Effect of Icosapent Ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: the EVAPORATE study

NCT02926027

Matthew Budoff MD
Professor of Medicine
UCLA School of Medicine
Lundquist Institute
Torrance CA
I would Like to thank my Collaborators:

Joseph B. Muhlestein MD,²
Deepak L. Bhatt MD, MPH,³
Viet T Le PA, MPAS,²,⁵
Heidi T May, PhD, MSPH ²
Kashif Shaikh MD,¹
Chandana Shekar MD,¹
April Kinniger MS,¹
Suvasini Lakshmanan, MD, MS,¹
Sion Roy MD,¹
John Tayek MD,¹
John R Nelson MD.⁴

1. Department of Medicine, Lundquist Institute at Harbor-UCLA Medical Center, Torrance CA
2. Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City UT
3. Brigham and Women’s Hospital Heart & Vascular Center and Harvard Medical School, Boston, Massachusetts;
4. California Cardiovascular Institute, Fresno CA
5. Rocky Mountain University of Health Profession, Provo UT
DISCLOSURES

- Dr Matthew J. Budoff discloses the following relationships: Research Funding: Amarin Pharma, Amgen, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Pfizer, Regeneron. Speakers Bureau: Amarin Pharma, Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingleheim, Novo Nordisk, Pfizer, Regeneron, Sanofi Aventis.

- Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, RegadoBiosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: BaimInstitute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, 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), BaimInstitute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by BoehringerIngelheim), 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), 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), 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); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, BoehringerIngelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Dynacap, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLxPharma, Takeda.

- This presentation includes off-label and/or investigational uses of drugs.

- Amarin Pharma Inc (Bridgewater NJ) provided funding and drug for The EVAPORATE trial.
Plaque Progression by CT Angiography
### TABLE 4 Cardiac Events After CTA-2

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th></th>
<th></th>
<th>Multivariable</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.94-1.06)</td>
<td>0.85</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.32 (0.24-24.55)</td>
<td>0.78</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.59 (0.39-10.70)</td>
<td>0.54</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.13 (0.24-4.27)</td>
<td>0.87</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.86 (0.22-4.06)</td>
<td>0.83</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;25 kg/m²</td>
<td>5.58 (1.46-26.52)</td>
<td>0.012</td>
<td>3.27 (0.66-24.42)</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.35 (0.62-9.51)</td>
<td>0.20</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous ACS</td>
<td>6.26 (1.15-116.32)</td>
<td>0.032</td>
<td>8.35 (1.06-209.55)</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin use</td>
<td>1.11 (0.27-7.44)</td>
<td>0.90</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain at CTA-2</td>
<td>3.09 (0.65-11.73)</td>
<td>0.14</td>
<td>1.00 (0.95-1.08)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRP at CTA-1</td>
<td>4.40 (1.08-16.67)</td>
<td>0.039</td>
<td>0.85 (0.07-9.01)</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRP at CTA-2</td>
<td>9.07 (2.38-43.11)</td>
<td>0.0014</td>
<td>2.18 (0.20-27.78)</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque progression</td>
<td>61.32 (11.24-1,137.73)</td>
<td>&lt;0.000</td>
<td>33.43 (4.13-78.03)</td>
<td>0.0006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 2.
Effect of Testosterone on Coronary Artery Plaque Volume

- Noncalcified: p=0.003
- Total: p=0.006
- Low Attenuation: p=0.14
- Fibrous Fatty: p=0.11
- Fibrous: p=0.01
- Dense Calcium: p=0.51

Placebo (n=65) vs. Testosterone (n=73)
Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
Effect of Vascepa (icosapent ethyl) on progression of coronary atherosclerosis in patients with elevated triglycerides (200–499 mg/dL) on statin therapy: Rationale and design of the EVAPORATE study

Matthew Budoff¹ | J. Brent Muhlestein²,³ | Viet T. Le² | Heidi T. May² | Sion Roy¹ | John R. Nelson⁴
EVAPORATE: Effect of EPA on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy

Randomized, Double-Blind, Placebo-Controlled Trial

Patient Population (N=80)
- 30–85 years of age
- TG: 135–499 mg/dL
- LDL-C >40 mg/dL and ≤115 mg/dL (on statin)
- ≥1 angiographic stenosis with ≥20% narrowing by CTA
- No history of MI, stroke, or life-threatening arrhythmia within the prior 6 months and no history of CABG

Primary endpoint
- Progression rates of low attenuation plaque

Secondary endpoints include
- Plaque morphology and composition
- (non-calcified, total, fibrous, fibrofatty, calcified)
- Markers of inflammation (Lp-PLA₂)
- LDL-C and HDL-C

The EVAPORATE study seeks to determine whether EPA 4 g/d will reduce plaque progression over 9 to 18 months compared to placebo in statin-treated patients

CABG=coronary artery bypass graft; CTA=computed tomography angiography.
INCLUSION CRITERIA

- Age $\geq 45$ years with atherosclerosis with at least one stenosis of 20%
- Fasting TG levels 135 to 499 mg/dL
- LDL-C $>40$ mg/dL and $\leq 115$ mg/dL and on stable statin therapy (±ezetimibe)
- eGFR $> 60$
METHODS

- Patients underwent baseline, 9 month and 18 month follow up CT angiogram
- Intention to Treat Analysis
- Semi-automated plaque analysis software (QAngioCT) Medis Medical Imaging Systems, Netherlands
The was a 2-look sequential design study, using the Lan-DeMets version of the O’Brien-Fleming group sequential boundaries (1 interim at 9-months + final analysis).

