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

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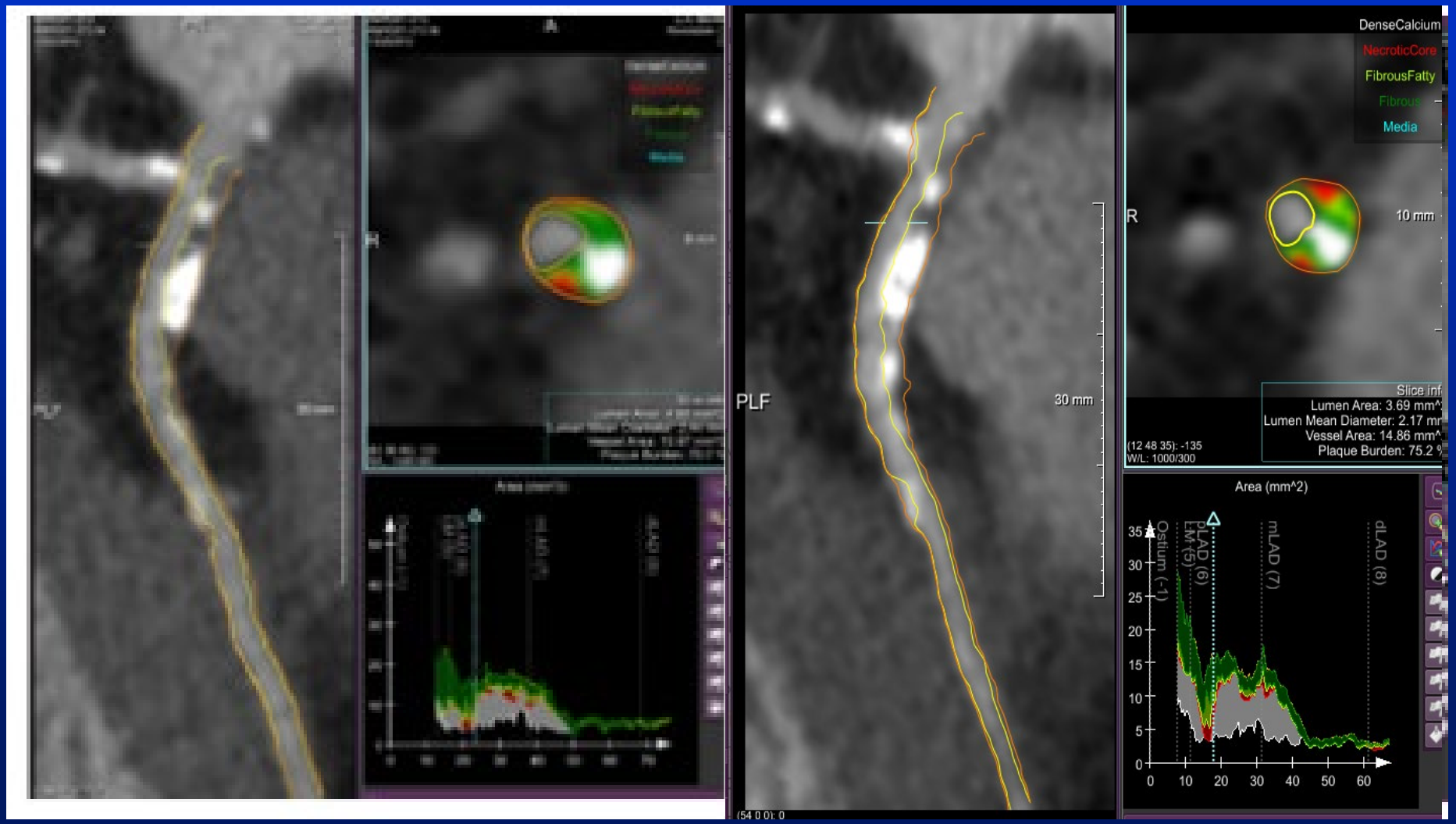
- **•This presentation includes off-label and/or investigational uses of drugs.**
- **•Amarin Pharma Inc (Bridgewater NJ) provided funding and drug for The EVAPORATE trial**.

