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Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies

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Mineral oil is often used as a clinical trial placebo. Pharmaceutical-grade mineral oil consists of a mixture of saturated hydrocarbons, with a purity and chemical structure that differs substantially from food-grade or technical-/industrial-grade mineral oils. Interest in mineral oil was piqued by suggestions that a portion of the substantially positive results of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) might be attributable to the theoretical negative effects of mineral oil rather than being due to the clinical benefits of icosapent ethyl. The objective of this review was to explore possible mineral oil safety and efficacy effects and contextualize these findings in light of the REDUCE-IT conclusions. A literature search identified studies employing mineral oil placebos. Eighty studies were identified and relevant data extracted. Adverse events associated with mineral oil were generally gastrointestinal and consistent with use as a lubricant laxative. Changes in triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and other biomarkers were inconsistent and generally not statistically significant, or clinically meaningful with mineral oil, as were changes in blood pressure. There was no consistent evidence that mineral oil in the amounts used in the REDUCE-IT or Effect of Vascepa on Progression of Coronary Atherosclerosis in Patients With Elevated Triglycerides on Statin Therapy (EVAPORATE) trials affects absorption of essential nutrients or drugs, including statins. These results were then considered alongside publicly available data from REDUCE-IT. Based on available evidence, mineral oil does not appear to impact medication absorption or efficacy, or related clinical outcomes, and, therefore, does not meaningfully affect study conclusions when used as a placebo at the quantities used in clinical trials.

Introduction

Mineral oil encompasses a wide variety of colourless, odourless mixtures of higher alkanes from a mineral source. Technical- or industrial-grade mineral oil is considered

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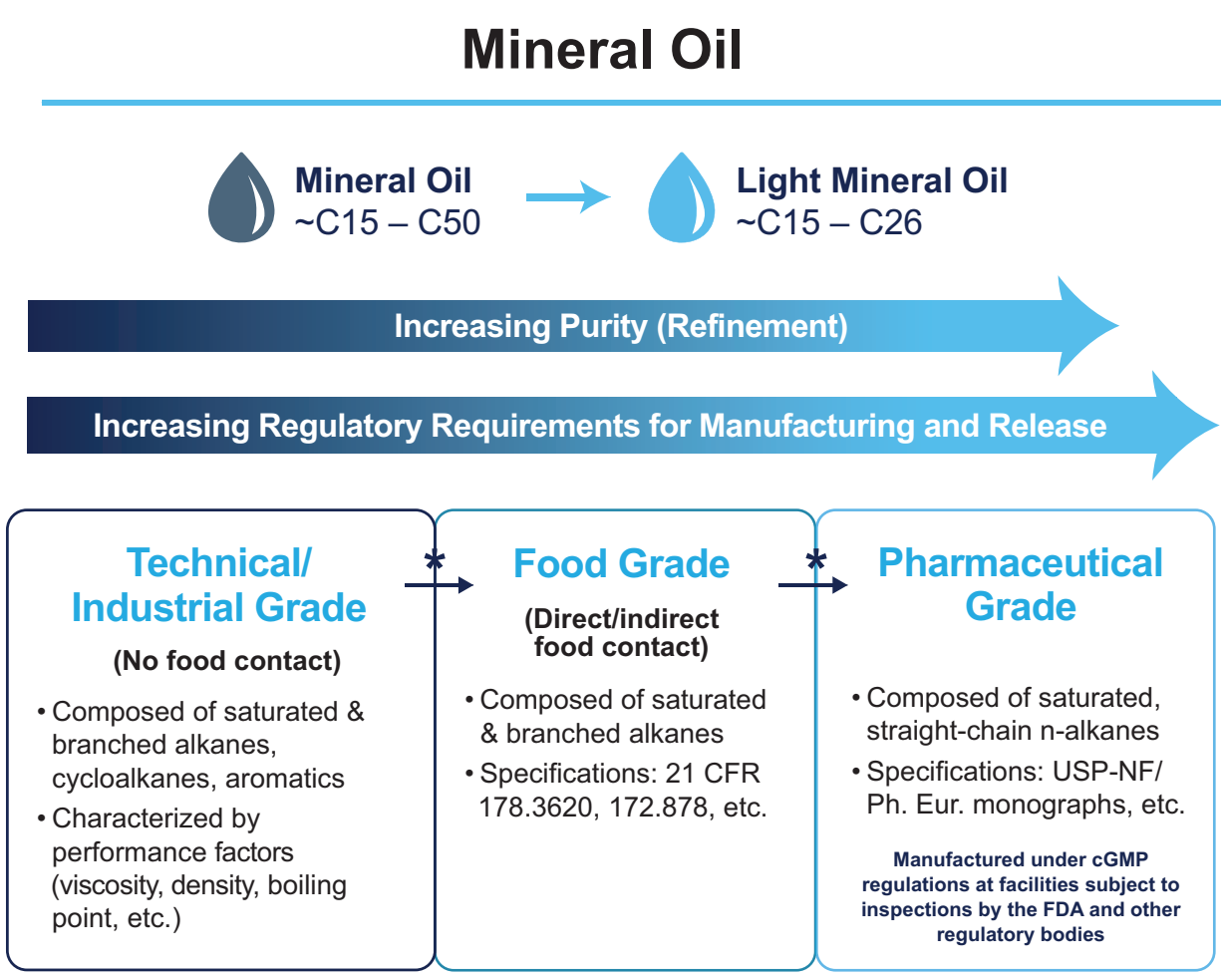

Figure 1 Mineral oil grade classifications.[7,29,30] C, carbon atoms; CFR, Code of Federal Regulations; cGMP, Current Good Manufacturing Practices; FDA, United States Food and Drug Administration; Ph Eur, European Pharmacopoeia; USP-NF, United States Pharmacopoeia-National Formulary. Asterisks and arrows represent refinement/hydrogenation processing steps: removal of impurities such as aromatic compounds, unsaturated compounds, and nitrogen- or sulfur-containing compounds.

