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

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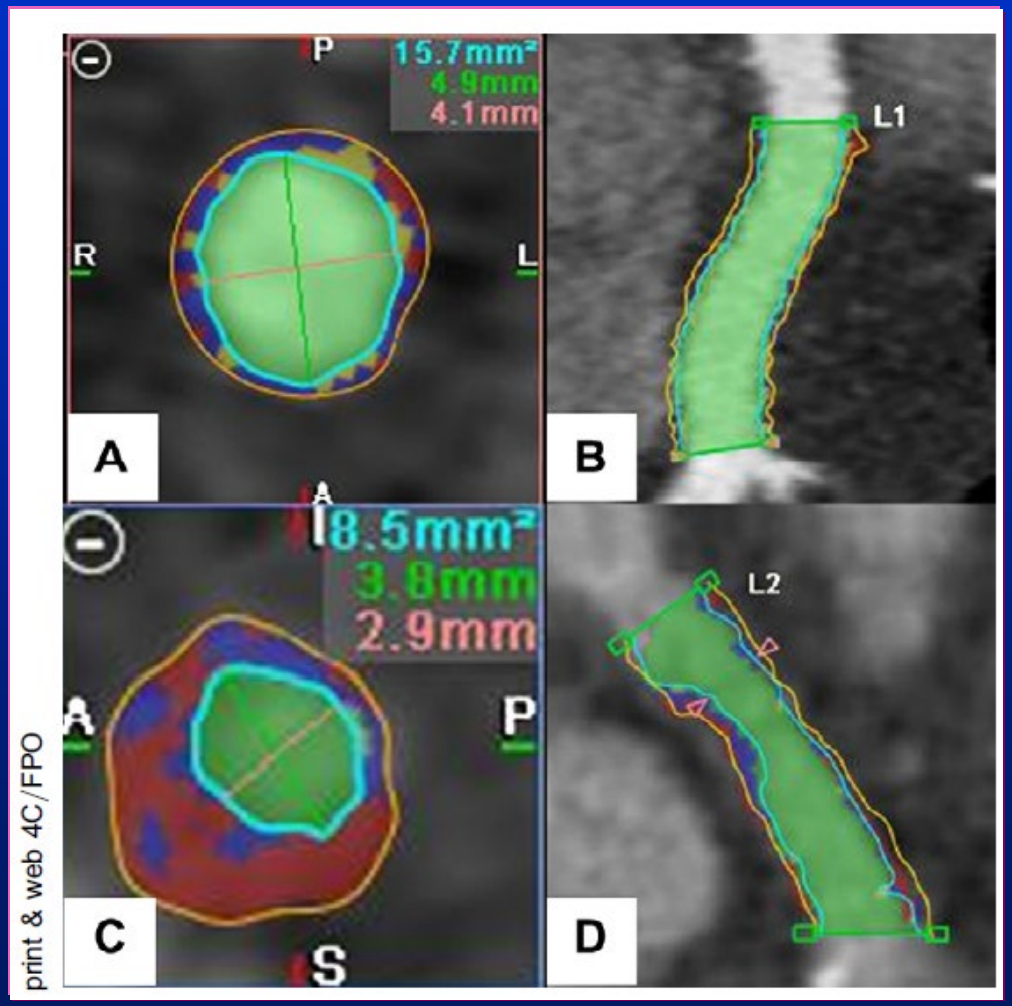
Plaque Progression with CT Angiography