Plaque Progression by CT Angiography



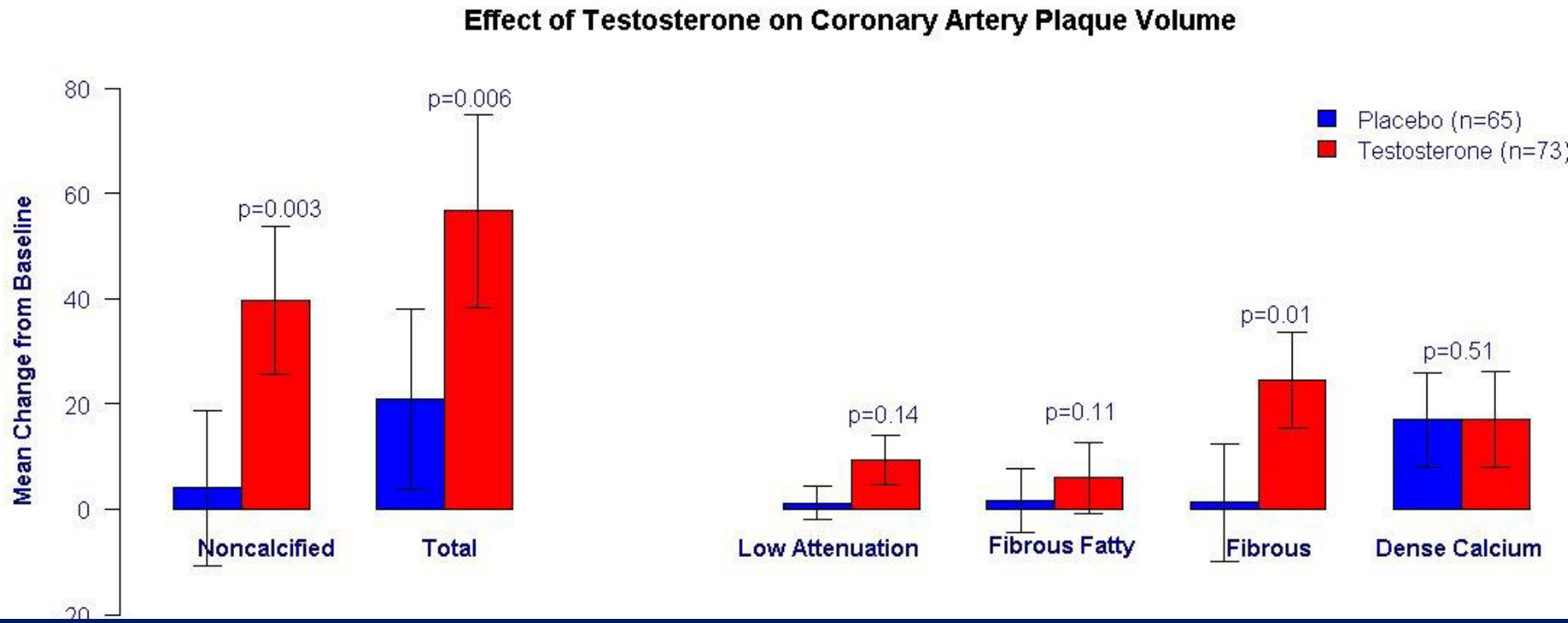
Plaque Progression and Events Motoyama JACC 2015

TABLE 4 Cardiac Events After CTA-2

	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	0.99 (0.94–1.06)	0.85	1.00 (0.95–1.08)	0.87
Male	1.32 (0.24–24.55)	0.78		
Hypertension	1.59 (0.39–10.70)	0.54		
Diabetes	1.13 (0.24–4.27)	0.87		
Dyslipidemia	0.86 (0.22–4.06)	0.83		
BMI >25 kg/m^2	5.58 (1.46–26.52)	0.012	3.27 (0.66–24.42)	0.15
Current smoking	2.35 (0.62–9.51)	0.20		
Previous ACS	6.26 (1.15–116.32)	0.032	8.35 (1.06–209.55)	0.043
Statin use	1.11 (0.27–7.44)	0.90		
Chest pain at CTA-2	3.09 (0.65–11.73)	0.14		
HRP at CTA-1	4.40 (1.08–16.67)	0.039	0.85 (0.07–9.01)	0.89
HRP at CTA-2	9.07 (2.38–43.11)	0.0014	2.18 (0.20–27.78)	0.51
Plaque progression	61.32 (11.24–1,137.73)	<0.0001	33.43 (4.13–78.03)	0.0006

Abbreviations as in Tables 1 and 2.

