

# Comparison of mineral oil and non-mineral oil placebo on coronary plaque progression by coronary computed tomography angiography

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## 1. Introduction

Light liquid paraffin (pharmaceutical grade mineral oil) has been used as a placebo in clinical trials of icosapent ethyl including MARINE, ANCHOR, and REDUCE-IT. Pharmaceutical grade mineral oil (distinct from technical/industrial or food grade mineral oils) was chosen as a suitable placebo to mimic the consistency, colour, and odourless properties of icosapent ethyl capsules. Since the results of REDUCE-IT, a few have raised questions regarding possible biological activity of mineral oil placebo due to small changes in some cardiac biomarkers including lipid levels and inflammatory markers in placebo arm patients, asking whether the mineral oil utilized in placebo capsules was physiologically inert or not.<sup>1</sup> Mineral oil has been utilized in humans as a laxative for decades (typically in doses of 15–45 g/day), and the general safety has been inferred from clinical utilization. The ~2 g twice per day of light liquid mineral oil taken by placebo group patients in clinical trials equates to less than a teaspoon per day.

EVAPORATE is an ongoing randomized, placebo-controlled trial that evaluates the effect of icosapent ethyl 4 g daily in statin-treated patients with elevated triglycerides on coronary plaque progression by coronary computed tomography angiography (coronary CTA) compared with mineral oil placebo to provide important imaging-derived mechanistic information that can add insight to clinical outcomes from REDUCE-IT.<sup>2</sup> Coronary plaque volumes, including total plaque and total non-calcified plaque derived by coronary CTA, have been measured and are known to be associated with myocardial ischaemia and adverse cardiac outcomes.<sup>3–5</sup> In the present observational study, we sought to compare differences in progression of total plaque and total non-calcified plaque volumes on coronary CTA in mineral oil placebo patients from EVAPORATE vs. the non-mineral oil placebo arm from another

randomized clinical trial, Garlic 5.<sup>6</sup> We hypothesized that progression of total plaque and total non-calcified plaque volumes on coronary CTA is independent of consumption of mineral oil placebo capsules.

## 2. Methods

The study design and rationale for EVAPORATE and Garlic 5 have been published previously.<sup>2,6</sup> Eligible patients in EVAPORATE had known coronary atherosclerosis, elevated triglycerides (200–499 mg/dL), and low-density lipoprotein levels (LDL-C)  $\leq 115$  mg/dL while on statins. In Garlic 5, to be eligible, participants had coronary artery calcium scores  $>20$  and known history of diabetes mellitus (DM).

We acquired coronary CTA scans for evaluation of coronary plaque volume at baseline and at 12 months in Garlic 5 subjects and at baseline and at 9 months in EVAPORATE subjects. We performed quantitative plaque assessment using semi-automated plaque analysis software (QAngioCT Research Edition Version 2.0.5; Medis Medical Imaging Systems).<sup>7</sup> Pharmaceutical grade mineral oil placebo used in EVAPORATE consisted of a purified liquid mixture of straight-chain saturated hydrocarbons that met the pharmaceutical compendial requirements of the US National Formulary (NF) for light mineral oil and of the European Pharmacopoeia (Ph. Eur.) for light liquid paraffin oil.<sup>8,9</sup> The total daily dose of mineral oil placebo was four 1 g soft gelatine capsules, with two capsules taken twice daily with meals. The material does not contain any functional groups and is virtually free of all aromatic hydrocarbons and unsaturated hydrocarbons, making it chemically inert and allowing for minimal absorption. The composition of physiologically inert placebo powder (P-31) in Garlic 5 includes (per 100 mg) microcrystalline cellulose: 89.83 mg, hydroxypropyl cellulose: 10.07 mg, and caramel: 0.10 mg.

