QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCES

OMEGA-3 SUPPLEMENTATION IN CABG PATIENTS: IMPACT ON ICU STAY, AND HOSPITAL STAY (A SYSTEMATIC REVIEW AND META-ANALYSIS)

BY

ASMA OUAGUENI

A Thesis Submitted to

the College of Health Sciences

in Partial Fulfillment of the Requirements for the Degree of

Masters of Science in Health Sciences

January 2024

COMMITTEE PAGE

The members of the Committee approve the Thesis of

Asma Ouagueni defended on 19/12/2023.

Prof. Hiba Bawadi
Thesis Supervisor

Prof. Zumin Shi
Thesis Co-Supervisor

Dr. Abdelhamid Kerkadi
Committee member/External examiner

Dr. Tahra El Obeid
Committee member /Internal examiner:

Dr. Ghadir Fakhri Al Jayyousi
Committee member /Internal examiner

Approved:

Asma Al-Thani, Dean, College of Health Science

ABSTRACT

OUAGUENI, ASMA, RAFIK., Masters of Science : January : 2024, Health Sciences

Title: Omega-3 Supplementation in CABG Patients: Impact on ICU Stay, and Hospital Stay (A Systematic Review and Meta-Analysis)

Supervisor of Thesis: Hiba, Ahmad, Bawadi.

Background: Coronary artery bypass graft surgery is a major surgery that can lead to inflammation and complications, including increased length of ICU stay and length of hospitalization. Omega-3 PUFA has anti-inflammatory properties, and it has been hypothesized that it may reduce these complications in CABG patients.

Objectives: To conduct a systematic review and meta-analysis on the effect of perioperative omega 3 PUFA supplementation on total ICU stay and total hospital stay in CABG patients.

Methods: Randomized controlled trials were included if they studied the effect of omega-3 PUFA supplementation (oral or intravenous) on ICU stay and length of hospitalization in CABG patients. Studies were searched for in Medline (PubMed), EMBASE, PsychINFO, CINAHL, and the Cochrane Central Register of Controlled Trial databases along with hand searching of reference lists. The quality and risk of bias of the included studies were evaluated by two independent reviewers using the revised Cochrane risk-of-bias tool. Meta-analysis was performed using fixed or random effect models according to the level of heterogeneity by mean difference with their 95% confidence intervals.

Results: Twelve studies were included in the qualitative analysis and 7 studies were included in meta-analysis. No statistical difference was observed between the omega 3 PUFA and control groups regarding ICU stay MD -0.25 (95% CI -0.68, 0.17). Omega-

3 PUFA was associated with a significant reduction in days of hospital stay -0.58 (95% CI -1.13, -0.04). Subgroup analysis showed that only oral omega 3 PUFA supplementation resulted in a statistically significant reduction in length of hospitalization after subgroup analysis with MD -0.6 (95% CI -1.17, -0.04).

Conclusion: This systematic review and meta-analysis suggests that perioperative omega-3 PUFA supplementation may reduce the length of hospitalization in CABG patients, especially when administered orally. However, the findings should be interpreted cautiously due to the high level of heterogeneity and the presence of concerns regarding the internal quality and external validity of the included studies.

DEDICATION

"Alhamdulillah, I am very thankful to Allah who is most gracious and merciful, for his countless blessings upon me. To my beloved family, my parents Rafik and Amina, who have always encouraged me to pursue my dreams and supported me throughout my master's journey. To my siblings Fatma Alzahraa, Anfale, Rajaa, Meriem, and Mohamed, for their unwavering love. To my dear and my biggest supporter Mahdi for his unwavering belief in me. To my precious grandmother Zohra, for her love and prayers, which have filled my heart with joy and gratitude. To my Best friends and to Usra, for their endless support and friendship. To everyone who has provided me with a kind word during difficult times. Without your love, care, and the mercy of Allah, I could not have completed my thesis. Alhamdulillah."