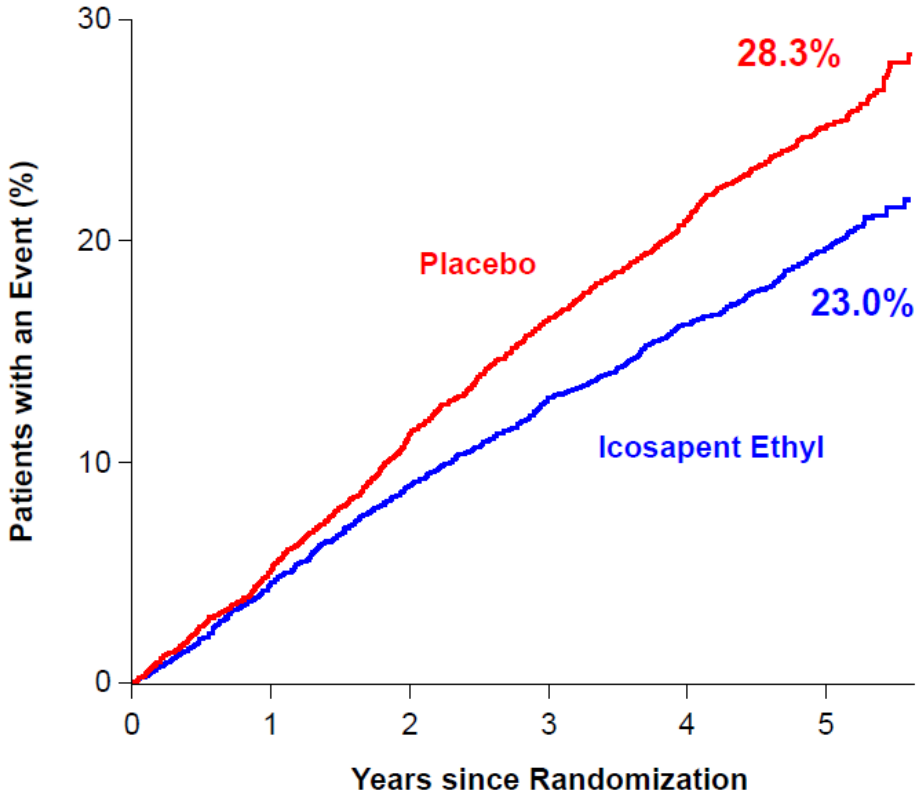
EFFECT OF TESTOSTERONE REPLACEMENT ON CORONARY PLAQUE VOLUME
BUDOFF et al. JAMA 2017



REDUCE IT – Bhatt et al NEJM

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75

(95% CI, 0.68–0.83)

EVAPORATE STUDY DESIGN

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WILEY CLINICAL CARDIOLOGY

TRIAL DESIGNS

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 Budoff[1] | J. Brent Muhlestein[2,3] | Viet T. Le[2] | Heidi T. May[2] | Sion Roy[1] | John R. Nelson[4]

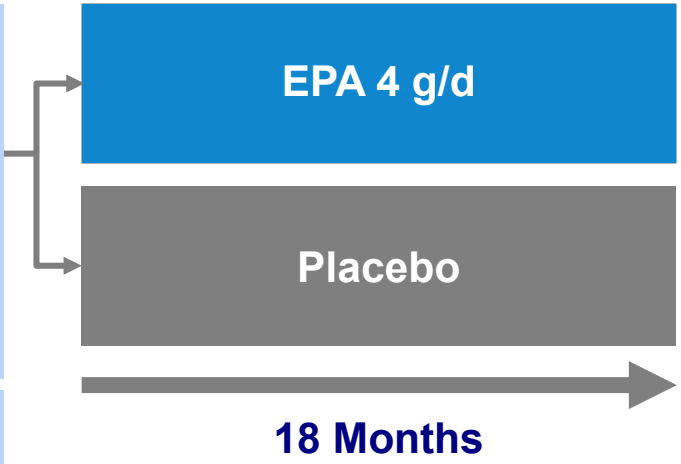
EVAPORATE: Effect of EPA on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy

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-PLA_2)
- LDL-C and HDL-C



The EVAPORATE study seeks to determine whether IPE 4g/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.

EVAPORATE Clinical Trial. https://clinicaltrials.gov/ct2/show/NCT02926027. Updated February 08, 2018. Accessed June 19, 2018.