IVUS vs CTA Plaque Progression

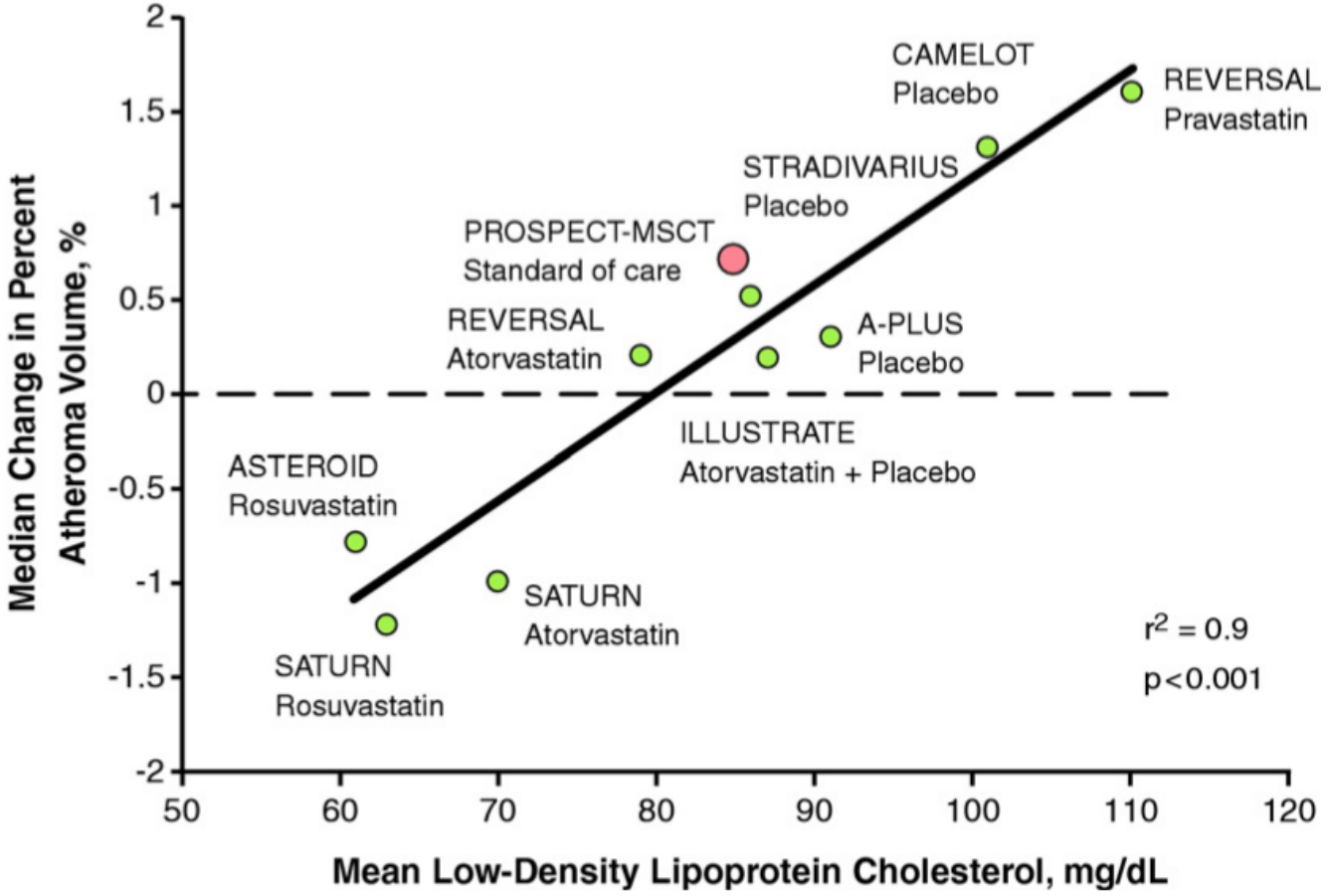