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**Table 1** Baseline characteristics

	Garlic 5 placebo (n = 28) Mean (SD)/count (%)	EVAPORATE placebo (n = 32) Mean (SD)/count (%)	P-value
Age (years)	58.7 (11.4)	58.6 (8.8)	0.97 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	30.8 (6.0)	32.5 (5.4)	0.24 <sup>a</sup>
Male	21 (72%)	19 (59%)	0.28 <sup>b</sup>
Hispanic	9 (31%)	15 (47%)	0.21 <sup>b</sup>
Type 2 diabetes	29 (100%)	21 (66%)	<0.001 <sup>c</sup>
Taking diabetic medications	29 (100%)	21 (66%)	<0.001 <sup>c</sup>
Hypertension	15 (52%)	23 (72%)	0.10 <sup>b</sup>
Taking anti-hypertensive medications	15 (52%)	23 (72%)	0.10 <sup>b</sup>
Hyperlipidaemia	24 (83%)	31 (97%)	0.09 <sup>c</sup>
Taking statins	24 (83%)	31 (97%)	0.09 <sup>c</sup>
Past smoker	11 (38%)	13 (41%)	0.83 <sup>b</sup>
Taking aspirin	21 (72%)	19 (59%)	0.28 <sup>b</sup>
Baseline HDL cholesterol (mg/dL)	40.1 (12.6)	37.3 (7.7)	0.29 <sup>a</sup>
Baseline LDL cholesterol (mg/dL)	72.6 (33.1)	89.9 (38.9)	0.07 <sup>a</sup>
Baseline triglycerides (mg/dL)	138.8 (79.4)	202.1 (96.7)	<0.01 <sup>a</sup>
Baseline total cholesterol (mg/dL)	140.3 (45.4)	156.3 (45.1)	0.17 <sup>a</sup>
Baseline hsCRP (mg/L)	3.5 (3.9)	2.8 (2.8)	0.42 <sup>d</sup>
Time between scans (months)	12.2 (0.7)	9.6 (1.2)	<0.001 <sup>a</sup>

BMI, body mass index.

<sup>a</sup>Independent t-test.

<sup>b</sup> $\chi^2$  test.

<sup>c</sup>Fisher's exact test.

<sup>d</sup>Wilcoxon rank-sum test.

The analysis of covariance test was used to examine rates of progression between the groups. The final model was adjusted for baseline plaque volume, age, sex, diabetes status, baseline triglyceride levels, and statin use. Total plaque and total non-calcified plaque volumes were log transformed to achieve a normal distribution. A *P*-value of <0.05 was considered significant. SAS software (version 9.4) was used for analyses.

### 3. Results

Mean [standard deviation (SD)] age of participants (*n* = 60) was 59 (9.9) years and 66% were male. A total of 28 participants from the Garlic 5 placebo arm and 32 participants from the EVAPORATE placebo arm were analysed. Participants had mean follow-up of 10.8 months. Baseline characteristics of the cohorts are listed in Table 1. There were no significant differences in major clinical characteristics including age, body mass index, hypertension, levels of LDL, total cholesterol, high-sensitivity C-reactive protein (hsCRP), or use of medications, including aspirin and statins. Due to eligibility criteria of the trials, the Garlic 5 placebo cohort was more likely to have diabetes and take diabetes medications, while the EVAPORATE placebo cohort was more likely to have high triglycerides.