crude, with purification leading to food and pharmaceutical grades. Refined mineral oil is composed of a mixture of high-molecular-weight, saturated, iso-, and cyclo-hydrocarbons.[1] When refined into saturated and branched alkanes, mineral oil is considered to be food grade (*Figure 1*). Food-grade mineral oils, at least in small amounts, are 'generally recognized as safe' ('GRAS') food additives by the Food and Drug Administration (FDA), the European Food Safety Authority (EFSA), and the European Commission (EC).[2-4] In large doses, food-grade mineral oil has been used to treat constipation, primarily in children.[5,6] Food-grade mineral oil can be further refined and hydrogenated to remove impurities, and these straight-chain n-alkanes, when manufactured under current Good Manufacturing Practices at facilities subject to inspections by the FDA and other regulatory bodies, are considered pharmaceutical grade (*Figure 1*).[7]

An ideal placebo is inert; however, omega-3 fatty acid (OM3 FA) intervention trials often employ biologically active oils. Saturated, monounsaturated, and omega-6 polyunsaturated fatty acids found in various ratios in olive, corn, safflower, sunflower, and coconut oils may impact various cardiovascular (CV) risk parameters differentially, including blood lipids, glucose metabolism, blood pressure, and inflammatory pathways. Use of these active comparators can make the detection of an effect from OM3 FA intervention more or less likely depending on the choice of placebo.

Due to its inert properties, highly refined, pharmaceutical-grade mineral oils are commonly used as trial placebos, especially when studying agents formulated in oil-based tablets/capsules or agents that are oils, including OM3 FAs (*Tables 1 and 2*). In 2015, the EC amended European Union regulations to add pharmaceutical-grade mineral oils to the list of substances/active ingredients that do not pose a risk.[4] Pharmaceutical-grade mineral oil was used as a placebo for icosapent ethyl (IPE), a highly purified and stable ethyl ester form of eicosapentaenoic acid (EPA), in the Multi-Center, Placebo Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension (MARINE), Effect of AMR101 (Ethyl Icosapentate) on Triglyceride Levels in Patients on Statins With High Triglyceride Levels (ANCHOR), Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention

Trial (REDUCE-IT), and Effect of Vascepa on Progression of Coronary Atherosclerosis in Patients With Elevated Triglycerides on Statin Therapy (EVAPORATE) trials.[8-13]

As highlighted previously, REDUCE-IT reported a significant reduction in major adverse CV events (MACE) by 25%, including a 20% reduction in CV death with IPE. REDUCE-IT randomized statin-treated patients with low-density lipoprotein cholesterol (LDL-C) controlled below 100 mg/dL, but persistently elevated triglyceride (TG) levels of 135–499 mg/dL, to receive EPA (in the form of IPE) 4 g/day (2 g twice daily) or mineral oil placebo 2 g twice daily and demonstrated substantial reduction in the MACE primary endpoint [hazard ratio (HR): 0.75; 95% confidence interval (CI): 0.68–0.83; $P < 0.001$].[8,14,15] While reduction in TG levels may contribute to overall outcomes, they likely did not contribute substantially to the degree of CV risk reduction observed.[16,17] Preclinical and clinical studies support IPE reducing CV events through multiple mechanisms of action, including several that are not fully understood.[18,19] However, a few critics have suggested that the observed reduction in CV risk was not only due to positive effects of IPE but also due to negative effects from the pharmaceutical-grade mineral oil control, a supposition based on small elevations in some lipid levels and inflammatory markers in the placebo arm.[20] The objective of this review is to critically investigate evidence of biological activity, or lack thereof, of mineral oil and review publicly available data from REDUCE-IT.

Methods

This review is based upon a literature search of several databases conducted in October 2019 including: Biomed Central, clinicaltrials.gov, EMBASE, FDA.gov, Google Scholar, Medline/Medline Plus, and PubMed. Additional searches included: Biological Abstracts, Davis' Drug Guide, Drug Delivery Systems, DrugInteractionInfo.org, Enhancement in Drug Delivery, Inchem.org, Medscape, Merck Index, Micromedex/Mayoclinic.com, patents (via Google Scholar), Toxnet.nlm.nih.gov/Hazardous Substances Data Bank, and Up-to-Date.

Key search terms employed included: 'mineral oil', 'paraffin oil', 'liquid paraffin', 'liquid petrolatum', and 'edible paraffin'. In addition, the following search terms were combined with the key search terms: 'placebo'/'control', 'plasma lipids'/'lipoproteins' (and related terms), 'statin', 'safety', 'toxicity', 'pharmacokinetics', 'reactivity', 'laxative', 'stool softener', 'gastric motility', 'generally recognized as safe'/'GRAS', and 'absorption'. Literature searches were performed in the databases mentioned using various combinations of the search terms listed above. Results were not restricted by publication date and both adult and paediatric titles were screened in an attempt to capture the universe of literature on mineral oil.

Identified articles were searched manually by two reviewers for use of mineral oil as placebo in clinical trials, reported changes in blood lipids, use as a laxative, safety, inert properties, and drug interactions. Articles were screened for relevance by title, abstract, and then full text. Only articles describing oral administration of mineral oil were included. Outputs from these searches formed the basis of this review. Citations of relevant articles were screened and added if not otherwise captured by the literature searches. Select REDUCE-IT outcomes were then considered to contextualize the findings from this literature review.

The intent of this review was to provide a broad overview of relevant literature describing mineral oil and its biological properties, with a focus on its impact on CV parameters and outcomes. There was variability in the study populations based on a variety of parameters, such as age (adult vs. paediatric) and region. There was also variability in the type of study (preclinical vs. clinical vs. manufacturing). Within the clinical studies, variation in endpoints existed due to different therapeutic areas and even within the same therapeutic area. Given the degree of heterogeneity, no one data synthesis standard could be applied. As such, relevant findings of each study were extracted, synthesized, and contextualized, including REDUCE-IT findings when appropriate, in a narrative fashion rather than a systematic review or meta-analysis. REDUCE-IT pre-specified and post hoc analyses assessing the potential impact of the mineral oil on efficacy and safety conclusions were summarized and discussed in conjunction with the broad literature overview on mineral oil.

Results

In total, 281 articles were screened. This review identified 80 studies that used some form of mineral oil as a placebo.

