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Comparison of Mineral Oil and Non-Mineral Oil Placebo on Coronary Plaque Progression by Coronary Computed Tomography Angiography

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Short title: Lack of Effect of Mineral Oil on Coronary Plaque Progression

Tweet: This study finds no evidence that mineral oil placebo in the quantities used have any harmful effect on plaque progression.

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Introduction

Liquid mineral oil or light paraffin oil has been used as a placebo in clinical trials of icosapent ethyl including MARINE, ANCHOR, and REDUCE –IT. Mineral oil was chosen as a suitable placebo to mimic the consistency, color, and odorless properties of icosapent ethyl capsules. Since the results of REDUCE-IT, a few have raised questions regarding 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.[1] Mineral oil has been utilized in humans as a laxative for decades (typically in doses of 15 – 45 grams/day), and the general safety has been inferred from clinical utilization. The ~2 grams 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 grams 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.[2] 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 ischemia and adverse cardiac outcomes.[3-5] 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 versus the non-mineral oil placebo arm from another randomized clinical trial, GARLIC 5.[6] 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.

Methods

The study design and rationale for EVAPORATE and GARLIC5 have been published previously.[2, 6] Eligible patients in EVAPORATE had known coronary atherosclerosis, elevated triglycerides (200–499 mg/dL), and low-density lipoprotein levels (LDL-C) ≤115 mg/dL while on statins. In GARLIC5, to be eligible, participants had coronary artery calcium scores greater than 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 GARLIC5 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).[7] Pharmaceutical grade mineral oil placebo used in EVAPORATE consisted of a purified liquid mixture of straight chain saturated hydrocarbons that met the compendial requirements of the United States National Formulary (NF) for light mineral oil and of the European Pharmacopoeia (Ph. Eur.) for light liquid paraffin oil.[8, 9] The total daily dose of mineral oil placebo was four 1 g soft gelatin 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 GARLIC5 includes (per 100 mg) microcrystalline cellulose: 89.83 mg, hydroxypropyl cellulose:10.07 mg, and caramel 0.10 mg.

Analysis of covariance test was used to examine rates of progression between the groups. The final model was adjusted for baseline plaque, 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.

Results

Mean (SD) age of participants (n=60) was 59 (9.9) years and 66% were male. A total of 28 participants from the GARLIC5 placebo arm and 32 participants from the EVAPORATE placebo arm were analyzed. 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 (BMI), hypertension, levels of LDL, total cholesterol, hs-CRP, or use of medications, including aspirin and statins. Due to eligibility criteria of the trials, the GARLIC5 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^3 in the EVAPORATE and 5.49 (1.45) mm^3 in the GARLIC5 placebo cohorts (p = 0.07). Mean (SD) level of log total non-calcified plaque volume at baseline was 4.5 (1.26) mm^3 in the EVAPORATE and 5.25 mm^3 (1.53) in the GARLIC5 placebo cohorts (p = 0.04). At follow up, mean (SD) level of log total plaque volume was 5.23 (1.17) mm^3 in the EVAPORATE and 5.78 (1.18) mm^3 in the GARLIC5 placebo cohorts (p = 0.08). Mean (SD) level of log total non-calcified plaque volume was 5.01 (1.14) mm^3 in the EVAPORATE and 5.54 mm^3 (1.21) in the GARLIC5 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 (β: 0.03± 0.13, p = 0.84) or log total non-calcified

plaque volume (β: 0.01 ± 0.16, p = 0.94) between the placebo participants

in EVAPORATE and GARLIC5. Adjusted multivariable analysis of covariance

tests also did not show any significant differences in progression in log total

plaque volume (β: 0.04± 0.13, p = 0.78) (Figure 1) or log total non-calcified

plaque volume (β: 0.09 ± 0.17, p = 0.58) between the two groups.

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.[10, 11] Changes in levels of LDL-C and inflammatory

markers have been commonly observed in statin-stabilized patients in clinical trials.[12] 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.[13] 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 analyzed, and our clear results on lack of differences in plaque progression between the two placebo groups demonstrates 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, greater than 65% of EVAPORATE participants did have diabetes, and the presence of diabetes was accounted for in our

multivariable analysis.[14] 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.[2, 3]

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.[1, 2, 15] 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.