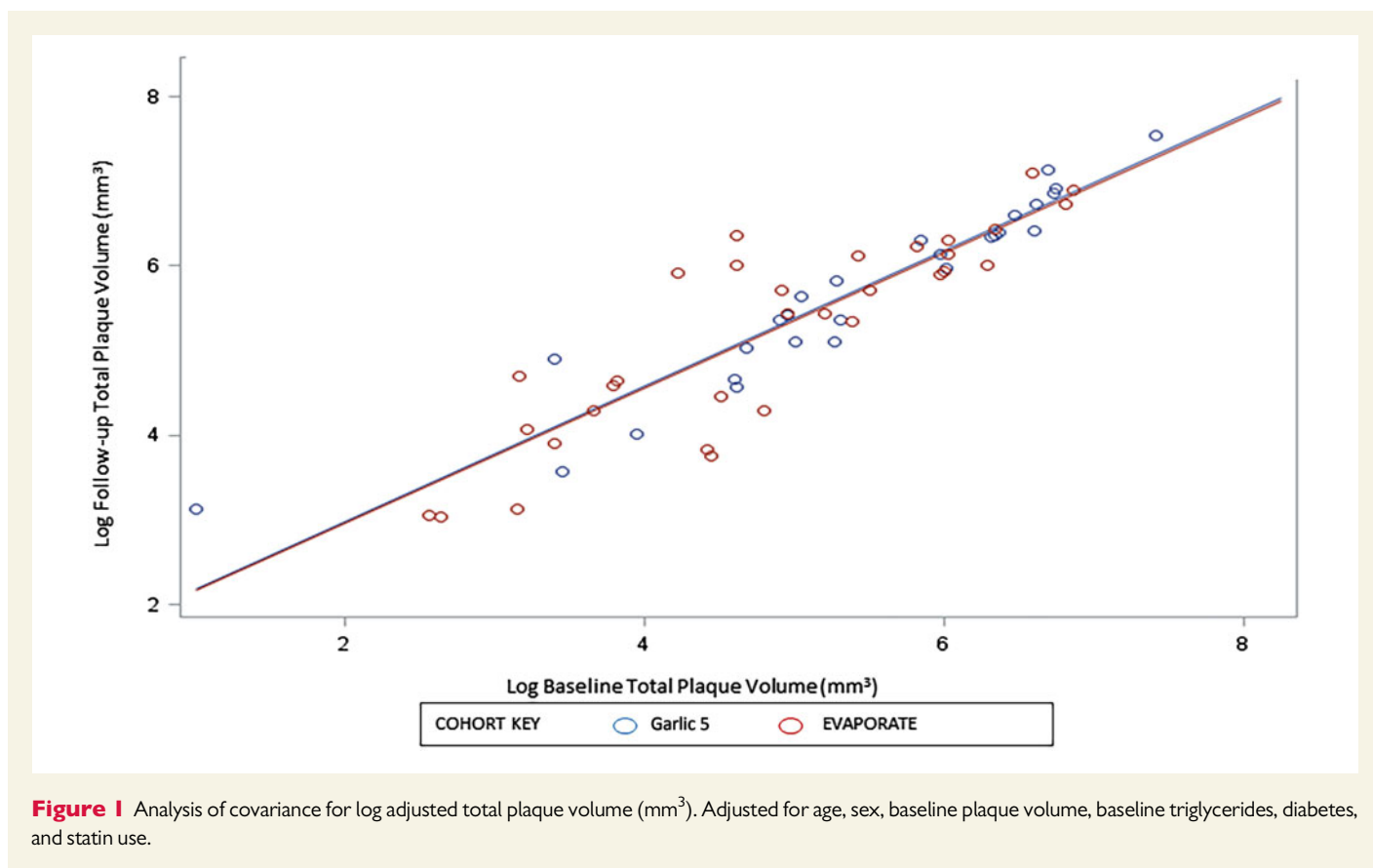
Mean levels of total plaque and total non-calcified plaque volumes were similar at baseline in both cohorts. Mean (SD) level of log total plaque volume at baseline was 4.85 (1.24) mm<sup>3</sup> in the EVAPORATE and 5.49 (1.45) mm<sup>3</sup> in the Garlic 5 placebo cohorts (*p* = 0.07). Mean (SD) level of log total non-calcified plaque volume at baseline was 4.5 (1.26) mm<sup>3</sup> in the EVAPORATE and 5.25 mm<sup>3</sup> (1.53) in the Garlic 5 placebo cohorts (*P* = 0.04). At follow-up, mean (SD) level of log total plaque