Mineral oil—use as a laxative

We found that the only reported biological activity of mineral oil was as a lubricant (i.e. non-stimulant) laxative.[21] Mineral oil treats constipation at doses of 15–45 mL, markedly higher than placebo doses.[5,22] As a lubricant laxative, mineral oil coats the bowel and stool mass with a waterproof film that retards water absorption, leading to retention of moisture in the stool. This softens the stool, easing its passage.[6,23] Mineral oil, as a laxative, has no direct effect on gastric motility, affecting colonic motility secondarily.[24,25]

Safety of mineral oil

Our literature review reported a lack of safety concerns with mineral oil across 80 cited studies. Adverse events (AEs) were generally categorized as unrelated to study treatment. The most common AEs attributed to mineral oil were abdominal pain and distention and watery stools, which are likely related to its laxative properties.[22] Other AEs include pneumonia secondary to aspiration[6,26] and various complications, including an autoimmune syndrome and death, following illegal direct injection of mineral oil as a dermal filler.[27,28]

Pharmaceutical-grade mineral oils are composed of saturated hydrocarbons that are highly refined to achieve extremely low levels of aromatic hydrocarbon impurities and to ensure elimination of carcinogenicity and compliance with international pharmacopoeia monographs (*Figure 1*).[7] Reports of mineral oil toxicity are related to non-

pharmaceutical-grade mineral oil and mainly due to peroxidation of aromatic and saturated hydrocarbon impurities rather than the mineral oil itself.[31]

In pharmacokinetic studies, mineral oil was undetectable in blood samples.[32] Some studies showed mineral oil bioaccumulation in humans as a result of exposure to industrial-/technical- or food-grade mineral oils, which have been detected in fat, mesenteric lymph nodes, liver, and spleen, with lower levels in the lung, kidney, brain, and heart.[33] These mineral oils are derived from food, cosmetics, release agents, lubricating oils, dust binders, packaging materials, and environmental contamination.[1,3] Bioaccumulation of industrial-/technical- or food-grade mineral oil has been reported with longer durations of oral exposure, particularly for n-alkanes with 20–40 carbons.[34] However, similar to above, these findings do not apply to pharmaceutical-grade mineral oil.

Concerns regarding long-term toxicity of mineral oil due to its accumulation in the liver are largely derived from animal studies that have been extrapolated to humans.[7] For example, liver granulomas related to mineral oil have been observed in F-344 rats with exposure, although such granulomas have not been reported in humans.[35,36] This response may be specific to this strain of rat and may not be relevant to humans, who respond to hydrocarbons more similarly to rat strains that do not produce granulomas.[35,36] Evidence from decades of clinical use support safety of alkanes from mineral oils in humans.[7]

Lack of effects on blood lipids

Of the 80 studies identified that used mineral oil, only 28 reported changes in blood lipids or blood pressure and are summarized in *Tables* 1–3. *Table 1* includes 11 studies in which patients had CV disease (CVD) and/or diabetes,[8-10,37-44] while *Table 2* includes 17 studies conducted in healthy volunteers or patients with non-CV conditions, such as schizophrenia, non-alcoholic steatohepatitis, renal disease, polycystic ovary syndrome, rheumatoid arthritis, HIV infection, alcohol dependence, and cancer.[45-61]

In studies with mineral oil arms, changes in TG levels and lipids, in general, were mixed and inconsistent. In trials conducted in patients with CVD or diabetes, TG levels changed by a range of −16% to +18.5%; six studies showed an increase in TG levels[9,10,37,39,41,43] and five showed a decrease (*Table 1*).[8,38,40,42,44] The greatest change in TG level (18.5%) was reported in a study of 21 patients with rheumatoid arthritis.[59]

Low-density lipoprotein cholesterol changes from baseline in these trials ranged from −6.1% to 9.2% (*Tables 1 and 2*).[8-10,37-44]High-density lipoprotein cholesterol (HDL-C) changes from baseline were generally small and ranged from −7.1% to +27.9% (*Table 1*).[8-10,37-44]

The only study in which mineral oil placebo was associated with a statistically, but not clinically, significant change was REDUCE-IT (>8000 patients), in which the median TG level increased from 216 mg/dL to 221 mg/dL at the end of year 1 ($P < 0.001$), a 2.2% increase which, in turn, was significantly different than the 18.3% reduction from baseline seen with IPE at year 1 ($P < 0.001$).[8] A statistically significant 10.2% (7.0 mg/dL) increase was observed in LDL-C values in the statin-controlled placebo group at the end of year 1 ($P < 0.001$) vs. a 3.1% (2.0 mg/dL) increase in the IPE group ($P < 0.001$). In REDUCE-IT, there was minimal association of outcomes to increases or decreases in LDL-C or TG levels during follow-up.[16]

The remaining studies were relatively small. Only the ANCHOR study had >100 patients taking a mineral oil regimen.[10] Six of the CV studies reported on statin use; the remainder did not document statin use (*Table 1*).[8-10,37,38,42] In the non-CV studies summarized in *Table 2*, the changes in TG, LDL-C, and HDL-C levels ranged from −16% to +19%, −6% to +3%, and −9% to +9%, respectively.[45-61] The only non-CV study in which any of these changes was statistically significant was a 12% increase in TG levels in terminal renal failure patients on chronic haemodialysis.[47] Statin use was not reported in 19 of 21 non-CV studies and was prohibited in the other 2 studies.[45,58]

Lack of effect on inflammatory markers

Of the 80 trials identified that used mineral oil, 16 reported high-sensitivity C-reactive protein (hsCRP) levels ranging from −15.9% to +33.3%; levels were increased in 10 studies,[8,40,42,53,55,56,62-64] decreased in 5 studies,[47,50,61,65,66] and unchanged in 1 study.[67] As with lipid parameters, most changes were inconsistent and not reported as statistically significant.