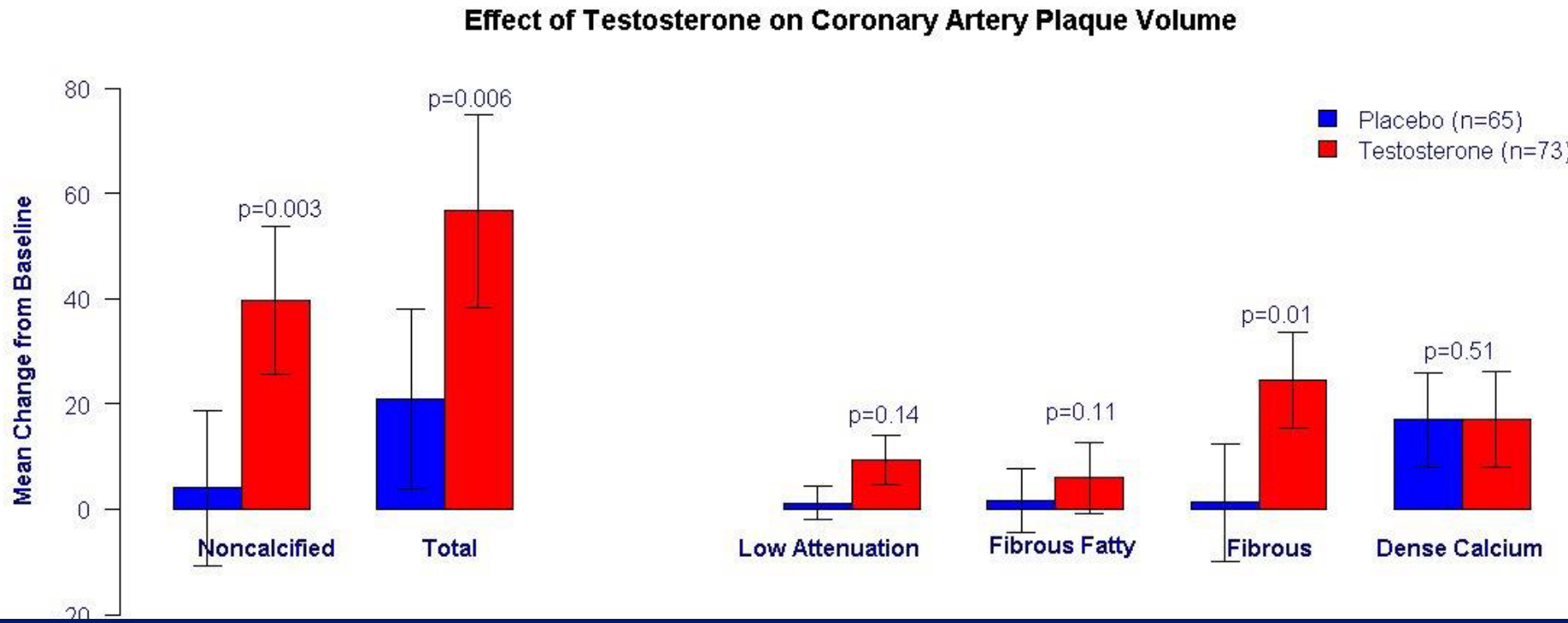


