy
  - **Consider Addition of Mineralocorticoid Receptor Antagonist**
  - Refer to Specialist With Expertise in BP Management
Lipid Management

Intensify lifestyle therapy and optimize glycemic control in patients with:

- Triglycerides $\geq 150 \text{ mg/dL}$; and/or
- Low HDL cholesterol
  - $<40 \text{ mg/dL}$ for men
  - $<50 \text{ mg/dL}$ for women

High- and Moderate-Intensity Statin Therapy

<table>
<thead>
<tr>
<th>High-intensity statin therapy (lowers LDL cholesterol by ≥50%)</th>
<th>Moderate-intensity statin therapy (lowers LDL cholesterol by 30 to 50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td>Pravastatin 40-80 mg</td>
<td>Pravastatin 40-80 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg</td>
<td>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

Note: Once-daily dosing. XL = extended release


Case Study

**Introduction**

- Mrs. M is a 47-year-old music teacher.
- She has diabetes and a 1-pack-week smoking history.
- Her HDL is 35 mg/dL and her LDL is 145 mg/dL.
- She has tried with little success to control her cholesterol with diet, she is not physically active and continues to smoke a pack a week.

Continued...
Discussion Question
What are Mrs. M’s CV risks factors and what would you recommend to curb her risk of ASCVD?
A. Smoking. Enroll her in a smoking cessation program
B. LDL ≥100 mg/dL and high intensity statin therapy
C. Age, gender and presence of diabetes. Recommend lifestyle therapy.
D. A, B and C
E. Family history, hypertension and obesity. Prescribe high intensity statin therapy.

Think-Pair-Share

• If Mrs. M was 52-years-old and had a father who suffered a stroke at age 65 years, how would this information alter your treatment recommendations?
Antiplatelet Agents

• Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD
• For patients with ASCVD and aspirin allergy, clopidogrel (75 mg/day) should be used.
• Dual antiplatelet therapy (aspirin + P2Y12 inhibitor) is reasonable for a year after acute coronary syndrome and may have benefits beyond this period.


Antiplatelet Agents

• Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with T1DM or T2DM at increased cardiovascular risk and not at increased risk of bleeding C
• Includes most men or women with diabetes age ≥50 years who have at least one additional major risk factor, including:
  - Family history of premature ASCVD
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria

Coronary Artery Disease

**Screening:**
- In asymptomatic patients, routine screening for CAD isn’t recommended and doesn’t improve outcomes, provided ASCVD risk factors are treated. A
- Consider investigations for CAD with:
  - Atypical cardiac symptoms
  - Signs/symptoms of associated vascular disease
  - EKG abnormalities

Pre-2008 Working Hypothesis
- DM $\rightarrow$ $\uparrow$ micro and macrovascular complications
- $\uparrow$ glucose is major physiologic problem in DM
- *Therefore $\downarrow$ glucose will improve DM and $\downarrow$ micro and macrovascular risk*
- So, 1st goal of DM therapy to $\downarrow$ glucose, regardless of mechanism
- True for microvascular complications and supported by T1DM data
Step 1: Assess cardiovascular disease

Presence of cardiovascular disease is compelling indication

If ASCVD Predominates:

**GLP-1 RA with proven cardiovascular benefit**
- Liraglutide > semaglutide > exenatide LAR

**SGLT2-i with proven cardiovascular benefit**
- Empagliflozin > canagliflozin
Among patients with ASCVD in whom HF coexists or is of concern, SGLT2 inhibitor are recommended

**Rationale:** Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction

Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2-i trials

**Caveat:** trials were not designed to adjudicate heart failure

Majority of patients did not have clinical heart failure at baseline

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**Summary**

Consider the presence or absence of ASCVD, CKD and HF

Start with metformin if tolerated, then:

- In patients with ASCVD a GLP-1 RA or SGLT2-i is recommended
- In patients with ASCVD and HF SGLT2-i is recommended
- In patients with CKD, with or without ASCVD consider an SGLT2-i

Agents with proven benefit are preferred

ASCVD, CKD and HF affects choice of additional glucose lowering medication
Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD,
Eliot A. Brinton, MD, Terry A. Jacobson, 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, Christie M. Ballantyne,
MD, on Behalf of the REDUCE-IT Investigators