volume was 5.23 (1.17) mm<sup>3</sup> in the EVAPORATE and 5.78 (1.18) mm<sup>3</sup> in the Garlic 5 placebo cohorts (*P* = 0.08). Mean (SD) level of log total non-calcified plaque volume was 5.01 (1.14) mm<sup>3</sup> in the EVAPORATE and 5.54 mm<sup>3</sup> (1.21) in the Garlic 5 placebo cohorts (*P* = 0.09). In a univariate covariance of analysis test, when adjusted for baseline plaque, there were no significant differences in progression of log total plaque volume ( $\beta$ : 0.03 ± 0.13, *P* = 0.84) or log total non-calcified plaque volume ( $\beta$ : 0.01 ± 0.16, *P* = 0.94) between the placebo participants in EVAPORATE and Garlic 5. Adjusted multivariable analysis of covariance tests also did not show any significant differences in progression in log total plaque volume ( $\beta$ : 0.04 ± 0.13, *P* = 0.78) (Figure 1) or log total non-calcified plaque volume ( $\beta$ : 0.09 ± 0.17, *P* = 0.58) between the two groups.

### 4. Discussion

We report that there were no significant differences in progression of total plaque and total non-calcified plaque volume by coronary CTA in mineral oil placebo participants compared with non-mineral oil placebo participants drawn from two different randomized, placebo-controlled trials. We did not observe any significant relationship between mineral oil placebo consumption and progression of coronary plaque volumes by coronary CTA in our multivariable analysis. The EVAPORATE trial, to our knowledge, is the first randomized trial with mineral oil placebo to study effects on coronary plaque imaging by coronary CTA. Coronary plaque volumes are associated with the pathogenesis of coronary artery disease.

Our results are consistent with prior omega-3 fatty acid trials that suggest no effect of mineral oil on surrogate markers of coronary artery disease, including triglycerides, LDL-C, fatty acids, and markers of



inflammation in placebo arm participants.<sup>10,11</sup> Changes in levels of LDL-C and inflammatory markers have been commonly observed in statin-stabilized patients in clinical trials.<sup>12</sup> In a randomized trial of omega 3 ethyl ester vs. control (no placebo) in participants with stable coronary artery disease, hsCRP levels were increased from baseline even in the control arm with no placebo.<sup>13</sup> These observations have been attributed to independent factors such as poor compliance with statins, time-dependent intra-individual variability of lipid/drug metabolism, and physiologic compensation to counteract statin-induced decreases in lipids. Small changes in placebo group biomarker values in large clinical trials are also commonly observed due to the principle of regression to the mean. A few have argued that mineral oil alters lipid levels by interfering with absorption of fat-soluble substances, including medications such as statins. In our analysis, there were no significant differences in use of antiplatelet or statins in the two groups analysed, and our clear results on lack of differences in plaque progression between the two placebo groups demonstrate that there are no specific effects of low-dose mineral oil on absorption of statins or other substances.

Our study has the following limitations. This is a *post hoc* analysis of observational data from two trials with differing inclusion criteria and thus subject to heterogeneity and residual confounding. The natural history of coronary atherosclerosis is known to differ between adults with and without diabetes, however, >65% of EVAPORATE participants did have diabetes, and the presence of diabetes was accounted for in our multivariable analysis.<sup>14</sup> The sample size is small and given the *post hoc* design, the study was not powered to detect significant differences between the groups. The follow-up period of 10.8 months, although relatively short, is similar to some other trials evaluating progression of coronary atherosclerosis.<sup>2,3</sup>

We conclude that progression of total plaque and total non-calcified plaque volumes on coronary CTA is not related to consumption of mineral oil in the quantities used in these placebo capsules.<sup>1,2,15</sup> The results of REDUCE-IT and EVAPORATE, as well as several other trials using mineral oil placebo capsules, should not be affected by the choice of this placebo.

**Conflict of interest:** M.J.B. has received grant support and is on the speaker's bureau for Amarin Pharmaceuticals. D.L.B. discloses the following relationships—Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, and Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of