Figure 3. Association Between Mean Low-Density Lipoprotein Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Studies

MDCT Coronary Imaging and CV Outcome Trials

Drug	CTA Progression	CVOT
Statin	+++ (Regression)	+++
Estrogen	Neutral	Neutral
Xarelto vs Warfarin	+ (slowed progression)	+
Fish Oil (EPA)	++ (slowed progression)	+++
Testosterone	Progression	Harmful
Eliquis vs Warfarin	+ (slowed progression)	+
Atorvastatin	+++ (regression)	+++

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



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.

Sekikawa – Nutrients 2019

Table 2. Primary outcome of atherosclerosis and the result of each included trial.

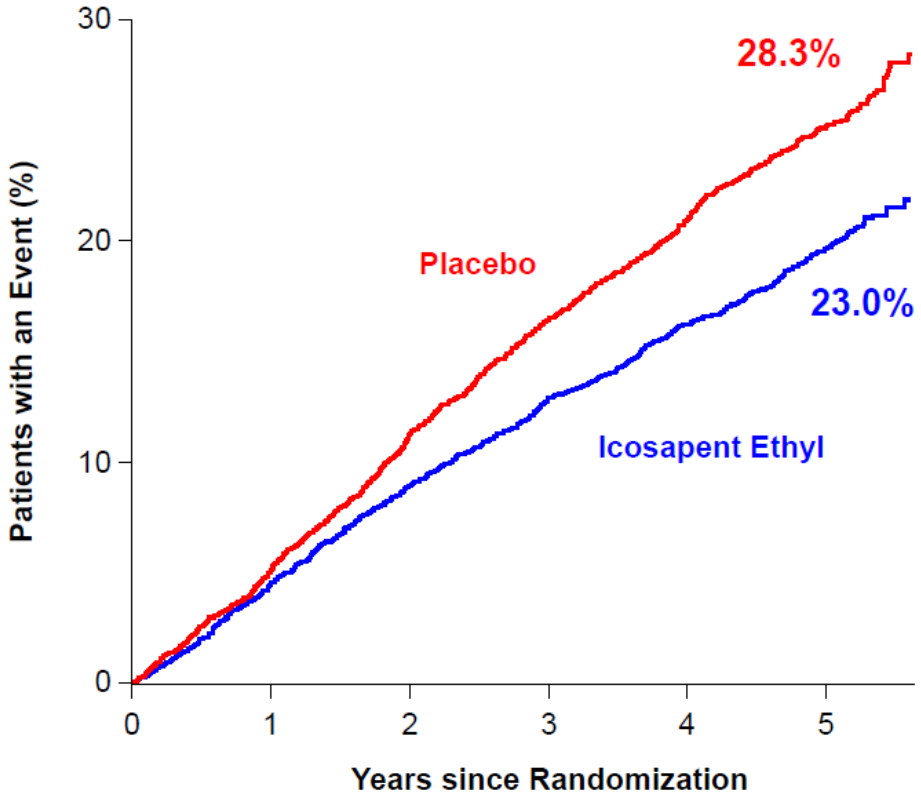
First Author, Year, Country, Reference	Imaging Techniques	Primary Outcome	Baseline Measurement Treatment vs. Control Groups	Difference in Primary Outcome between the End of Intervention and Baseline in Each of Treatment and Control Groups Treatment vs. Control Groups	Net Difference between Intervention and Control Groups	*p*-Value for Net Difference
Alfaddagh, 2017, US [17]	cCTA	Percent change in non-calcified plaque volume (%)	26.4 (14.3, 39.7) vs. 23.7 (14.3, 36.8)	1.71 ± 19.9 vs. 4.75 ± 16.44	−3.04	0.14
Bhatia, 2016, UK [27]	B-Mode ultrasound	Change in mean carotid IMT (mm)	0.649 ± 0.095 vs. 0.674 ± 0.098	0.0124 ± 0.0115 vs. 0.0157 ± 0.0138	−0.003	0.17
Mita, 2006, Japan [26]	B-mode ultrasound	Annual change in maximum carotid IMT (mm/year)	1.505 ± 0.412 vs. 1.706 ± 0.423	−0.084 ± 0.113 vs. −0.005 ± 0.108	−0.079	<0.01
Niki, 2016, Japan [19]	IVUS	Change in lipid plaque volume (mm^3)	18.5 ± 1.3 vs. 17.8 ± 1.3	−3.5 ± 0.2 vs. 1.5 ± 1.0	−5.0	<0.01
Nishio, 2014, Japan [18]	OCT	Change in fibrous-cap thickness (um)	47.5 ± 7.4 vs. 46.5 ± 10.9	−54.8 ± 27.9 vs. −23.5 ± 11.6	−31.3	<0.01
Watanabe, 2017, Japan [20]	IVUS	Change in normalized total atheroma volume (mm^3)	74.2 (55.9, 99.2) vs. 74.2 (57.5, 96.8)	−8.49 ± 2.37 vs. −2.90 ± 4.74	−5.59	<0.01

cCTA: coronary computed tomographic angiography, IVUS: integrated backscatter intravascular ultrasound; OCT: optical coherence tomography, IMT: intima-media thickness; SD: standard deviation; Baseline measurement is expressed as mean (SD) or median (inter-quartile range).

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]

STUDY DESIGN

- A randomized, double-blind, placebo-controlled EVAPORATE study was performed to evaluate the effects of icosapent ethyl 4 g/d on atherosclerotic plaque in statin-treated patients with coronary atherosclerosis
- TG levels of 135 to 499 mg/dL, and low-density lipoprotein cholesterol levels of 40 to 115 mg/dL

INCLUSION CRITERIA

1. Age ≥45 years with atherosclerosis with at least one stenosis of 20%
2. Fasting TG levels ≥150 mg/dLand <500 mg/dL
3. LDL-C >40 mg/dLand ≤100 mg/dLand on stable statin therapy (±ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

Key Exclusion Criteria

- Severe (NYHA class IV) heart failure
- Contrast Allergy
- Renal Insufficiency (eGFR <60)
- Hypersensitivity to fish and/or shellfish

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
- Markers of inflammation (Lp-PLA_2)
- LDL-C and HDL-C

Estimated Study Completion Date: September 2019

The EVAPORATE study seeks to determine whether IPE 4g/d will result in a greater change from baseline in plaque volume measured by serial multidetector computed tomography (MDCT) than placebo in statin-treated patients