INCLUSION CRITERIA

- Age ≥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 ≤115 mg/dL and on stable statin therapy (±ezetimibe)
- eGFR > 60

METHODS

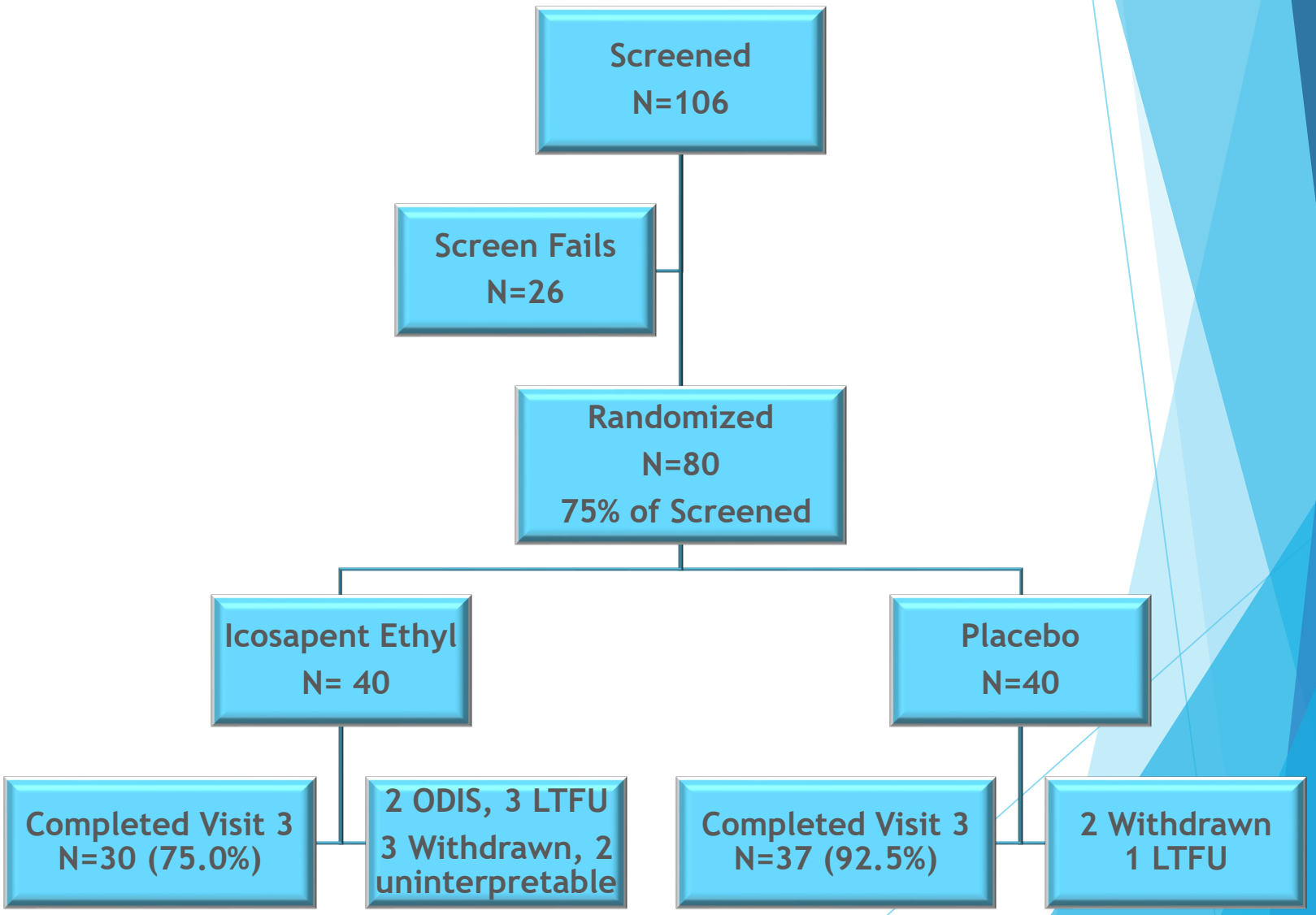
- Patients underwent baseline, 9 month and 18 month follow up CT angiogram
- Intention to Treat Analysis
- Semi-automated plaque analysis software (QAngioCT) Medis Medical Imaging Systems, Netherlands