A statistically significant increase in hsCRP level was reported in REDUCE-IT (from 2.1 mg/L at baseline to 2.8 mg/L) after 2 years and at the last visit ($P < 0.001$), compared with a decrease in the IPE arm (from 2.2 mg/L to 1.8 mg/L; $P = 0.04$ after 2 years).[8] hsCRP is subject to high intra- and inter-individual variability and is heavily influenced by transient conditions, such as minor trauma, inflammatory processes, and infections.[68] However, concentrations were measured only at three time points in REDUCE-IT (baseline, year 2, and last visit)[8]; given that hsCRP values are highly variable, clinical significance of these observations is unlikely, particularly in statin-treated patients. Formal analyses of a theoretical mineral oil effect evaluated during an FDA Advisory Committee showed that hsCRP changes had little to no impact on the primary and secondary composite endpoints of REDUCE-IT (*Figure 2*, Supplementary material online, *Table S1*).[16] Inconsistent increases and decreases in other inflammatory markers across a range of conditions, including interleukin (IL)-6,[56,62,66,69,70] IL-1β,[56,61,70,71] IL-10,[69] tumour necrosis factor-α,[37,56,61,69,70,72] intercellular adhesion molecule 1,[62] monocyte chemoattractant protein-1,[71] and immunoglobulin E[52] have been reported. However, these changes have been small and in general, the clinical significance of hsCRP changes in CV outcome trials is unclear.

Lack of effect on blood pressure

As with blood lipids, most trials identified through our literature searches did not report on-study blood pressure within mineral oil arms. Trials that did report blood pressure are summarized in *Table 3*, and include seven studies.[40-42,54,60,61,73] More than half of the studies were conducted in CV or high-risk patients, and, similar to blood lipids, results were highly variable. For systolic blood

Table 1 Reported biomarker changes in mineral oil placebo groups from cardiovascular disease and diabetes studies

Author	n^a	Dose and mineral oil used	Patient population	Statins	Duration of treatment	TG (% change, BL to EOT)	LDL-C (% change, BL to EOT)	Non-HDL-C (% change, BL to EOT)	HDL-C (% change, BL to EOT)
Bhatt *et al.*,[8] 2019	4090	4 g/day, mineral oil	Aged ≥45 years with established CV disease or aged ≥50 years with diabetes and ≥1 additional CV risk factor	Required; 63.0% moderate intensity; 30.0% high intensity	Median 4.9 years	−6.5%	+10.5%	+4.6%	+5.0%
Bays *et al.*,[9] 2011	75	4 g/day, LLP	TG ≥500 mg/dL and ≤2000 mg/dL	Allowed	12 weeks	+9.7%	−3.0%	+7.8%	0%
Ballantyne *et al.*,[10] 2012	227	4 g/day, not specified	TG ≥200 and <500 mg/dL; LDL-C ≥40 mg/dL and <100 mg/dL	Required	12 weeks	+5.9%	+8.8%	+9.8%	+4.8%
Kabir *et al.*,[37] 2007	14	3 g/day, paraffin oil	Type 2 diabetes mellitus; without HTG	Allowed ($n = 5$)	8 weeks	+10.5%	0%	NR	+7.1%
Gholamhosseini *et al.*,[38] 2015	31	Edible paraffin	Men with CV disease	84% in placebo group on statin	8 weeks	−11.2%	+6.7%	NR	+12.2%
Hosseini *et al.*,[39] 2013	35	5 mL/day, mineral oil	Type 2 diabetes mellitus	NR	2 months	+6.0%	+3.0%	NR	+3.9%
Mortazavi *et al.*,[40] 2018	23	4 g/day, edible paraffin	Male subjects aged 45–55 years with CV disease and ≥50% occlusion in 1 coronary artery	NR	8 weeks	Decreased 21.59 mg/dL	Increased 9.43 mg/dL	NR	Increased 3.81 mg/dL
Golzari *et al.*,[41] 2019	18	2 g/day, edible paraffin	Diabetes for ≥1 year, aged 35–50 years, and taking antidiabetic drugs for ≥3 months	NR	8 weeks	+3.1%	+3.4%	NR	+0.4%
Agh *et al.*,[42] 2017	21	Edible paraffin	Men with CAD, ≤50% stenosis in ≥1 major coronary artery in the last 3 months, and BMI ≤30 kg/m^2 Individuals using warfarin excluded from participation	Statin therapy in 92% (does not refer specifically to the control arm)	8 weeks	−11.5%	+9.2%	NR	+27.9%
Mazaherioun *et al.*,[43] 2017	44	2.7 g, edible paraffin	Men aged >30 years and premenopausal women aged >30 years; BMI 25–40 kg/m^2 with type 2 diabetes	NR	10 weeks	+3.0%	+1.7%	NR	−3.9%
Ramezani *et al.*,[44] 2018	20	4 soft gel edible paraffin capsules/day	Coronary vascular disease	NR Patients not taking fibrates	8 weeks	−8.9%	+8.5%	NR	+3.0%

BL, baseline; BMI, body mass index; CAD, coronary artery disease; CV, cardiovascular; EOT, end of treatment; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported; OM3, omega-3 fatty acid; TG, triglycerides.

[a]Number of participants in the mineral oil placebo group.

Table 2 Reported effect on lipid parameters in mineral oil placebo groups from non-CV disease and diabetes studies

Author	n^a	Dose and mineral oil used	Patient population	Statins	Duration of treatment	TG	LDL-C	Non-HDL-C	HDL-C
De Truchis *et al.*,[45] 2007	62	2 g/day, paraffin oil	HIV patients on antiviral therapy; BL TG >200 mg/dL and <1000 mg/dL	Patients taking lipid-lowering drugs excluded	8 weeks	+6.4%	NR	NR	+8.08%
Horrobin *et al.*,[46] 1991	10	4 g/day over 7 days, liquid paraffin	Healthy adults	NR	10 days	No change	NR	NR	NR
Lemos *et al.*,[47] 2012	60	2 g/day, mineral oil	Terminal renal failure undergoing chronic haemodialysis	NR	120 days	+12.5%	−6.1%	NR	+1.7%
Emsley *et al.*,[48] 2008	33	2 g/day, medicinal liquid paraffin	Schizophrenia or schizoaffective disorder and coexistent tardive dyskinesia	NR	12 weeks	−13.3%	0%	NR	−7.1%
Fogaça *et al.*,[49] 2011	11	NA, paraffin	Alcohol-dependent patients	NR	90 days	NR	NS	NR	NS
Mohammadi *et al.*,[50] 2012	31	2 g/day, liquid paraffin	Women with polycystic ovary syndrome	NR	8 weeks	−4.8%	0%	NR	−0.9%
Peet and Horrobin,[51] 2002	6	4 g/day; liquid paraffin	Schizophrenia; all six patients on clozapine	NR	12 weeks	+15.8%	NR	NR	NR
Yang *et al.*,[52] 1999	18	5 g/day, paraffin oil	Atopic dermatitis	NR	1 month 4 months	−1.8% 0%	+2.4% +1.0%	NR	+3.6% +6.4%
Nogueira *et al.*,[53] 2016	28	4 mL/day, mineral oil	Non-alcoholic steatohepatitis	NR	6 months	BL: 148.6 mg/dL EOT: NR P = NS	BL: 116.6 mg/dL EOT: NR P = NS	NR	BL: 52.1 mg/dL EOT: NR P = NS
Allain *et al.*,[54] 2009	8	3 g/day, paraffin oil	Healthy volunteers	NR	6 weeks	No significant change	No significant change	NR	No significant change
Mirmasoumi *et al.*,[55] 2018	30	1 g/day, liquid paraffin	Polycystic ovary syndrome	NR	12 weeks	+8.6%	+3.1%		+1.9%
Paixao *et al.*,[56] 2017	22	2 g/day, mineral oil	Breast cancer patients	NR	30 days	−16%	−3.1%	NR	+2.1%
Mejia-Montilla *et al.*,[57] 2018	85	Mineral oil capsule	Women with polycystic ovary syndrome and vitamin D deficiency	NR	12 weeks	+0.8%	+1.7%	NR	−3.4%
Ghorbanihaghjo *et al.*,[58] 2012	43	1 g, paraffin pearl in the fasted state	Adult females diagnosed with RA and on a fixed therapeutic schedule for	Patients taking lipid-lowering drugs excluded	3 months	NR	NR	NR	BL: 38.6 mg/dL EOT: 38.2 mg/dL