If a p-value of <0.006 was achieved at 9 months then the study would be terminated because the efficacy boundary will have had been achieved.

Here we present the pre-specified interim 9 month data.
CONSORT DIAGRAM

Screened N=106

Screen Fails N=26

Randomized N=80
75% of Screened

Icosapent Ethyl N=40
Completed Visit 3 N=30 (75.0%)
2 ODIS, 3 LTFU
3 Withdrawn, 2 uninterpretable

Placebo N=40
Completed Visit 3 N=37 (92.5%)
2 Withdrawn 1 LTFU
## Key Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Icosapent Ethyl (N=30)</th>
<th>Placebo (N=37)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean / Count</strong></td>
<td><strong>Std(%)</strong></td>
<td><strong>Mean / Count</strong></td>
<td><strong>Std(%)</strong></td>
</tr>
<tr>
<td>Age, years</td>
<td>55.6 (7.7)</td>
<td>58.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Male</td>
<td>16 (53%)</td>
<td>20</td>
<td>54%</td>
</tr>
<tr>
<td>BMI</td>
<td>34.4 (6.4)</td>
<td>33.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Time between Visit 1 and 3 (months)</td>
<td>9.4 (1.0)</td>
<td>9.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Ethnicity Hispanic</td>
<td>18 (60%)</td>
<td>19</td>
<td>51%</td>
</tr>
<tr>
<td>Race, White</td>
<td>27 (90%)</td>
<td>29</td>
<td>78%</td>
</tr>
<tr>
<td>Aspirin Use</td>
<td>14 (47%)</td>
<td>22</td>
<td>59%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>22 (73%)</td>
<td>25</td>
<td>68%</td>
</tr>
<tr>
<td>Family History</td>
<td>8 (27%)</td>
<td>13</td>
<td>35%</td>
</tr>
<tr>
<td>Statin Use</td>
<td>30 (100%)</td>
<td>37</td>
<td>100%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (77%)</td>
<td>28</td>
<td>76%</td>
</tr>
<tr>
<td>Past Smoking</td>
<td>13 (43%)</td>
<td>16</td>
<td>43%</td>
</tr>
</tbody>
</table>


Primary Outcome (ITT)

• At 9 Month Prespecified Interim Analysis, compared with placebo, **Icosapent Ethyl** slowed progression by:

  - **21%** for low attenuation plaque (p=0.469)
  - **19%** for total non-calcified plaque (p=0.010)
  - **42%** for total plaque (p=0.0004)
  - **57%** for fibrous plaque (p=0.011)
  - **89%** for calcified plaque (p=0.001)
  - Increase in Fibrofatty plaque (p=0.650)

• Consistent efficacy across multiple subgroups
• Including baseline triglycerides from 135-499 mg/dL
Fully adjusted median Plaque Progression at 9 months

- Low Attenuated Plaque: 94% Placebo, 74% Icosapent Ethyl (P=0.469)
- Total Non-Calcified Plaque: 43% Placebo, 35% Icosapent Ethyl (P=0.010)
- Total Plaque: 26% Placebo, 15% Icosapent Ethyl (P=0.0004)
- Fibro-fatty: 25% Placebo, 25% Icosapent Ethyl (P=0.650)
- Fibrous: 40% Placebo, 17% Icosapent Ethyl (P=0.011)
- Calcification: 9% Placebo, 1% Icosapent Ethyl (P=0.001)
PLACEBO RATES OF PROGRESSION

Adjusted multivariate analysis of covariance tests did not show any significant difference in progression of TP volume (β: 0.04 ± 0.13 P = 0.7) or TNCP volume (β: 0.09 ± 0.17, P = 0.5) in the two groups.
LIMITATIONS

- Primary Endpoint not significant at interim timepoint – study will continue to 18 months as planned
- Shorter Follow up than Prior CTA Studies (9 months)
- 4 endpoints demonstrated significant slowing of progression, including both total plaque and total non-calcified plaque volumes
- Small cohort with expected 16% drop-out
- (due to patient preference, loss to follow up and non-diagnostic CT at follow up)
EVAPORATE: Conclusions

- Mechanistic Study using serial Coronary CT Angiography demonstrating atherosclerotic benefits of Icosapent Ethyl as adjunct to statin on plaque characteristics at 9 months, and study is continuing to 18 months as planned.

- Demonstrated that placebo progression rates using mineral oil is similar to non-mineral oil (cellulose) using same methodology, scanner and laboratory in a matched cohort.