GOED is aware of interventional clinical studies that have reported a potential increased risk of atrial fibrillation in patients taking EPA/DHA products, and of meta-analyses summarizing these results. The most recent (and most comprehensive) meta-analyses (Gencer2021 and Yan2022) have reported that the risk of atrial fibrillation increases with EPA+DHA dosage, which is strongly indicative that this adverse effect is real. However, due to limitations in the existing research, determining the real magnitude of the effect has been a challenge, and it is too early to determine a quantitative assessment of its frequency, so a "not known" description is probably more appropriate. The reasons for this are multiple:

1. Systematic Bias

The existing combined research covered by the meta-analyses of Gencer2021 and Yan2022 is at high risk of three serious types of systematic bias: reporting bias, informative censoring bias, and self-reporting bias. The effect of each would be to artificially inflate the risk estimates.

There are, to date, at least 42 clinical trials of duration > 1year using an EPA+DHA agent that have reported cardiovascular outcomes (Bernasconi2021). However only 7 of these trials have reported the effect of EPA+DHA on atrial fibrillation. It is possible that only trials that considered atrial fibrillation as a pre-specified outcome, or those for which the effect was large enough to surprise the researchers, would report this outcome. If that is the case, then this creates a reporting bias because it would leave a majority of trials where the observed effect was smaller out of the published meta-analyses, which would artificially inflate the reported pooled risk ratio.

The reported risk is further exaggerated by the presence of informative censoring bias (Samuel+Nattel2021). If, as reported by Maki2017, EPA+DHA reduce the risk of cardiac death, or (Bernasconi2021) the risk of multiple cardiovascular outcomes, then EPA+DHA-treated patients had more time and opportunity to develop atrial fibrillation than controls, potentially inflating the incidence of atrial fibrillation in the omega-3 arms of clinical trials.

Finally, estimates of risk are possibly further inflated by an unusual form of self-reporting bias. ASCEND (Bowman2018) originally reported a 2.1% risk of atrial fibrillation in the treated arm, and 1.7% in the placebo arm, for a non-statistically significant risk ratio of 1.23. Atrial fibrillation was not a pre-specified outcome, and its occurrence was only reported to the investigators by the patients themselves. However, subsequent analysis of medical records (Parish2020) found that the real number of cases was underestimated (total numbers were 7.6% and 7.7% in the control and EPA+DHA arms, respectively, essentially the same risk). This raises the possibility that self-reporting, for insufficiently understood reasons, may artificially increase the reported risk of atrial fibrillation due to EPA+DHA, compared to controls. Of the seven trails covered by Yan2022, four relied on self-reporting to estimate the risk of atrial fibrillation (ASCEND, REDUCE-IT, STRENGTH, Risk&Prevention).

2. Comparison between placebo and treated arms

While risk ratios reported by clinical trials are sometimes large, the absolute risks are relatively small. We believe that the correct way to estimate the risk of atrial fibrillation that may be attributed to EPA+DHA treatment is the difference between the absolute risks in the treated and

control arms.

For the trials covered by Yan2022, these numbers are reported in Table 1:

Trial	Control Arm	EPA+DHA Arm	EPA+DHA Attributable risk
ASCEND	1.7%	2.2%	0.5%
REDUCE-IT	2.1%	3.1%	**1.0%**
STRENGTH	1.3%	2.2%	0.9%
Risk&Prevention	1.5%	1.8%	0.3%
VITAL	3.3%	3.6%	0.3%
GISSI-HF	1.4%	1.5%	0.1%
OMEMI	4.0%	7.2%	**3.2%**

Table 1: Absolute atrial fibrillation risk in the control and treated arms of interventional clinical trials, and the risk attributable to EPA+DHA intervention

While the risks, for all trials and arms, surpass the 1/100 (1.0%) cutoff used to assign a "common" risk label, in only two of the trials did the risk attributable to EPA+DHA surpass this cutoff.

REDUCE-IT (Bhatt2019), a high-dosage trial (3.88 g/day of EPA), found an increase in absolute risk of 1.0%, but does not report a confidence interval, making it difficult to determine whether this is a "common" or "uncommon" risk. Even if the real additional risk exceeds 1.0%, it is unclear whether the results of REDUCE-IT (whose composition is a practically pure EPA ethyl ester) can be applied to an ethyl ester containing both EPA and DHA.

OMEMI (Kalstad2021) used 0.85 g/day of EPA+DHA to find an unexpectedly large increased risk of 3.2%. However, the 95% confidence interval for the hazard ratio (1.84 [0.98-3.45]) is too wide to determine with any statistical certainty whether there is indeed increased risk, and whether this increased risk surpasses the 1/100 threshold.

To summarize, for most trials identified to date, the reported potential increased risk of atrial fibrillation that can be attributed to EPA+DHA intervention is under 1.0%, and for the two trials that meet or exceed the threshold, statistical uncertainty makes it impossible to determine whether the real risk is greater or smaller than 1.0%. Additionally, individual studies are at high risk of informative censoring and self-reporting bias, and the totality of the evidence, as reported by recent meta-analyses, is at high risk of reporting bias. These biases would all tend to overestimate the risk.

Estimating the real risk of developing atrial fibrillation that can be attributed to EPA+DHA is challenging. The data presented in Table 1 is consistent with a risk classification of "uncommon" (1/1000 to 1/100), even for the dosages used by Omacor (1.68 or 3.36 g/day), and known systematic biases make any estimate uncertain – the totality of evidence available to date make better estimates impossible.

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