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## References

- Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;**380**:11–22.
- Budoff M, Brent Muhlestein J, Le VT, May HT, Roy S, Nelson JR. 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. *Clin Cardiol* 2018;**41**:13–19.
- Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, Wenger NK, Bhasin S, Barrett-Connor E, Swerdloff RS, Stephens-Shields A, Cauley JA, Crandall JP, Cunningham GR, Ensrud KE, Gill TM, Matsumoto AM, Molitch ME, Nakanishi R, Nezarat N, Matsumoto S, Hou X, Basaria S, Diem SJ, Wang C, Cifelli D, Snyder PJ. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA* 2017;**317**:708–716.
- Motomaya S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, Harigaya H, Kan S, Anno H, Takahashi H, Naruse H, Ishii J, Hecht H, Shaw LJ, Ozaki Y, Narula J. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol* 2015;**66**:337–346.
- Gaur S, Ovrehus KA, Dey D, Leipsic J, Botker HE, Jensen JM, Narula J, Ahmadi A, Achenbach S, Ko BS, Christiansen EH, Kaltoft AK, Berman DS, Bezerra H, Lassen JF, Norgaard BL. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. *Eur Heart J* 2016;**37**:1220–1227.
- Shaikh K, Kinninger A, Cherukuri L, Birudaraju D, Nakanishi R, Almeida S, Jayawardena E, Shekar C, Flores F, Hamal S, Sheikh MS, Johanis A, Benedict CU, Budoff MJ. Aged garlic extract reduces low attenuation plaque in coronary arteries of patients with diabetes: a prospective, randomized, placebo-controlled double-blind study. *Exp Ther Med* 2020;**19**:1457–1461.
- Matsumoto S, Nakanishi R, Li D, Alani A, Rezaeian P, Prabhu S, Abraham J, Fahmy MA, Dailing C, Flores F, Hamal S, Broersen A, Kitslaar PH, Budoff MJ. Aged garlic extract reduces low attenuation plaque in coronary arteries of patients with metabolic syndrome in a prospective randomized double-blind study. *J Nutr* 2016;**146**:427s–432s.
- 2016 U.S. Pharmacopoeia-National Formulary [USP 39 NF 34], Vol. 1. Rockville, MD: United States Pharmacopoeial Convention, Inc.; 2015. Official Monographs/Mineral Oil; p. 4885–4886.
- Commission Regulation (EU) 2015/1608 of 24 September 2015 amending Annex IV to Regulation (EC) No 396/2005 of the European Parliament Inc. The Official Journal of the European Union. <https://www.efta.int/sites/default/files/documents/legal-texts/eea/other-legal-documents/adopted-joint-committee-decisions/2016%20-%20English/074-2016.pdf>.
- De Truchis P, Kirstetter M, Perier A, Meunier C, Zucman D, Force G, Doll J, Katlama C, Rozenbaum W, Masson H, Gardette J, Melchior JC. Reduction in triglyceride level with N-3 polyunsaturated fatty acids in HIV-infected patients taking potent antiretroviral therapy: a randomized prospective study. *J Acquir Immune Defic Syndr* 2007;**44**:278–285.
- Kabir M, Skurnik G, Naour N, Pechtner V, Meugnier E, Rome S, Quignard-Boulangé A, Vidal H, Slama G, Clement K, Guerre-Millo M, Rizkalla SW. Treatment for 2 mo with n 3 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. *Am J Clin Nutr* 2007;**86**:1670–1679.
- Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**:685–696.
- Alfaddagh A, Elajami TK, Ashfaq H, Saleh M, Bistrián BR, Welty FK. Effect of eicosapentaenoic and docosahexaenoic acids added to statin therapy on coronary artery plaque in patients with coronary artery disease: a randomized clinical trial. *J Am Heart Assoc* 2017;**6**:e006981. doi:10.1161/JAHA.117.006981.
- Rana JS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VY, Chinnaiyan K, Chow BJ, Cury R, Delago A, Feuchtnner G, Hadamitzky M, Hausleiter J, Kaufmann P, Karlsberg RP, Kim YJ, Leipsic J, Labounty TM, Lin FY, Maffei E, Raff G, Villines TC, Shaw LJ, Berman DS, Min JK. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography Evaluation For Clinical Outcomes): an International Multicenter Registry. *Diabetes Care* 2012;**35**:1787–1794.
- Bhatt DL. REDUCE-IT: residual cardiovascular risk in statin-treated patients with elevated triglycerides: now we can REDUCE-IT! *Eur Heart J* 2019;**40**:1174–1175.