Statistical Analysis

- 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



Key Baseline Characteristics

	Icosapent Ethyl (N=30)		Placebo(N=37)		
	Mean / Count	Std(%)	Mean / Count	Std(%)	p
Age, years	55.6	(7.7)	58.3	8.6	0.195
Male	16	(53%)	20	54%	0.953
BMI	34.4	(6.4)	33.3	6.9	0.531
Time between Visit 1 and 3 (months)	9.4	(1.0)	9.9	2.7	0.232
Ethnicity Hispanic	18	(60%)	19	51%	0.479
Race, White	27	(90%)	29	78%	0.595
Aspirin Use	14	(47%)	22	59%	0.296
Diabetic	22	(73%)	25	68%	0.608
Family History	8	(27%)	13	35%	0.458
Statin Use	30	(100%)	37	100%	1.000
Hypertension	23	(77%)	28	76%	0.925
Past Smoking	13	(43%)	16	43%	0.214

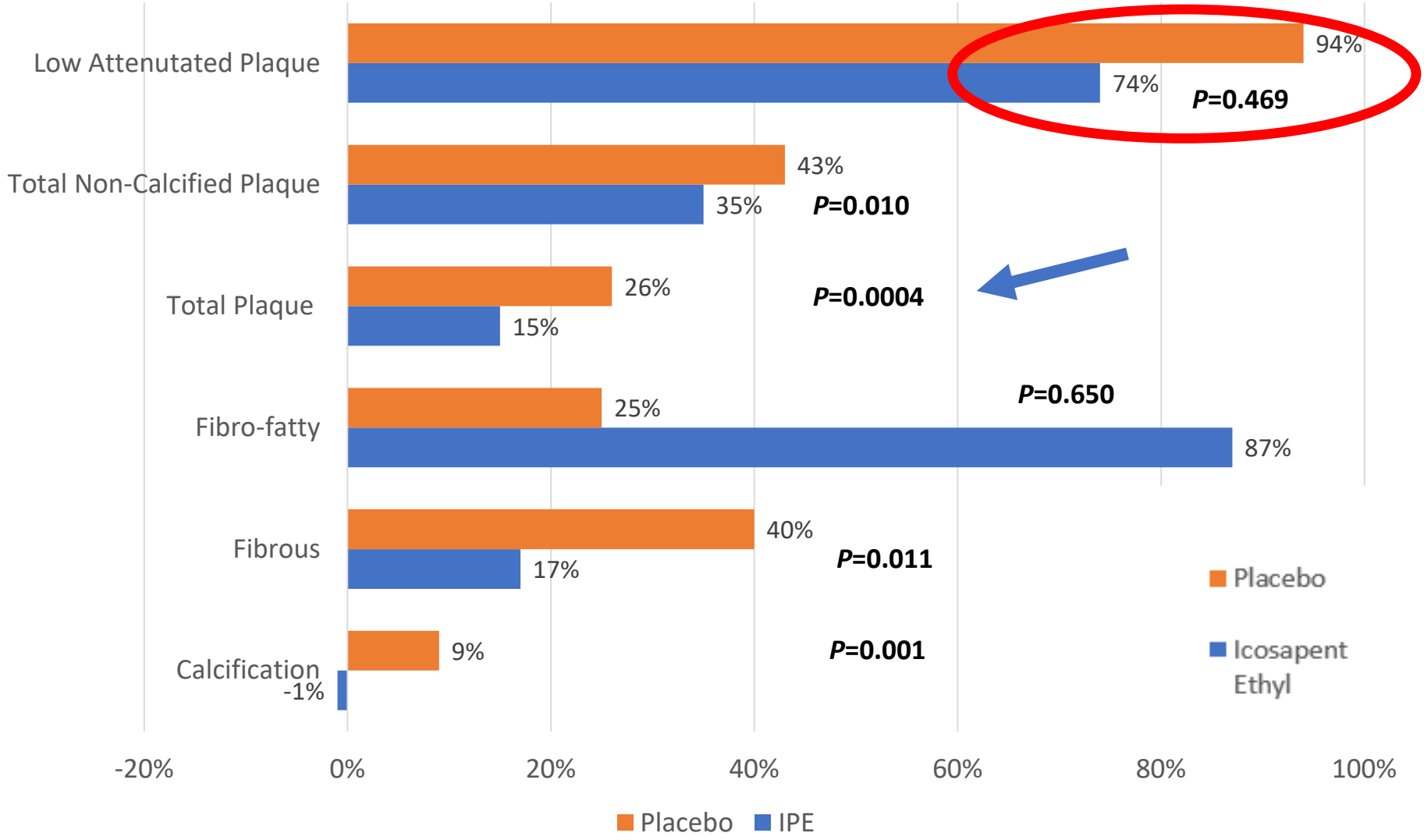
Primary Outcome (ITT)