ACKNOWLEDGMENTS

I praise and thank Allah SWT for His greatness and for giving me the strength and courage to complete this thesis. Special thanks to all my doctors who taught me during the years of Master program. I am grateful to my supervisor, Professor. Hiba Bawadi for providing me the opportunity to engage in the field of research and for her continuous supervision and support throughout the process of completing this thesis project. I would like to thank Professor. Zumin Shi for his guidance in conducting the research. Finally, I would like to express my deep sense of gratitude to Professor. Mujahed Shraim for his guidance, encouragement, and constructive comments that helped me in completing this thesis project.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1: Introduction

Coronary artery disease is one of the leading causes of mortality and morbidity worldwide [1], therefore, it is managed by multiple procedures including allowing the patient to undergo coronary artery bypass graft (CABG) surgery which is an alternate route (graft) is connected before and after the obstruction leading to allowing the blood to bypass it and renourish the blood flow to the affected areas. Coronary artery bypass graft (CABG) or heart bypass surgery is the most common cardiac surgery procedure in the globe as the average incidence rate is estimated to be 62 per 100,000 persons in Europe and 200,000 cases per year in the United States [2,3]. CABG surgery is a medical procedure that is undergone to improve obstructive coronary artery disease (CAD) [4]. CABG surgery is known to cause inflammation in the body and multiple post-surgical complications leading to increasing length of ICU stay and length of hospitalization post-surgery [5].

Many factors are associated with developing coronary artery disease including smoking[6] , obesity[7,8], and poor diet [9] . Lifestyle factors play a crucial role in the development of CAD, and healthy lifestyle interventions such as diet can effectively reduce the risk of the disease [10,11]. Following Mediterranean diet[12], healthy eating index[13], and dietary approaches to stop hypertension (DASH) diets[14] are suggested to protect against heart diseases. These diets have in common to be rich in omega 3 poly unsaturated fatty acids (PUFA)s. Omega 3 PUFAs are a group of poly unsaturated fatty acids that are obtained from marine and plant sources[15,16]. Three types of omega-3 humans can be obtained from diet which are: Docosahexaenoic acid (DHA), eicosatetraenoic acid (EPA) and their precursor Alpha-linolenic acid (ALA)[17]. In clinical settings the enrichment of Parenteral nutrition (PN) with omega 3 in perioperative status has adverse advantages in terms of length of hospitalization, ICU

admission and reduction in infection rates [18]. These improvements are due to the anti-inflammatory properties of omega 3 PUFAs [19,20].

The effect of perioperative supplementation of omega 3 PUFA on open heart surgeries including coronary artery bypass graft surgeries has been assessed in the literature by several clinical trials and systematic reviews. As it is found to improve post-surgical outcomes including post operative arterial fibrillation (POAF) in open heart surgeries and reducing the risk of mortality post-operatively [21,22]. The effect of omega 3 PUFA on post operative atrial fibrillation is studied extensively and many systematic reviews were conducted in the literature [23-26]. However, other important clinical outcomes such as length of ICU stay, and length of hospitalization post-CABG surgery were not studied extensively and two systematic reviews conducted in 2017 looked at the effect on all open-heart surgeries and the exposures were not limited to only omega 3 PUFA [27,28]. To our knowledge, no systematic reviews have summarized the literature on the effect of only perioperative omega 3 PUFA for patients undergoing mainly CABG surgery and the impact on ICU stay and length of hospitalization.

Aim:

The aim of this thesis is to systematically review and summarize the findings of randomized controlled trials assessing the impact of perioperative omega 3 PUFA administration for patient undergoing CABG surgery and the effect on ICU stay and length of hospitalization.

Objectives:

- To systematically review and summarize the findings of randomized controlled trials on the effect of omega PUFA on ICU stay and length of hospitalization post CABG surgery.
- To conduct a meta-analysis on the effect of perioperative omega 3 PUFA on

post-CABG clinical outcomes (ICU stay) and length of hospitalization.

Chapter 2: Literature Review

Coronary Artery Disease (CAD)

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide [46,47]. In U.S. over 375,000 deaths were due to CAD in 2021 [48]. About 5% of adults aged 20 and older have CAD, and it is responsible for 20% of deaths in adults under 65 years old [48,49]. It is a chronic inflammatory condition characterized by the formation of atherosclerotic plaques within the coronary arteries [50]. Atherosclerotic plaques are composed of lipids, inflammatory cells, and fibrous tissue that can narrow or block the coronary arteries, reducing blood flow to the heart muscle [51]. CAD can manifest as a variety of clinical presentations, including stable angina, unstable angina, myocardial infarction (MI), and sudden cardiac death [52].

