JACC: HEART FAILURE VOL. ■, NO. ■, 2019

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Omega-3 Fatty Acids and Heart Failure

Evidence and Still Open Questions*

Aldo P. Maggioni, MD

Approximately 10 years ago, the first large-scale clinical trial testing omega-3 fatty acids versus placebo in nearly 7,000 patients with heart failure (HF) was publicly presented and published (1). The trial showed that adding 1 gram daily of omega-3 fatty acids to the best medical treatment of those days resulted in a 9% reduction of all-cause mortality and 8% reduction of the combined outcome measure of all-cause death or hospitalization for cardiovascular (CV) reasons over a median follow-up period of 3.9 years. The beneficial effect was modest but statistically significant and obtained in a context of a very reassuring safety and tolerability profile. The favorable message of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca-Heart Failure) trial was mechanistically supported by some other smaller studies suggesting a positive effect of omega-3 fatty acids on left ventricular remodeling, endothelial function, and inflammatory markers (2-3). However, current international guidelines are not giving much consideration to these evidences, not considering at all omega-3 fatty acids (American Heart Association/American College of Cardiology guidelines 2017) or suggesting a weak recommendation (Level 2b/B in the European Society of Cardiology guidelines 2016).

The paper by Block et al. (4) may reopen the discussion on the role of omega-3 fatty acids in the context of prevention and treatment of HF. This study clearly showed a significant independent inverse correlation between circulating levels of omega-3 fatty acids, specifically eicosapentaenoic acid (EPA), and the occurrence of HF over a long median follow-up period of 13 years. In addition, having analyzed the MESA (Multi-Ethnic Study of Atherosclerosis) cohort of patients, authors concluded that plasma levels of EPA can predict the occurrence of HF in all ethnicities. The same authors also offer a pathophysiologic plausibility to these results, showing in animal models with HF that these dietary supplements can preserve left ventricular function and reduce interstitial fibrosis.

A limit of this study is that, due to the relatively low number of cases with HF with preserved ejection fraction, it is not possible to have reliable information on the potential protective role of elevated plasma levels of omega-3 fatty acids on this specific HF condition. Even more important is the consideration that a small number of subjects presented with plasma levels of omega-3 fatty acids sufficiently high to be considered as protective of HF occurrence. This last observation opens the door to the question on the potential preventive role of different dosages of omega-3 fatty acids generally tested and used up to now at the low dosage of 1 gram per day (1). The use of higher dosages of omega-3 fatty acids has been supported by 2 recent studies: the OMEGA-REMODEL (Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction) trial (5) and the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) (6).

In 358 post-infarction patients, the OMEGA-REMODEL trial showed that a 6-month treatment with 4 grams daily of omega-3 fatty acids on top of the current guideline-based standard of care was associated with a reduction of adverse left ventricular remodeling, myocardial fibrosis, and serum biomarkers of systemic inflammation.

The large-scale randomized clinical trial, REDUCE-IT, showed in 8,179 patients with elevated levels of

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the ANMCO Research Center, Heart Care Foundation, Florence, Italy. Dr. Maggioni has received honoraria for participation in committees of studies sponsored by Bayer, Novartis, and Fresenius.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2019.04.007

triglycerides and with an established cardiovascular disease (70% in secondary prevention) or with diabetes mellitus and at least 1 additional risk factor (30% in primary prevention) that the treatment with 4 g/day of EPA was able to significantly reduce by 25% the primary combined endpoint of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, over a median follow-up period of 4.9 years. High dosages of EPA also significantly reduced the typical endpoint of trials of CV prevention (CV death, nonfatal myocardial infarction, and nonfatal stroke) but had no effect on occurrence of HF, contradicting, in some way, the evidence provided by Block et al. (4). However, the rate of occurrence of HF events during the course of the follow-up was low, not allowing a reliable estimate of the EPA effects on this relevant secondary endpoint of the trial.

Which could be the role of omega-3 fatty acids in the field of CV medicine in 2019? With respect to primary CV prevention, several trials showed neutral effects with the use of a dosage of omega-3 fatty acids of 1 gram per day, therefore excluding a relevant role of this treatment (at this dosage) in high-risk patients, but without a prior atherothrombotic event. As far as secondary prevention is concerned, the high dosage of 4 grams per day of EPA was clearly shown to be effective in preventing major atherothrombotic events, including CV death, but not HF.

Considering specifically HF, the study from Block et al. (4) suggests that high circulating levels of omega-3 fatty acids can prevent HF occurrence. The question is: is it sufficient to give dietary advice of an increased fish consumption, or do we need to take purified pharmaceutical supplements such as those tested in trials? In other words, shall we have to go to the fish market or to the pharmacy to elevate our circulating levels of omega-3 fatty acids and, in this way, to try to prevent (or treat) HF?

The recent trials and the observations of the MESA cohort suggests that with very high plasma levels of omega-3 fatty acids we can obtain a reduction of major CV events (6), a prevention of HF occurrence (4), and a favorable effect on the left ventricular remodeling processes (5). High plasma levels of omega-3 fatty acids can probably be achieved just with the use of purified pharmacological preparations.

In any case, if we want to move from hypotheses to more reliable evidence, it is probably the time to redesign adequately sized randomized clinical trials testing high dosages of omega-3 fatty acids on top of current optimized pharmacological and non-pharmacological therapies with the aim: 1) to improve the clinical outcomes of patients with documented overt HF (HF Stage C); and 2) to prevent the occurrence of HF in patients with structural heart disease but without signs or symptoms of HF (HF Stage B). Considering the favorable tolerability and safety profile of this therapeutic approach, any positive results of these trials could provide us with an additional strategy to improve the outcomes of patients with HF or at high risk to develop it.

ADDRESS FOR CORRESPONDENCE: Dr. Aldo Pietro Maggioni, ANMCO Research Centre, Heart Care Foundation, Via La Marmora, 36-50121 Florence, Italy. E-mail: maggioni@anmco.it.

REFERENCES

1. GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. Lancet 2008;372:1223–30.

2. Nodari S, Triggiani M, Campia U, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. J Am Coll Cardiol 2011;57:870–9.

3. Moertl D, Hammer A, Steiner S, Hutuleac R, Vonbank K, Berger R. Dose-dependent effects of omega-3-polyunsaturated fatty acids on systolic left ventricular function, endothelial function, and markers of inflammation in chronic heart failure of non-ischemic origin: a double-blind, placebo-controlled, 3-arm study. Am Heart J 2011;161:915 e1–9.

4. Block RC, Liu L, Herrington DM, et al. Predicting risk for incident HF with omega-3 fatty acids: from MESA. J Am Coll Cardiol HF 2019;7:XXX-XX.

5. Heydari B, Abdullah S, Pottala JV, et al. Effect of omega-3 acid ethyl esters on left ventricular remodeling after acute myocardial infarction: the OMEGA-REMODEL randomized clinical trial. Circulation 2016;134:378–91.

6. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11–22.

KEY WORDS heart failure and prevention, omega 3 fatty acids