(continued)

Table 2 Continued

Author	*n*[a]	Dose and mineral oil used	Patient population	Statins	Duration of treatment	TG	LDL-C	Non-HDL-C	HDL-C
			≥2 months before study entry						
Kremer *et al.*,[59] 1985	21	1.8 g/day, non-digestible paraffin wax	Rheumatoid arthritis	NR	12 weeks	+18.5%	NR	NR	NR
Ferreira *et al.*,[60] 2019	80	5 oral drops of placebo (1% powdered lemon flavour, 0.2% ethylene-diamine-tetraacetic acid, liquid flavour qs, and liquid petrolatum qsp in 20 mL)	Post-menopausal women aged 50–65 years	NR	9 months	+1.6%	−2.2%	NR	−0.4%
Rashidmayvan *et al.*,[61] 2019	22	1 g/day, paraffin oil	Patients aged 20–60 years with non-alcoholic fatty liver disease	NR	8 weeks	−1.0%	−1.0%	NR	+1.7%

BL, baseline; CV, cardiovascular; EOT, end of treatment; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported; NS, not significant; TG, triglycerides.
[a]Number of participants in the mineral oil placebo group.

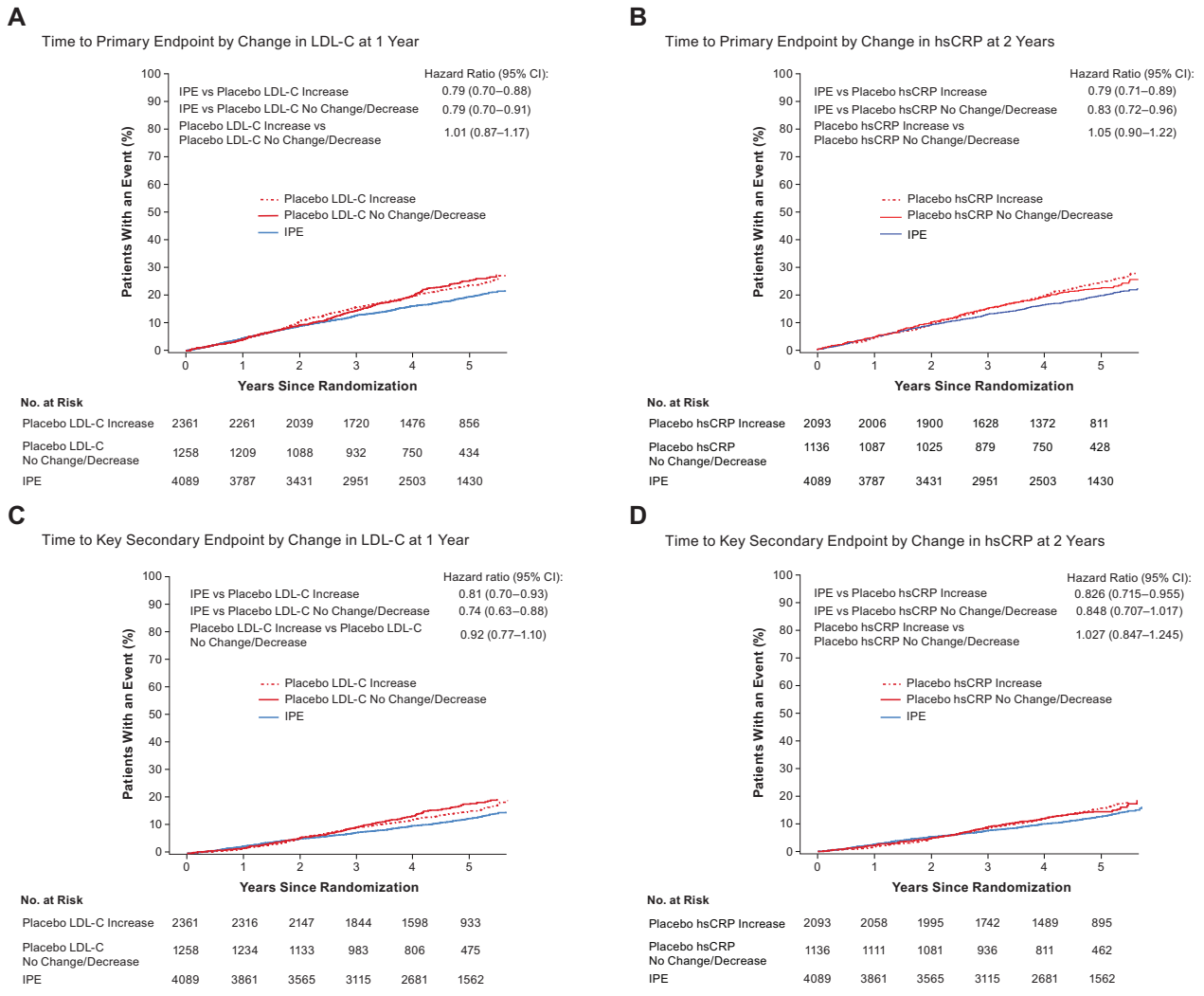

Figure 2 Time to key primary and key secondary composite endpoint for icosapent ethyl and placebo by low-density lipoprotein cholesterol (*A* and *C*) and hsCRP (*B* and *D*) increase or no change/decrease (intent-to-treat population). The icosapent ethyl and placebo groups were compared regarding increases and no change/decreases in low-density lipoprotein cholesterol or high-sensitivity C-reactive protein levels for key REDUCE-IT primary and key secondary composite endpoints. Changes in these biomarkers did not influence time to primary and key secondary endpoints. CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; IPE, icosapent ethyl; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