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

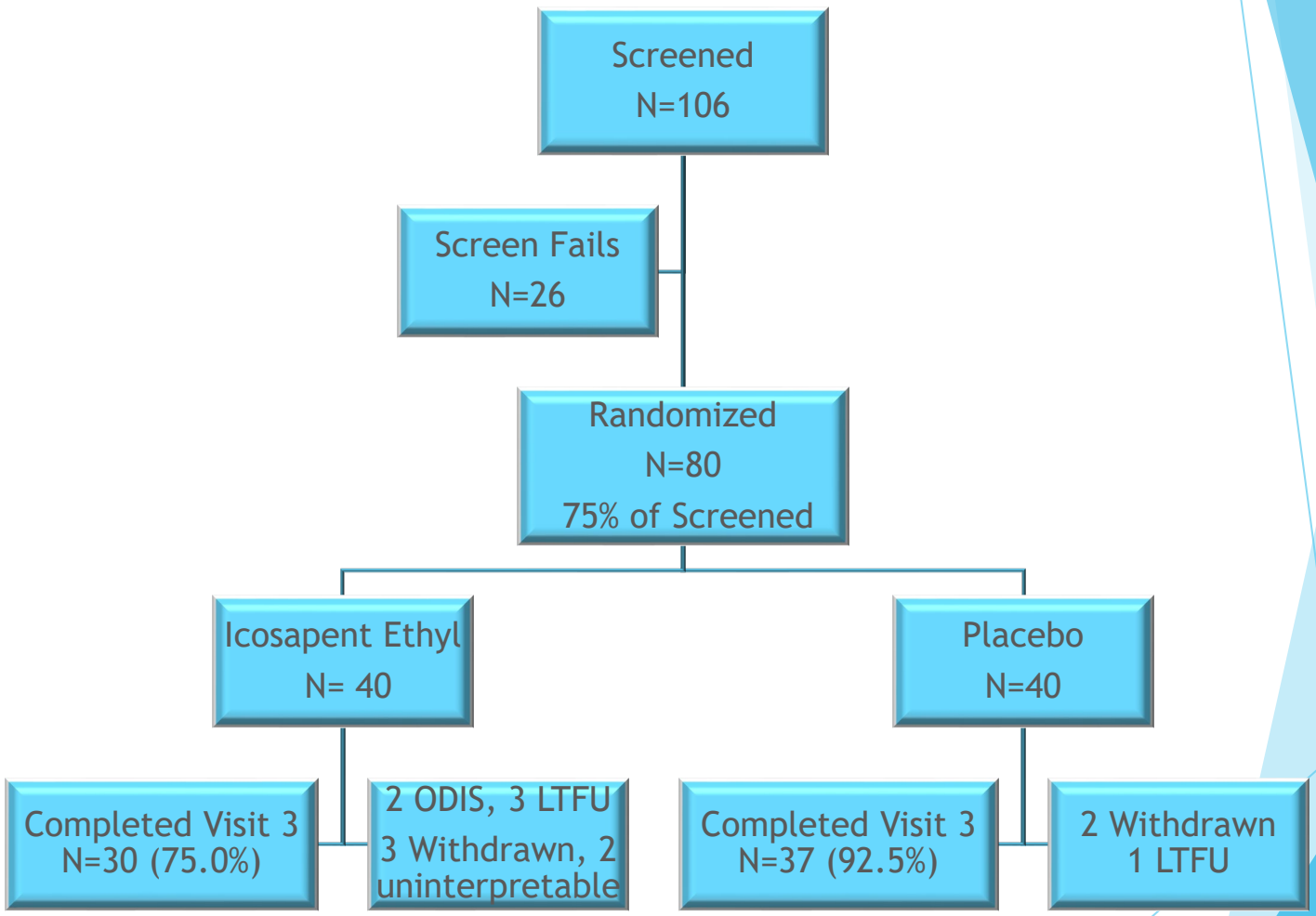
EVAPORATE Clinical Trial. https://clinicaltrials.gov/ct2/show/NCT02926027. Updated February 08, 2018. Accessed June 19, 2018.