The precise etiology of CAD is unknown, but it is thought to be a complex multifactorial disease involving both genetic and environmental factors. Modifiable risk factors for CAD include smoking[53], dyslipidemia[54], hypertension[55], diabetes mellitus [56], obesity[8], and physical inactivity[57]. Non-modifiable risk factors include age[58], gender[59], family history, and race/ethnicity[60].

Significant advances have been made in the diagnosis and treatment of CAD in recent decades. These advances include the development of new pharmacologic therapies, such as statins, antiplatelet agents, and beta-blockers[52]. The antiplatelets agents such as aspirin help to prevent blood clots from forming in the coronary arteries [61]. Beta-blockers help to slow down the heart rate and make the heart work less hard. This can help to prevent heart attacks and strokes [62]. Surgical interventions are also used such as angioplasty. Angioplasty is also known as percutaneous coronary intervention (PCI) is a procedure that is used to quickly open up a blocked coronary artery during a heart attack [63]. In case of acute coronary syndrome (ACS) Coronary artery bypass grafting

(CABG) is a surgical procedure can be when primary percutaneous coronary intervention (PCI) is not feasible or when complications arise [64].

Coronary artery Bypass graft (CABG) Surgery

Coronary artery bypass grafting (CABG) is a surgical procedure to restore blood flow to the heart muscle bypassing blockages in the coronary arteries and involves anastomosing saphenous vein grafts or arterial conduits to the distal coronary arteries beyond the sites of stenosis or occlusion [65]. In the U.S.. there are over 200,000 CABG surgeries performed annually [66]. Patients underwent CABG in cases of high grade blockages in the coronary arteries including left main diseases >50%, blockage of >70% in three-vessel coronary artery disease, two-vessel disease[65]. It is considered a high-risk surgery as it is associated with increased risk of mortality and morbidity post-operatively [67]. CABG surgery carries a risk of complications, including perioperative stroke (1-2%), wound infection (1%), graft failure (up to 25%), renal dysfunction (2-3%), atrial fibrillation (20-50%), and death (1-2%) [68]. Due to these complications, around 14% of Medicare-post CABG patients readmit to the emergency department [69,70].The risk of complications is dependent on the patient's individual characteristics and the specific details of the surgery, such as the type of CABG performed, the number of grafts, and the patient's comorbidities[71].

Surgical Trauma

Surgical trauma is a general disruption in a patient's hemodynamic, metabolic, and immune responses post-operatively[29]. The terminology that describes metabolic instabilities after a trauma is "stress response" [30]. Stress response to surgical trauma is similar to that of accidental injury. The response to surgery was studied by many scientists for many years. Based on the hemodynamic, metabolic, and hormonal status, the "Ebb" and "Flow" terminologies were developed by the scientist Cuthbertson in

1932 to describe the traumatic injury phases [31]. The hypercatabolism and hypermetabolism resulted from the stress response to surgery leads to the development of undesirable outcomes including muscle wasting, impaired immune function, increased risk of infection and deteriorated wound healing, organ failure, and death [32]. Therefore, it is important to ameliorate the systemic inflammatory, hormonal, and metabolic responses through nutrition supplementation and pharmaceutical treatments. Nutritional supplementation with anti-inflammatory and antioxidant molecules such as zinc [33], vitamin C,[34] and omega-3 polyunsaturated fatty acids[35] and combinations of nutrients [36] have yielded positive effects on post-surgical trauma.

Due to the anti-inflammatory and immunomodulatory roles of omega 3 PUFAs, it is highly suggested to be used in cases of hyper-inflammatory status such as surgeries [22,35,37-43]. Docosahexaenoic acid (DHA) and ecosapentanoic acid (EPA) are the building blocks of anti-inflammatory lipid mediators, as well as specific pro-resolving lipid mediators [44]. Through multiple reaction pathways, PUFAs can be involved in the regulation of the inflammatory response. Therefore, increasing omega-3 PUFA while may be a useful strategy for steering the immune response toward resolution of inflammation[45].