pressure, reported changes ranged from a 0.3 mmHg decrease to a 2.5 mmHg increase.

Lack of absorption interference

Mineral oil's activity as a laxative (coating the bowel and stool with waterproof film) has been postulated by some to have a theoretical impact on absorption of drugs and essential nutrients. It has been suggested that mineral oil may interfere with the absorption of vitamins A, D, E, and K, although the evidence of this is generally weak and contradictory.[74] Although a few have warned about the possibility of interference by mineral oil on absorption of drugs and nutrients, this appears to be based on theoretical concern rather than actual data, and the risk is likely clinically insignificant.[26,75] Mineral oil likely has no clinically significant impact on absorption of vitamins such as A, E, and K.[21,26] Studies have shown that fatty acids or vitamin D3 formulated in a nanoemulsion delivery system of indigestible mineral oil is less bioavailable than a similar emulsion of digestible corn oil.[76,77] The relevance of these findings to absorption of fat-soluble vitamins and drugs not formulated in a nanoemulsion is not clear, as a vitamin D intervention study using pure liquid paraffin as a placebo found no reduction in vitamin D levels in the placebo group.[73]

Databases of drug–drug interactions provide no evidence of an interaction between mineral oil and statins or other medications.[78,79] A recent analysis compared plaque morphology changes in the mineral oil placebo arms of two coronary plaque studies; the EVAPORATE trial, which used the same mineral oil placebo as REDUCE-IT, compared with a

Table 3 Reported effects on blood pressure in studies with mineral oil placebo groups

Author	*n*[a]	Dose and mineral oil used	Patient population	Statins	Duration of treatment	SBP	DBP	MAP
Mortazavi *et al.*,[40] 2018	23	4 g/day, edible paraffin	Male subjects aged 45–55 years with CV disease and ≥50% occlusion in 1 coronary artery	NR	8 weeks	Decreased 0.29 mmHg	Increased 0.24 mmHg	NR
Golzari *et al.*,[41] 2019	18	2 g/day, edible paraffin	Diabetes for ≥1 year, aged 35–50 years, and taking antidiabetic drugs for ≥3 months	NR	8 weeks	BL: 124.11 mmHg EOT: 124.89 mmHg	BL: 80.00 mmHg EOT: 80.00 mmHg	BL: 94.70 mmHg EOT: 94.96 mmHg
Agh *et al.*,[42] 2017	21	Edible paraffin	Men with CAD, ≤50% stenosis in ≥1 major coronary artery in the last 3 months, and BMI ≤30 kg/m^2 Individuals using warfarin excluded from participation	Statin therapy in 92% (does not refer specifically to the control arm)	8 weeks	BL: 125.43 mmHg Change: −0.28 mmHg	BL: 77.86 mmHg Change: +0.23 mmHg	NR
Allain *et al.*,[54] 2009	8	3 g/day, paraffin oil	Healthy volunteers	NR	6 weeks	NR	NR	Increased from 87.0 to 90.4 mmHg during hyperinsulinemic clamp; $P < 0.05$
Ferreira *et al.*,[60] 2019	80	5 oral drops of placebo (1% powdered lemon flavour, 0.2% ethylene-diamine-tetra-acetic acid, liquid flavour qs, and liquid petrolatum qsp in 20 mL)	Post-menopausal women aged 50–65 years	NR	9 months	BL: 136.5 mmHg EOT: 139.0 mmHg $P = NS$	BL: 81.0 mmHg EOT: 81.3 mmHg $P = NS$	NR
Rashidmayvan *et al.*,[61] 2019	22	1 g/day, paraffin oil	Patients aged 20–60 years with non-alcoholic fatty liver disease	NR	8 weeks	BL: 125.45 mmHg EOT: 127.77 mmHg $P = NS$	BL: 79.45 mmHg EOT: 77.59 mmHg $P = NS$	NR
Mozaffari-Khosravi *et al.*,[73] 2015	20	1 oral capsule pure liquid paraffin per week	Aged 25–50 years with definite diagnosis of hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) and presence of vitamin D deficiency	NR	8 weeks	BL: 145.1 mmHg EOT: 146.0 mmHg	BL: 93.1 mmHg EOT: 94.1 mmHg	BL: 110.4 mmHg EOT: 111.4 mmHg

BL, baseline; BMI, body mass index; CAD, coronary artery disease; CV, cardiovascular; DBP, diastolic blood pressure; EOT, end of treatment; MAP, mean arterial pressure; NR, not reported; OM3, omega-3 fatty acid; SBP, systolic blood pressure.

[a]Number of participants in the mineral oil placebo group.

