Editorial

ANNALS OF MEDICINE & SURGERY

OPEN

Cardiovascular outcomes and coronary artery disease prevention secondary to icosapent ethyl: a meta-analysis of randomized clinical trials

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We read the letter of concern by Sephy Philip, PharmD, published about our paper titled 'Cardiovascular outcomes of ethyl eicosapentaenoic acid in diabetes mellitus: a meta-analysis,' which was retracted on 11 November 2022, in the journal 'Annals of Medicine and Surgery'[1]. The letter published by Mr Phillip has raised a valid concern about Icosapent ethyl (IPE), an ester form of an ethyl eicosapentaenoic acid[2]. We highly appreciate the feedback provided by Mr Philip. Our meta-analysis had systematic search strategy errors, specifically using Boolean Operators, including "OR" and "AND" binders. We used the keywords "Vascepa" and "eicosapentaenoic acid (EPA)" as major items in our search strategy rather than the medical subject heading (MeSH). This can sometimes introduce a potential mistake as it includes synonyms with an entirely different class of action of medications. This was brought to our attention immediately after the paper was published in October 2022. A study published by Professor José Antonio Salvador-Oliván, MD, PhD, in April 2019 included 137 systematic reviews, and interestingly, up to 92.7% of studies had some systematic search strategy errors[3]. Furthermore, the study also reported that 78.1% of the errors were the effect of recalls, which constitutes the most common source of error. The most common search errors can be due to errors in natural language processing or can be related to MeSH terms. Also, to improve the quality of the manuscript, it is important to check the MeSH database in PubMed, see associated Keywords, and run multiple advanced search methodologies[3].

We performed a root cause analysis of our search strategy and methodology. We found that IPE is a highly purified prescribed ester form of EPA rather than EPA, and this terminology varies in different major clinical trials[4–6]. Furthermore, there has been data that simple fish oil-omega-3 docosahexaenoic acid (DHA) and EPA are not helpful in the secondary prevention of cardiovascular disease compared to the prescribed IPE form[7]. Our initial manuscript included Trials such as ORIGIN[8], ASCEND[9], Alpha Omega[10], and JELIS[5]; among these trials, only one trial had IPE, and the rest of the trials had a combination of EPA and DHA, so our results were skewed as search strategy missed significant studies. We took immediate action and retracted our paper in November 2022 after publication at the end of October 2022.

We re-performed a high-quality systematic search strategy based on the methodology mentioned by Bramer *et al.*[11] and Atkinson *et al.*[12] We registered our meta-analysis on PROSPERO (ID: CRD42023443467). Ours aligns with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR-2 (Assessing the methodological quality of Systematic Reviews-2) guidelines[13,14]. (Supplementary S1, Supplemental Digital Content 1, http://links.lww.com/MS9/A542 and Supplementary S2, Supplemental Digital Content 2, http://links.lww.com/MS9/A543). We included patients aged greater than 18 years taking IPE in addition to a statin in the experimental group (IPE) vs. patients taking a statin alone or with a placebo in the control group (Control). We only included randomized controlled trials (RCTs) reporting on cardiovascular outcomes in our analysis. We excluded those not reporting on cardiovascular outcomes[15–21], those reporting on carotid artery parameters[22,23], and those not involving IPE[8–10,24]. A systematic search was conducted on PubMed and Embase using MeSH terms and Keywords such as: "eicosapentaenoic acid ethyl ester," "ethyl-EPA," "ethyl eicosapentaenoic," "Icosapent-ethyl," "Epadel" (brand name of IPE used outside US[25]), "AMR-101", or "Vascepa." These terms were combined using the Boolean operator "OR." Analysis was done using *CRAN-R* software to calculate pooled effect sizes. A meta-bin module was used along with the Mantel–Haenszel random-effects model to calculate the pooled relative risk (RR) with a probability value of $P < 0.05$, considered statistically significant. The "test for overall effect" was reported as a *z*-value corroborating the 95% confidence interval's inference. Higgins *I*-squared (I^2) was determined to measure statistical heterogeneity where values of 50% or less corresponded with low to moderate heterogeneity, while

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:4941–4943

Received 20 February 2024; Accepted 25 February 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 3 July 2024

http://dx.doi.org/10.1097/MS9.0000000000002215

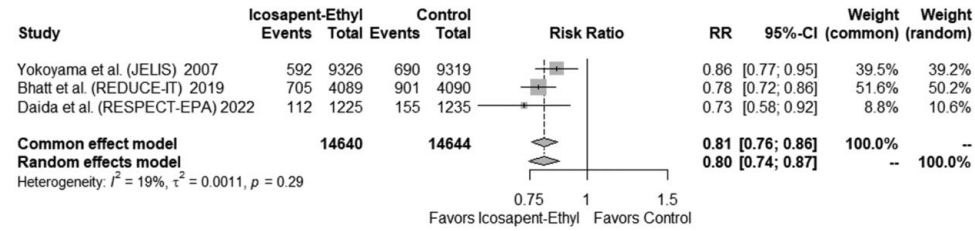

Figure 1. Primary outcome – composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and revascularization.

values at least 75% indicated high heterogeneity[26,27]. Quality assessment was done using the Cochrane Risk of Bias tool[28].