Omega 3 poly-unsaturated fatty acids

Omega 3 polyunsaturated fatty acids (PUFAs) or ω-3 brought their name from their chemical structure of having in common a first unsaturated bond (double bond) in the 3rd carbon atom in the methyl (-CH3) end [17]. Omega 3 PUFA is a group of diverse fatty acids, but only 3 molecules are important to the human body which are the α linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)[17]. Since alpha-linolenic acid (ALA) cannot be synthesized by the body and because it is essential

for the maintenance of homeostasis, it must be obtained through dietary sources such as vegetable oil and nuts, flax seeds, and flaxseed oil, green vegetables mainly in purslane, fruits mostly in kiwi and a small amount of animal fat mainly in grass-fed animals [15]. As a result, it qualifies as an essential omega-3 polyunsaturated fatty acid (PUFA)[72,73]. The body uses essential omega 3 PUFA (ALA) by undergoing reactions of chain elongation and desaturation to form other biologically important metabolites which are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [74,75]. Although it is known that ALA is the only essential omega 3 PUFA, it does not form enough DHA and EPA where less than 8% and 4% of body requirements are converted to EPA and DHA, respectively[76,77]. Therefore, the consumption of dietary-rich sources of DHA and EPA mainly from sea food sources can increase their levels effectively [16]. The richest food items of EPA and DHA omega 3 are the marine foods mainly in the cold-water fatty fishes including anchovies and salmon containing EPA and DHA as (2300-2400mg/4oz) and (1200-2400 mg/4oz) respectively[78].

Omega 3 as an anti-inflammatory molecule

The omega 3 PUFA related immunity and inflammatory response reactions are modulated by DHA mainly with participation of EPA by different proposed mechanisms. The first mechanism is by being a precursor for some cell signaling lipid mediators functioning as anti-inflammatory called proresolvings or specialized pro-resolving mediators (SPMs) which are resolvins, protectins and docosatrienes [79]. Their role is characterized by the initiation of inflammation termination or resolution for the restoration of homeostasis [80]. There are two classes of resolvins grouped according to their precursors either from EPA known as E-series (RvE) or DHA known as D-series (RvD) resolvins [81]. The formation of RvE from EPA can be enhanced by the acetylated cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) and Cytochrome P450 [81,82].

Enzymatic conversion of omega-3 polyunsaturated fatty acids into SPMs actively disrupts inflammatory circuits and skews the immune response toward repair and homeostasis [83]. Additionally, certain SPMs suppress viral replication and ameliorate the severity of viral pneumonia in experimental models [84,85]. However, DHA has much wider roles in terminating inflammation by the formation of much wider ranges of pro-resolving molecules including D-series resolvins, protectins and maresins where the latter is a macrophage mediator in resolving inflammation (MaR1) [19,86,87]. The macrophages mediators resolve inflammation by promoting the formation of macrophages through monocytes differentiation that leads to phagocytosis and down-regulating inflammation. These macrophages are activated by the lipid mediators produced from DHA and EPA that has been mentioned previously.

Furthermore, some researchers found that the stimulation of G-protein coupled receptor (GPR 120) by DHA - a DHA receptor in the cell membrane- lead to significant reduction of inflammation [88]. Also, inflammation resolution may be promoted by altering the cell membrane lipid microdomains which are important in the inflammation related cell signaling pathways[89]. DHA can reduce the TLR4, which is a proinflammatory molecule leading to the resolution of inflammation [90]. Omega 3 (EPA and DHA) also are found to resolve inflammation in Alzheimer's Disease (AD) by the stimulation of microglial phagocytosis- a type of macrophage in the central nervous system(CNS)- of specific peptide called Aβ which is believed to induce inflammation, together with the down-regulatory roles of the pro-inflammatory cytokines and the stimulation of neuroprotective brain-derived neurotrophic factor (BDNF) which is proposed as a promising treatment of AD [20]. (Figure 1) summarizes the proposed mechanisms of action of omega 3 molecules (DHA and EPA) in resolving inflammation.