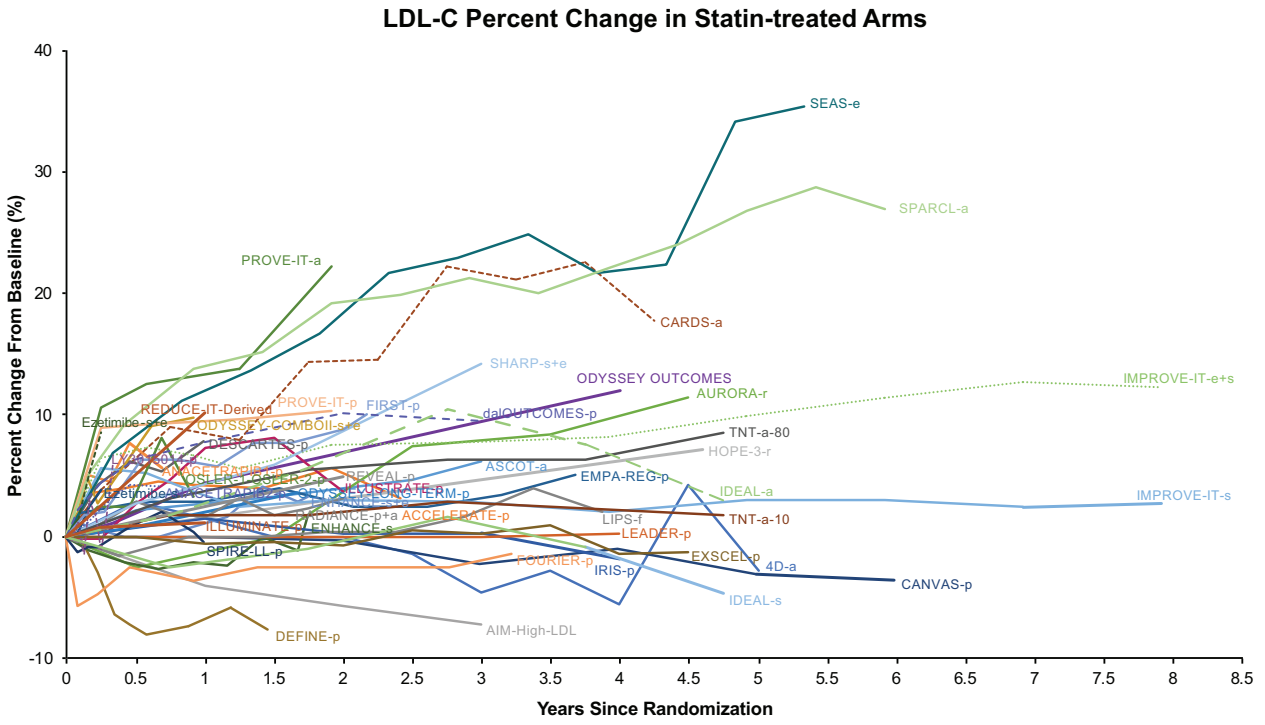

Figure 3 Overview of the low-density lipoprotein cholesterol percentage changes observed in statin-treated cohorts from recent (published since 2003) cardiovascular outcome trials and other long-term studies that reported at least two statin-treated low-density lipoprotein cholesterol measurements over time, along with a comparison to low-density lipoprotein cholesterol changes in the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT). All plots represent statin-only arms, as represented by placebo (p) or statin (r = rosuvastatin, s = simvastatin, a = atorvastatin) or +e (ezetimibe), depending on the study. 4D, Die Deutsche Diabetes Dialyse Studie; ACCELERATE, Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes; AIM-HIGH, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; ASCOT, Anglo-Scandinavian Cardiovascular Outcomes Trial; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects On Regular Haemodialysis: an Assessment of Survival and Cardiovascular Events; CANVAS, Canagliflozin Cardiovascular Assessment Study; CARDS, Collaborative Atorvastatin Diabetes Study; dalOUTCOMES, Effects of the Cholesterol Ester Transfer Protein Inhibitor Dalcetrapib in Patients with Recent Acute Coronary Syndrome; DEFINE, Determining the Efficacy and Tolerability of Cholesteryl Ester Transfer Protein (CETP) Inhibition with Anacetrapib; DESCARTES, Durable Effect of PCSK9 Antibody Compared with Placebo Study; EMPA-REG, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; ENHANCE, Effect of Ezetimibe Plus Simvastatin vs. Simvastatin Alone on Atherosclerosis in the Carotid Artery; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; FIRST, Evaluation of Choline Fenofibrate (ABT-335) on Carotid Intima-Media Thickness (cIMT) in Subjects with Type IIb Dyslipidaemia with Residual Risk in Addition to Atorvastatin Therapy; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HOPE-3, Heart Outcomes Prevention Evaluation-3; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid-Lowering; ILLUMINATE, Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events; ILLUSTRATE, Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; IRIS, Insulin Resistance Intervention After Stroke; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LIPS, Lescol Intervention Prevention Study; ODYSSEY-COMBO-II, Efficacy and Safety of Alirocumab vs. Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolaemia; ODYSSEY OUTCOMES: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; OSLER-1, Open Label Study of Long Term Evaluation Against LDL-C Trial; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy; RADIANCE, Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor; REVEAL, Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification; SEAS, Simvastatin Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; SPIRE, Studies of PCSK9 Inhibition and the Reduction of Vascular Events; TNT, Treating to New Targets.

non-mineral oil placebo used in another prospective randomized trial (Garlic 5).[80] The two trials were of similar design, with coronary computed tomography angiography performed in EVAPORATE at baseline and 9 months, and in Garlic 5 at baseline and 12 months. Although populations in the two trials were slightly different, the study did not observe any difference in progression of coronary plaque volumes between mineral oil placebo (EVAPORATE) and cellulose-based placebo (Garlic 5) in multivariable analysis, with virtually identical rates. In addition, a recent meta-analysis by the US Department of Defense, including 21 studies of 869 patients, concluded that, at most, the mineral oil quantities used in REDUCE-IT raised LDL-C levels by <5 mg/dL.[81]

Analyses prepared for an FDA public Advisory Committee showed that LDL-C levels did not influence time to primary and secondary endpoints in REDUCE-IT (*Figure 2*). Similar findings were demonstrated with changes with other biomarkers (Supplementary material online, *Table S1*). The FDA concluded that statin absorption interference was unlikely if the statin is administered separately from mineral oil, and regardless of administration timing, had little impact on the overall conclusions of REDUCE-IT.[82] An analysis of LDL-C percentage changes in CV outcome trials with

Table 4 Treatment-emergent adverse events from REDUCE-IT

	Icosapent ethyl ($n = 4089$)	Placebo ($n = 4090$)	***P*-value**[a]
Patients with at least one TEAE,[b] *n* (%)	3343 (81.8)	3326 (81.3)	0.63
Serious TEAE	1252 (30.6)	1254 (30.7)	0.98
TEAE leading to withdrawal of study drug[c]	321 (7.9)	335 (8.2)	0.60
Serious TEAE leading to withdrawal of study drug[c]	88 (2.2)	88 (2.2)	1.00
Serious TEAE leading to death[d]	94 (2.3)	102 (2.5)	0.61

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the safety population. Events that were positively adjudicated as clinical endpoints are not included. From Ref.[8] Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

[a]*P* value from Fisher's exact test.