Our search yielded 844 articles. After removing duplicates and initial screening, 38 articles were left, which underwent full-length screening. Among them, three studies fulfilled our inclusion and exclusion criteria[5,6,29,30] (Supplementary S3, Supplemental Digital Content 3, http://links.lww.com/MS9/A544). These studies included 29 284 patients in IPE and 14 644 patients in the Control group. The mean age of patients included in the studies treated with IPE was 62.42 ± 6.84 years, while the mean age of patients in the control group was 62.43 ± 7.59 years (Supplementary S4, Supplemental Digital Content 4, http://links.lww.com/MS9/A545 and Supplementary S5, Supplemental Digital Content 5, http://links.lww.com/MS9/A546).

The primary outcome [composite of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina, and coronary revascularization] showed a statistically significant difference in favor of the IPE group (RR: 0.80; 95% CI = 0.74–0.87; $P < 0.0001$; Fig. 1). This effect was not seen in primary prevention cases (RR: 0.86; 95% CI = 0.73–1.02; $P = 0.07$); however, IPE was beneficial in secondary prevention as compared to the control arm (RR: 0.76; 95% CI = 0.70–0.83; $P < 0.0001$) (Supplementary S6, Supplemental Digital Content 6, http://links.lww.com/MS9/A547). Secondary efficacy outcomes such as fatal or non-fatal MI (RR: 0.72; 95% CI = 0.62–0.82; $P < 0.0001$), unstable angina requiring hospitalization (RR: 0.73; 95% CI = 0.62–0.85; $P < 0.0001$), coronary revascularization (RR: 0.76; 95% CI = 0.62–0.94; $P = 0.0117$) were statistically significant in favor of the IPE group. While other secondary efficacy outcomes, such as stroke (RR: 0.87; 95% CI = 0.63–1.21; $P = 0.415$), all-cause mortality (RR: 0.97; 95% CI = 0.80–1.18; $P = 0.79$), cardiovascular death (RR: 0.83; 95% CI = 0.69– .00; $P = 0.05$) and sudden cardiac death (RR: 0.78; 95% CI = 0.55–1.10; $P = 0.148$) did not show statistically significant changes. Among safety outcomes, there was a statistically significant bleeding risk in patients taking IPE as compared to control (RR: 1.50; 95% CI = 1.13–1.99; $P = 0.005$). However, in terms of total adverse events (RR: 1.08; 95% CI = 0.94–1.25; $P = 0.296$) and gastrointestinal adverse events (RR: 1.45; 95% CI = 0.61–3.45; $P = 0.396$), there was no significant difference (Supplementary S7, Supplemental Digital Content 7, http://links.lww.com/MS9/A548).

Moderate-to-severe heterogeneity was mostly seen in all-cause mortality outcomes, coronary revascularization, stroke, total adverse events, and gastrointestinal events. This could be explained by sampling error. Moreover, if the number of studies is less than 10, it is impossible to differentiate between true heterogeneity and findings merely by chance[31]. The risk of bias analysis is shown in Supplementary S8 (Supplemental Digital Content 8, http://links.lww.com/MS9/A549).

Our results show that IPE use was associated with lower odds of the primary composite outcome compared to a control group of patients. At the same time, no difference was seen in cardiovascular mortality and all-cause mortality between the groups. Further, we found that IPE use was associated with lower odds of fatal and non-fatal MI and revascularization needs, but not stroke. Our analysis included studies that lead to clinical guidelines of American College of Cardiology (ACC) Expert Consensus 2021 that stated indication of IPE as an adjunct to statins for patients with triglycerides greater than 150 mg/dl with established coronary artery disease/atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus with two ASCVD risk factors[32]. Our analysis correlates with the guidelines after adding the RESPECT EPA trial, given that IPE is helpful in the secondary prevention of established cardiovascular disease with triglyceride greater than 150 mg/dl. We concluded that IPE is beneficial in the secondary prevention of cardiovascular mortality under guideline-directed recommendations. Finally, we thank Mr Philip for his input and feedback.

Ethical approval

Ethics approval was not required for this meta-analysis.

Consent

Informed consent was not required for this meta-analysis.

Source of funding

None.

Author contribution

Y.S.: study concept and design, data collection, analysis, and writing the paper; M.C.A.: study concept and design and critical review.

Conflicts of interest disclosure

We do not hold any conflicts of interest with any pharmaceutical company, including personal or professional. The letter to the editor is solely for educational purposes and medication awareness among the healthcare community.

Research registration unique identifying number (UIN)

PROSPERO 2023, CRD42023443467.

Guarantor

Yasar Sattar, MD; M. Chadi Alraies, MD.

Data availability statement

Publically available data.

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