TABLE 2 EVAPORATE study endpoints

Primary endpoint
Change in low-attenuation plaque volume as measured by MDCTA and defined as −50 to 50 HU
Secondary endpoints
Incident plaque rates; quantitative changes in different plaque types and morphology
Changes in markers of inflammation including Lp-PLA_2 and hsCRP
Changes in lipids and lipoproteins including standard lipid panel, lipoproteins, remnants, Apo-A1/remnant ratio, EPA, AA, and EPA/AA ratio
Relationship between changes in the above with noncalcified coronary plaque burden and/or plaque-vulnerability features

Abbreviations: AA, arachidonic acid; Apo-A1, apolipoprotein A1; EPA, eicosapentaenoic acid; EVAPORATE, Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy study; hsCRP, high-sensitivity C-reactive protein; HU, Hounsfield

EVAPORATE 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

Fully adjusted median Plaque Progression at 9 months

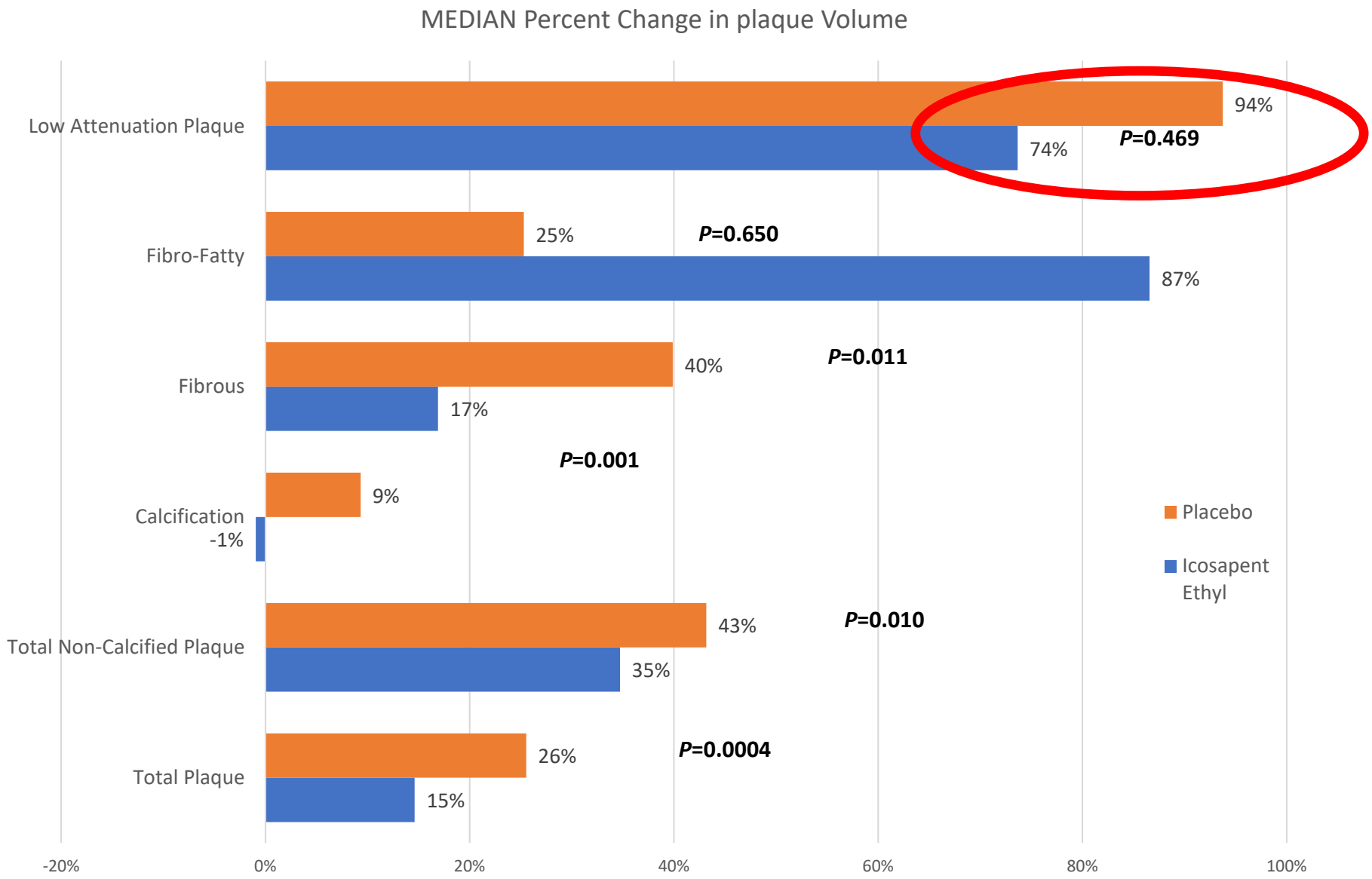


TABLE 3: Plaque Changes by Treatment Group

PLAQUE TYPE		Baseline			Followup			Difference			ANCOVA	
Calcification	n	median	std	p*	median	std	p*	median	std	Δ%	unadj. P	adj. p
Icosapent	30	82.8	126.1	0.12	52.9	115.6	0.25	-0.8	47.0	-1%	0.0002	0.0010
Placebo	37	24.9	92.2		41.3	83.9		2.3	35.6	9%		
Fibrous												
IPE	30	115.7	189.3	0.50	107.2	185.6	0.59	19.6	146.9	17%	0.008	0.0109
Placebo	37	57.1	125.0		116.1	126.0		22.8	63.8	40%		
Fibro-Fatty												
IPE	30	15.1	56.5	0.88	38.1	73.3	0.92	13.1	39.5	87%	0.588	0.6500
Placebo	37	16.1	44.5		40.5	60.8		4.1	46.5	25%		
Low Attenuation Plaque												
IPE	30	7.3	43.3	0.74	20.9	87.7	0.80	5.4	72.3	74%	0.390	0.4692
Placebo	37	5.4	45.0		16.1	82.4		5.1	83.4	94%		
Total Non-Calcified Plaque												
IPE	30	143.7	269.4	0.55	203.4	311.3	0.58	49.9	141.2	35%	0.006	0.0103
Placebo	37	95.8	194.2		213.9	233.3		41.3	143.6	43%		
Total Plaque												
IPE	30	259.1	339.6	0.31	279.7	390.8	0.34	37.9	226.6	15%	0.0002	0.0004
Placebo	37	136.9	260.8		235.0	286.4		34.9	146.0	26%		