[b]All TEAEs are coded using the Medical Dictionary for Regulatory Activities version 20.1.

[c]Withdrawal of study drug excludes patients who were off drug in study for 30 days or more, and restarted study drug.

[d]The most common serious TEAEs leading to death by system organ class were neoplasms (1.1%); infections and infestations (0.4%); respiratory, thoracic, and mediastinal disorders (0.2%); cardiac disorders (0.2%); and vascular disorders (0.1%). No serious TEAEs leading to death by system organ class were statistically significant across treatment groups except for cardiac disorders, which occurred in 3 (0.1%) of icosapent ethyl patients and 15 (0.4%) of placebo patients ($P = 0.008$).

statin-treated cohorts from 2003 to 2019 showed that 79% of studies reported increases in LDL-C after statin stabilization similar to those observed in REDUCE-IT placebo patients (*Figure 3*).

Discussion

This comprehensive review found no consistent pattern of changes in lipid levels and inflammatory markers in patients given mineral oil. Even in those studies where statistically significant changes were reported, changes were generally small and were of no clinical significance. No relevant safety concerns, including CV AEs, have been identified with oral administration of mineral oil, including in children receiving a high volume to treat constipation.[6,22,26]

There appears to be no effect on CV outcomes of the observed LDL-C increase in placebo patients in REDUCE-IT, and such a change in statin-controlled patients is not expected to be predictive of CV outcomes. Even if one were to explore a theoretical increase in CV risk due to the observed increase in LDL-C within the placebo group, the 5 mg/dL difference between the placebo and treatment groups would be estimated to increase the risk of CVD events by 2–3% in the placebo group,[83–87] which cannot account for the overall robust and consistent REDUCE-IT findings, including a 25% relative risk reduction in the primary endpoint, and a 32% reduction in total ischaemic events.[88,89] The REDUCE-IT results are also in agreement with the observed risk reduction in the JELIS study, which did not administer a mineral oil placebo within the control group.[8,90] The independent Data and Safety Monitoring Committee (DMC) of REDUCE-IT met regularly and monitored changes in biomarkers in the placebo arm, and changes in LDL, TGs, and hsCRP in the placebo arm were not significantly associated with CV outcomes.[91]

Consistent with the REDUCE-IT DMC's findings, the FDA independent analysis concluded that the small degrees of changes in biomarkers could not account for the 25% relative risk reduction seen in REDUCE-IT, with the ultimate conclusion that such small theoretical impacts, if real, would not change the overall study conclusions.[82] This conclusion is in agreement with our review of the mineral oil literature.

Finally, it is worth noting that examination of the rates of treatment-emergent AEs between IPE and mineral oil placebo in REDUCE-IT showed no significant differences, whether a very sensitive or very specific definition was used (*Table 4*).[8] In fact, the actual rates were almost identical in the two treatment arms. Thus, in the overall trial, the drug was tolerated as well as and as safely as the placebo. Importantly, this also means that the placebo was tolerated as well and as safely as the drug, arguing against any clinically meaningful toxicity from the mineral oil placebo.

Limitations

This review has several limitations. It is likely that not all studies using a mineral oil placebo were identified, as many do not describe the composition of placebo in detail. Nonetheless, a lack of data reporting the use of mineral oil likely suggests little to no clinical impact of mineral oil in such studies. For all studies identified, mineral oil was the placebo (except for paediatric constipation studies); as a result, no placebo-controlled trials reported the clinical and biochemical effects of mineral oil. Nonetheless, the substantial use in clinical studies, with a general lack of AEs being associated with mineral oil, suggests a lack of safety concerns.

Many of the studies identified were small and not designed or powered to evaluate possible effects of mineral oil (or the active comparator) on lipids and

inflammatory markers. Although REDUCE-IT is a comparatively larger study, it too was not powered to compare differences in biomarkers. As such, although small changes in biomarkers may be statistically significant, their clinical significance is debatable. These studies covered a range of clinical conditions, so not all data included lipid levels and inflammatory markers. The studies in this analysis included a range of mineral oil formulations and intakes ranging from 1 to 5 g/day, over varying lengths of administration, which potentially complicated data interpretation.

Conclusions

The preponderance of evidence identified in this review confirms that mineral oil is essentially inert, with no systemic effects in humans when taken orally, other than a lubricating laxative effect in the gastrointestinal tract. While some changes in select biomarkers were reported in REDUCE-IT patients randomized to mineral oil placebo, similar increases in lipid biomarkers within statin-treated patients have been seen in other contemporary lipid CV outcome trials, and importantly, no clinical impact of such biomarker changes in the REDUCE-IT placebo group was observed. Prespecified and *post hoc* analyses of REDUCE-IT support that on-treatment EPA levels, not choice of placebo, overwhelmingly accounted for the robust REDUCE-IT clinical findings.[16] Multiple analyses by distinct and independent groups conclude that even if theoretical mineral oil effects were real, such effects would be small and would not impact study conclusions or the robustness of the CV event risk reduction observed in REDUCE-IT.

Supplementary material

Supplementary material is available at *European Heart Journal Supplements* online.

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Conflict of interest

B.O. reports serving as the Amarin DMC chair, Boehringer Ingelheim GLORIA AF-US co-coordinator, Sanofi Aventis consultant, and Respicardia consultant. M.J.B. has received grant support and is on the speaker's bureau for Amarin Pharma, Inc. S.P., L.J., C.C., A.G., R.J., and R.D. are stock shareholders and employees of Amarin Pharma, Inc. D.L.B. serves as the Chair and International Principal Investigator for REDUCE-IT, with research funding from Amarin to Brigham and Women's Hospital. D.L.B. discloses the following relationships—Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, 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), Contego Medical (Chair, PERFORMANCE 2), 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 the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, 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), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, and Takeda. The other authors have no conflict of interest to declare.

Data availability

No new data were generated or analysed in support of this research.

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