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;36:774-77.
Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>1121 (2.9)</td>
<td>1155 (3.0)</td>
<td>0.97 (0.87–1.08)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>1301 (3.3)</td>
<td>1394 (3.6)</td>
<td>0.93 (0.83–1.03)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3085 (7.9)</td>
<td>3188 (8.2)</td>
<td>0.96 (0.90–1.01)</td>
<td>0.12</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>574 (1.9)</td>
<td>554 (1.8)</td>
<td>1.03 (0.86–1.21)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>117 (0.4)</td>
<td>109 (0.4)</td>
<td>1.07 (0.76–1.51)</td>
<td></td>
</tr>
<tr>
<td>Unclassified/other</td>
<td>142 (0.4)</td>
<td>135 (0.3)</td>
<td>1.05 (0.77–1.43)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>670 (2.2)</td>
<td>843 (2.2)</td>
<td>1.03 (0.95–1.13)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Revascularization

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td>3044 (9.3)</td>
<td>3040 (9.3)</td>
<td>1.00 (0.93–1.07)</td>
<td></td>
</tr>
<tr>
<td>Noncoronary</td>
<td>305 (2.7)</td>
<td>330 (2.9)</td>
<td>0.92 (0.75–1.13)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3290 (10.0)</td>
<td>3313 (10.2)</td>
<td>0.99 (0.94–1.04)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Any major vascular event

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratios (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5930 (15.2)</td>
<td>6071 (15.6)</td>
<td>0.97 (0.93–1.01)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing 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.

Adapted with permission from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks. Meta-analysis of 10 trials involving 77917 individuals. JAMA Cardiol. 2018;3:225-234. [https://creativecommons.org/licenses/by-nc/4.0/]

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Inclusion Criteria for Secondary Prevention Cohort

One or more of the following:

1. Documented coronary artery disease
   - Multi vessel CAD (≥50% stenosis in ≥2 major epicardial coronary arteries – with or without antecedent revascularization
   - Prior MI
   - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome with ST-segment deviation or biomarker positivity

2. Documented cerebrovascular or carotid disease
   - Prior ischemic stroke
   - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
   - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis
   - History of carotid revascularization

3. Documented peripheral artery disease
   - Ankle-brachial index <0.9 with symptoms of intermittent claudication
   - History of aorto-iliac or peripheral artery intervention

Inclusion Criteria for Primary Prevention Cohort

1. Diabetes mellitus requiring medication AND
2. ≥50 years of age AND
3. ≥1 additional risk factor for CVD
   - Men ≥55 years and women ≥65 years
   - Cigarette smoker or stopped smoking within 3 months
   - Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;
   - HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
   - hsCRP >3.0 mg/L
   - Renal dysfunction: Creatinine clearance >30 and <60 mL/min
   - Retinopathy
   - Micro- or macroalbuminuria
   - ABI <0.9 without symptoms of intermittent claudication

Patterns with diabetes and CVD are counted under Secondary Prevention Cohort.
Key Exclusion Criteria

1. Severe (NYHA class IV) heart failure
2. Severe liver disease
3. History of pancreatitis
4. Hypersensitivity to fish and/or shellfish