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Table 1: Baseline Characteristics

	GARLIC5 Placebo (n=28)	EVAPORATE Placebo (n=32)	P value	
	Mean (SD) / Count (%)	Mean (SD) / Count (%)		
Age (years)	58.7 (11.4)	58.6 (8.8)	0.97	.
BMI (kg/m2)	30.8 (6.0)	32.5 (5.4)	0.24	.
Male	21 (72%)	19 (59%)	0.28	*
Type 2 Diabetes	29 (100%)	21 (66%)	<0.001	.
Taking Diabetes Medications	29 (100%)	21 (66%)	<0.001	.
Hypertension	15 (52%)	23 (72%)	0.10	*
Taking Anti-Hypertensive Medications	15 (52%)	23 (72%)	0.10	*
Hyperlipidemia	24 (83%)	31 (97%)	0.09	.
Taking Statins	24 (83%)	31 (97%)	0.09	.
Past Smoker	11 (38%)	13 (41%)	0.83	*
Taking Aspirin	21 (72%)	19 (59%)	0.28	*
Baseline HDL Cholesterol	40.1 (12.6)	37.3 (7.7)	0.29	.
Baseline LDL Cholesterol	72.6 (33.1)	89.9 (38.9)	0.07	.
Baseline Triglycerides	138.8 (79.4)	202.1 (96.7)	<0.01	.
Baseline Total Cholesterol	140.3 (45.4)	156.3 (45.1)	0.17	.
Baseline HsCRP	3.5 (3.9)	2.8 (2.8)	0.42	^
Time Between Scans (Month)	12.2 (0.7)	9.6 (1.2)	<0.001	†

. Independent T Test, *Chi-Square test, -Fisher Exact test, ^Wilcoxon

Cohort Key: GARLIC5 —⊖— EVAPORATE —⊖—
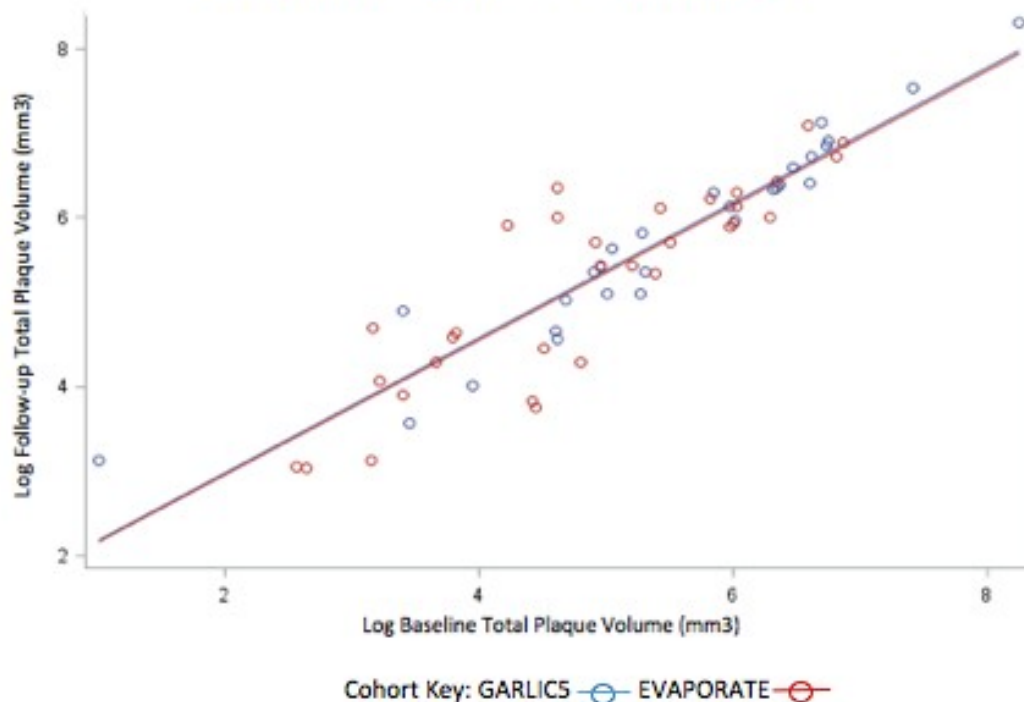
*Adjusted for Age, Sex, Baseline plaque volume, Baseline Triglycerides, Diabetes, and Statin Use

Figure 1: Analysis Of Covariance for Log Adjusted Total Plaque Volume (mm³)