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Evidence Report/Technology Assessment
Number 92

Effects of Omega-3 Fatty Acids on Arrhythmogenic Mechanisms in Animal and Isolated Organ/Cell Culture Studies

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report, *Effects of Omega-3 Fatty Acids on Arrhythmogenic Mechanisms in Animal and Isolated Organ/Cell Culture Studies*, was requested and funded by the Office of Dietary Supplements, National Institutes of Health. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services of a particular drug, device, test, treatment, or other clinical service.

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Structured Abstract

Context. Epidemiological studies and clinical trials have reported beneficial effects of fish or fish oil consumption on cardiovascular disease outcomes including sudden death and arrhythmia. The mechanisms of this reported benefit are, however, unclear.

Objectives. As one component of a series of reports on the impact of omega-3 fatty acids on cardiovascular disease, we also performed a systematic review of the literature on whole animal and isolated organ and cell culture studies to assess the effects of omega-3 fatty acids on arrhythmogenic mechanisms and outcomes.

Data Sources. We searched Medline, Embase, Biological Abstracts, and Commonwealth Agricultural Bureau databases for potentially relevant English language studies.

Study Selection. We screened over 1,807 abstracts and retrieved 295 full text articles. Eighty-six studies met our inclusion criteria and provided data to address the key questions in this report. We used comparative studies of whole animal, isolated organ and cells derived from omega-3 fatty acid-fed animals, and isolated organ and cell culture studies, in which the studies quantified the amount of omega-3 fatty acid in the intervention, to assess the effects of the interventions on arrhythmogenic mechanisms and outcomes.

Data Extraction. From each qualifying study, we extracted information about the study design, animal characteristics and model, the amount of omega-3 fatty acid used in the animal diet or in the experiments, the chemical agents used , the conditions under which the experiments were conducted, and outcomes. For whole animal studies, we extracted information about the randomization and blinding techniques to assess methodological quality.

Data Synthesis. Thirteen whole animal studies (rat models) were included in a meta-analysis that compared the anti-arrhythmic effects of ALA or fish oil to omega-6 oils. These meta-analysis results showed that fish oil supplementation showed a significant risk reduction in the number of deaths, ventricular tachycardia (VT), and ventricular fibrillation (VF). The combined risk ratio (RR) for deaths was 0.48 (95% CI: 0.24-0.95). With fish oil supplementation, for VT the RR was 0.49 (95%CI 0.29-0.83), and 0.68 (95%CI 0.50-0.91), for ischemia and reperfusion-induced arrhythmias, respectively. With fish oil supplementation, for VF, the RR was 0.21 (95%CI 0.07-0.63), and 0.44 (95%CI 0.25-0.79), for ischemia and reperfusion-induced arrhythmias, respectively. There was no significant effect for ALA oil supplementation, however.

There were twenty-one studies using isolated organs and cells from whole animals fed omega-3 fatty acids that examined the following parameters: contractile, basoelectromechanical, ion pumps and ion movements, ion currents, and ion channels. Although seven of these studies evaluated the effect of omega-3 fatty acid enriched diets on contractile parameters, they each compared different diets and used different experimental conditions.

Thirty-nine studies evaluated the effect of omega-3 fatty acids on isolated organ and cell cultures. Omega 3 fatty acids were applied either directly to the cell culture medium (free) or

incubated with the cells to allow incorporation into membrane phospholipids (bound). These studies examined parameters similar to the whole animal isolated organ and cell studies. Seven studies of arrhythmia reported that omega- 3 fatty acids (predominantly EPA and DHA but in one instance ALA) appeared to have a protective effect against spontaneous or induced arrhythmias in both rat and guinea pig models. Four of these studies, however, were from the same collaborative group. In the presence of various arrhythmogenic agents and across the different types of species studied, omega-3 fatty acids compared to controls were reported to consistently decrease contraction rate, thereby exerting a protective effect with respect to arrhythmia. In studies without an arrhythmogenic agent, the results were inconsistent, with three showing a decrease in contractility and three showing no effect.

Conclusions. Fish oil supplementation (EPA and/or DHA) might have anti-arrhythmic effects when compared with omega-6, monounsaturated, or saturated fatty-acids in pre-fed fish oil in studies of various animal species. Fish oil supplements in rats showed significant protective effects for ischemia- and reperfusion- induced arrhythmias by reducing the incidence of ventricular tachycardia and fibrillation but no beneficial effects for ALA supplementation were found. The arrhythmic effects for infused omega-3 fatty-acid treatments are still unknown.

In studies using isolated organs and cells from animals fed omega-3 fatty acids and in studies using isolated organ and cell culture where fatty acids were directly applied to the culture medium, the question regarding plausible biochemical or physiological mechanisms to explain the potential antiarrhythmogenic effects of omega 3 fatty acids cannot be answered definitively at this time, despite some apparent trends. Due to numerous sub-parameters within each of the major electrogenesis areas (i.e. ion channels, ion currents, ion pumps and ion movement, contractility) studied , and a variety of experimental conditions, it is more difficult to draw a conclusion about the various parameters.

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