Biomarker Effects from Baseline to 9months

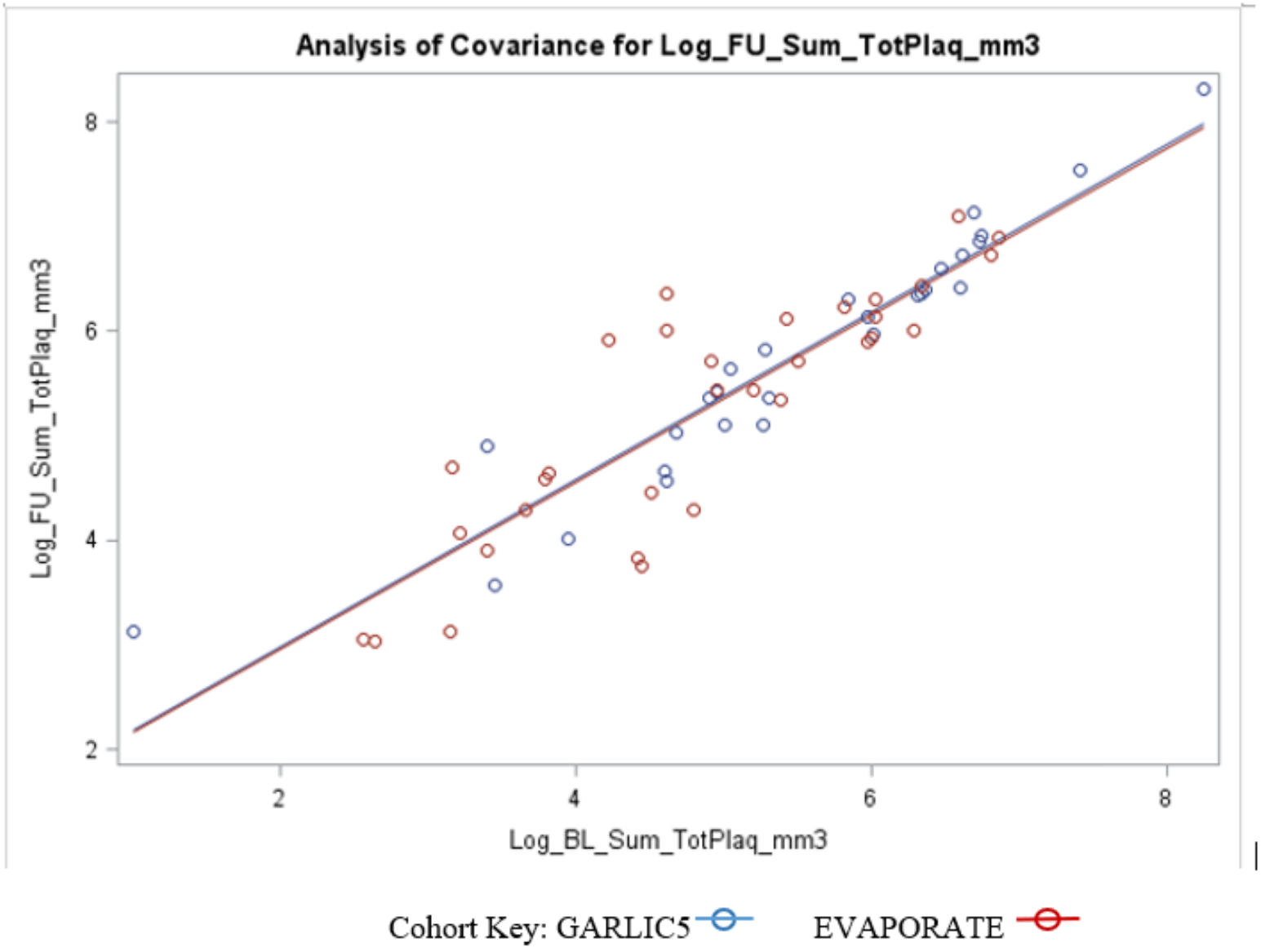
	Icosapent Ethyl (N=30)		Placebo(N=37)		Mean Between Group Difference at 9 months		
	Visit 1	Visit 3	Visit 1	Visit 3	Absolute Δ from V1	%Δ from V1	p
Cholesterol	151.8	142.2	158.8	149.4	-0.3	0%	0.973
HDL	36.8	36.0	37.2	37.2	-0.8	-2%	0.530
LDL	89.2	85.4	92.4	88.2	0.3	0%	0.961
Triglycerides	190.9	156.7	199.8	183.7	-18.1	-9%	0.458
AA	265.5	213.5	263.3	265.0	-50.0	-19%	0.002
AA to EPA Ratio	13.6	4.9	11.1	13.2	-10.7	-88%	<.0001
Cholesterol	151.8	142.2	158.8	149.4	-0.3	0%	0.973
DHA	54.3	47.4	63.3	55.7	0.6	1%	0.913
EPA	20.8	89.3	29.9	21.9	77.0	298%	<.0001
LA	1015.9	861.6	1005.9	977.7	-135.6	-13%	0.046
Monounsaturated FA Index	25.5	24.2	24.9	25.5	-1.7	-7%	0.015
Omega3 FA Index	2.1	4.6	2.7	2.2	2.9	121%	<.0001
Omega6 FA Index	38.2	35.1	37.4	37.7	-3.7	-10%	0.024
Omega6 to 3 Ratio	20.2	10.3	16.8	19.4	-12.5	-68%	<.0001
hsCRP	4.6	5.0	3.8	3.2	0.9	22%	0.7583

RESULTS

- At 9 Month Prespecified Timepoint, compared with placebo, icosapent ethyl slowed progression by:
- **21%** for low attenuation plaque (p=0.469)
- **42%** for total plaque (p=0.0004)
- **19%** for total non-calcified plaque (p=0.010)
- **57%** for fibrous plaque (p=0.011)
- **89%** for calcified plaque (p=0.001)
- No Effect on Fibrofatty plaque (p=0.650)

- Consistent efficacy across multiple subgroups
- Including baseline triglycerides from 135-500 mg/dL

PLACEBO RATES OF PROGRESSION



LIMITATIONS

- Shorter Follow up than Prior CTA Studies (9 months)
- Primary Endpoint not significant at interim timepoint – study will continue to 18 months as planned
- 4 of 5 secondary endpoints demonstrated significant slowing of progression
- Small cohort with expected 15% drop-out (due to patient preference and non-diagnostic CT at baseline or follow up)

EVAPORATE: Conclusions

- First study using MDCT to evaluate the effects of IPE as adjunct to statin on plaque characteristics in a population with high TG levels demonstrating significant changes in most plaque markers at 9 months, and study is continuing to 18 months as planned
- Demonstrated that progression rates on mineral oil placebo is similar to non-mineral oil placebo cohort using same methodology, scanner and laboratory
- Important data to understand a mechanism of benefit of icosapent ethyl