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

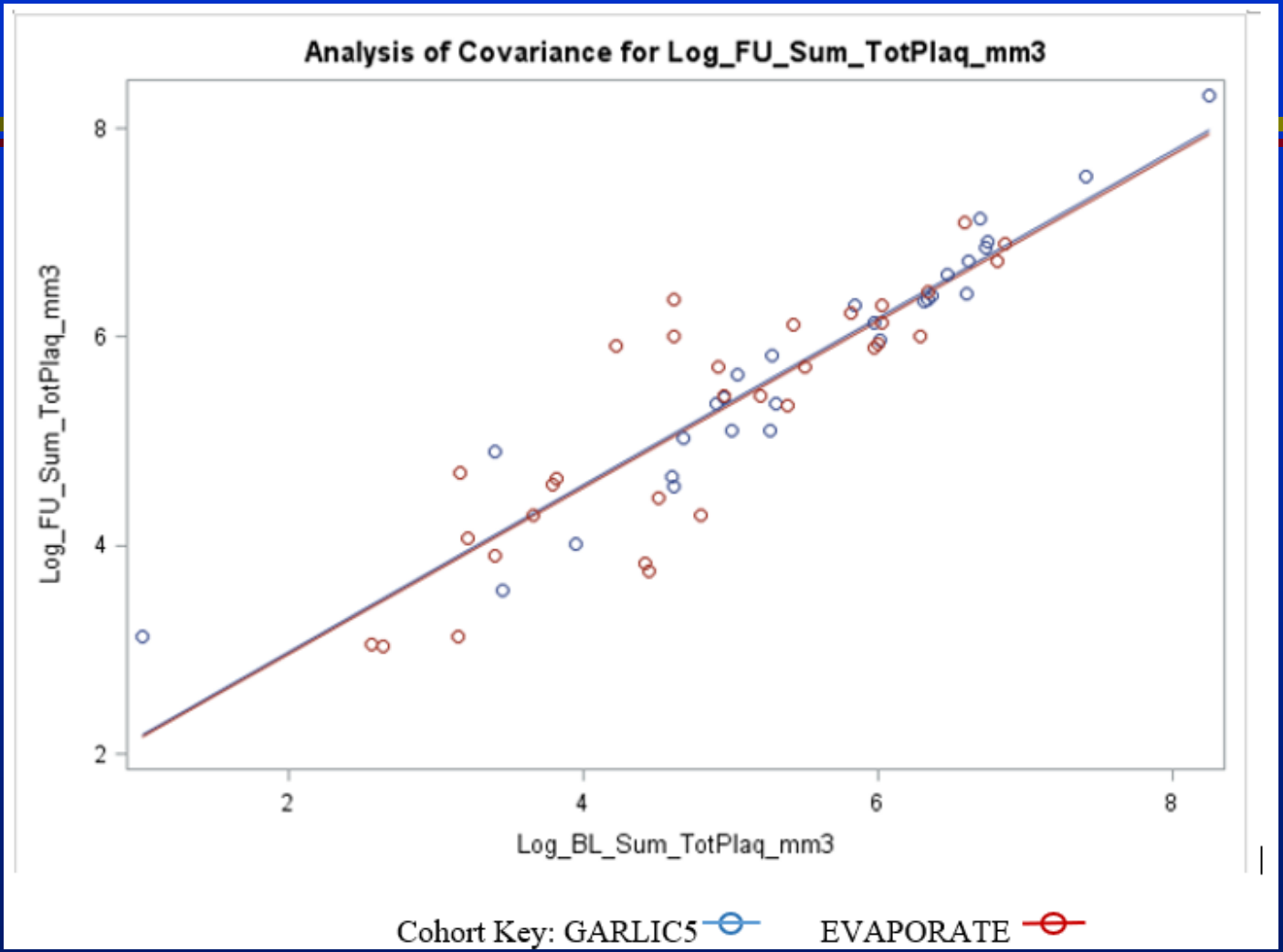
- **21%** for low attenuation plaque (p=0.469)
- **19%** for total non-calcified plaque (p=0.010)
- **42%** for total plaque (p=0.0004)
- **57%** for fibrous plaque (p=0.011)
- **89%** for calcified plaque (p=0.001)
- **Increase** in Fibrofatty plaque (p=0.650)

- **Consistent efficacy across multiple subgroups**
- **Including baseline triglycerides from 135-499 mg/dL**

Fully adjusted median Plaque Progression at 9 months



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.