Key Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Median (Q1-Q3)</td>
<td>64.0 (57.0 - 69.0)</td>
<td>64.0 (57.0 - 69.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1162 (28.4%)</td>
<td>1195 (29.2%)</td>
</tr>
<tr>
<td>Non-White, n (%)</td>
<td>398 (9.7%)</td>
<td>410 (9.8%)</td>
</tr>
<tr>
<td>Westernized Region, n (%)</td>
<td>2906 (71.1%)</td>
<td>2905 (71.0%)</td>
</tr>
<tr>
<td>CV Risk Category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Prevention Cohort</td>
<td>2892 (70.7%)</td>
<td>2893 (70.7%)</td>
</tr>
<tr>
<td>Primary Prevention Cohort</td>
<td>1197 (29.3%)</td>
<td>1197 (29.3%)</td>
</tr>
<tr>
<td>Ezetimibe Use, n (%)</td>
<td>262 (6.4%)</td>
<td>262 (6.4%)</td>
</tr>
<tr>
<td>Statin Intensity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>254 (6.2%)</td>
<td>267 (6.5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2533 (61.9%)</td>
<td>2575 (63.0%)</td>
</tr>
<tr>
<td>High</td>
<td>1290 (31.5%)</td>
<td>1226 (30.0%)</td>
</tr>
<tr>
<td>Type 2 Diabetes, n (%)</td>
<td>2367 (57.9%)</td>
<td>2363 (57.8%)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL), Median (Q1-Q3)</td>
<td>216.5 (176.5 - 272.0)</td>
<td>216.0 (175.5 - 274.0)</td>
</tr>
<tr>
<td>HDL-C (mg/dL), Median (Q1-Q3)</td>
<td>40.0 (34.5 - 46.0)</td>
<td>40.0 (35.0 - 46.0)</td>
</tr>
<tr>
<td>LDL-C (mg/dL), Median (Q1-Q3)</td>
<td>74.0 (61.5 - 88.0)</td>
<td>76.0 (63.0 - 89.0)</td>
</tr>
<tr>
<td>Triglycerides Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 mg/dL</td>
<td>412 (10.1%)</td>
<td>429 (10.5%)</td>
</tr>
<tr>
<td>150 to &lt;200 mg/dL</td>
<td>1193 (29.2%)</td>
<td>1191 (29.1%)</td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>2481 (60.7%)</td>
<td>2469 (60.4%)</td>
</tr>
</tbody>
</table>
Effects on Biomarkers from Baseline to Year 1

<table>
<thead>
<tr>
<th>Biomarker*</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Absolute Change from Baseline</th>
<th>% Change from Baseline</th>
<th>% Change P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>216.5</td>
<td>175.0</td>
<td>216.0</td>
<td>221.0</td>
<td>-44.5</td>
<td>-19.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>118.0</td>
<td>113.0</td>
<td>118.5</td>
<td>130.0</td>
<td>-15.5</td>
<td>-13.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>74.0</td>
<td>77.0</td>
<td>76.0</td>
<td>84.0</td>
<td>-5.0</td>
<td>-6.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>40.0</td>
<td>39.0</td>
<td>40.0</td>
<td>42.0</td>
<td>-2.5</td>
<td>-6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log hsCRP (mg/L)</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
<td>-0.4</td>
<td>-22.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EPA (µg/mL)</td>
<td>26.1</td>
<td>144.0</td>
<td>26.1</td>
<td>23.3</td>
<td>+114.9</td>
<td>+358.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Apo B and hsCRP were measured at Year 2.

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

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
**Key Secondary End Point:**
CV Death, MI, Stroke

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

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**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>Primary Composite (ITT)</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>Key Secondary Composite (ITT)</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>Cardiovascular Death or Nonfatal Myocardial Infarction</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>Fatal or Nonfatal Myocardial Infarction</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>Urgent or Emergent Revascularization</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>Cardiovascular Death</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>Hospitalization for Unstable Angina</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>Fatal or Nonfatal Stroke</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>Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke</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>Total Mortality</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>
### Treatment-Emergent Adverse Event of Interest: Serious 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>Bleeding related disorders</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>
</tbody>
</table>

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 icosapent ethyl versus 10 placebo; P=0.55)
Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced important CV events by 25%, including:

- 20% reduction in death due to cardiovascular causes
- 31% reduction in heart attack
- 28% reduction in stroke

Low rate of adverse effects, including:

- Small but significant increase in atrial fibrillation/flutter
- Non-statistically significant increase in serious bleeding

Consistent efficacy across multiple subgroups

- Including baseline triglycerides from 135-500 mg/dL
- Including secondary and primary prevention cohorts
Summary: Cardiovascular Risk

• Assess a patient’s cardiovascular risk at least annually in all patients with diabetes
• Antihypertensive therapy can reduce ASCVD events, heart failure, and microvascular complications
• Statin therapy has beneficial effects on ASCVD outcomes
• Aspirin is effective in reducing CV morbidity and mortality in high-risk patients with previous MI/stroke
• Certain antihyperglycemic therapies can reduce major adverse CV events and mortality

Helpful Resources
Professional Education

- Free online continuing education on cardiovascular risk – including hypertension self-assessment program

Professional.Diabetes.org/CE

Thank You!