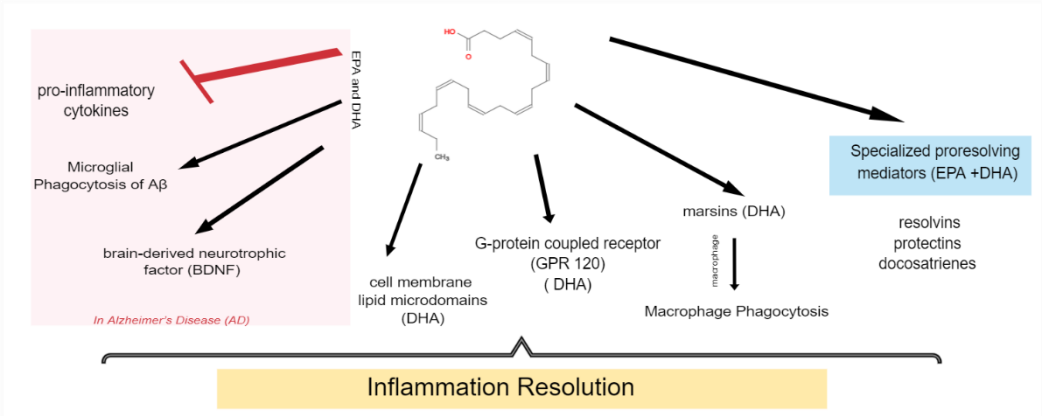


Figure 1. Summary of Inflammatory resolution roles of EPA and DHA through different mechanisms.

Surgical Trauma and post-surgical complications

The systematic response to a surgery is a series of interrelated physiological changes that take place in reaction to a surgical insult [91]. These responses include the overlap of a variety of immunological, endocrine, metabolic, and hemodynamic processes. These physiological changes are similar to other kinds of injuries resulting from burns, infections and traumatic injuries. The response to surgery or other traumas is described by the term systematic inflammatory response syndrome (SIRS) [92]. The stress response to surgery is divided into 2 phases 'ebb' and 'flow'. The initial "ebb phase" is shorter and lasts for 2-3 days is characterized by reductions in cardiac output, basal metabolic rate, oxygen consumption (VO2), and glucose tolerance. While the latter "flow phase" lasts for more than one week depending on surgery or injury severity characterized by being hypermetabolic and catabolic state as having increases in cardiac output, respiratory rate, VO2 , hyperglycemia, skeletal muscle catabolism, and a negative nitrogen balance [93].

Endocrine response:

The afferent stimuli triggers the stress response by sending impulses from the site of the injury to the hypothalamus, which in turn triggers the hypothalamic-pituitary adrenal (HPA) axis to maintain homeostasis following an injury [93] [94,95]. The hypothalamus produces Corticotrophin-releasing hormone (CRH) that stimulate the release of adrenocorticotropic hormone (ACTH) in the blood stream by the anterior pituitary gland. The adrenal cortex also produces glucocorticoid in response to the ACTH resulting in cortisol [91]. The negative feedback that controls the level of cortisol secretion by inhibiting CRH and ACTH secretion becomes blunted during and after surgery resulting in supranormal and continuous release of cortisol. Cortisol is a catabolic hormone that leads to hyperglycemia through gluconeogenesis in liver impacting the surgical outcomes negatively [93]. Furthermore, increased growth hormone (GH) production from the anterior pituitary gland led to further increase in gluconeogenesis and insulin resistance while the antidiuretic hormone (ADH) from posterior pituitary gland results in reabsorption of water and reducing renal output. While on the sympatho-adrenal response results in increased catecholamine release causing hypertension and tachycardia. Other hormones affected by the surgical trauma include, insulin, glucagon, catecholamines, leading to the exacerbation the stress response to surgery [93].

Immune response:

The degree of immune response is multifactorial, but the extent of trauma, infection, and nutritional status are important determinates. It involves the release of pro-inflammatory and anti-inflammatory cytokines and cell-mediated response [91].

Inflammatory markers of including IL-1. IL-6 and tumor necrosis factor-alpha and acute phase proteins such as procalcitonin (PCT) and C-reactive protein (CRP) are massively produced. Uncontrolled inflammatory response results in multiple organ failure (MOF) or stress-induced organ dysfunction correlated with postoperative complications and infections resulting in increased length of hospitalization and mortality [93].

The effect of omega-3 supplementations on traumatic surgical outcomes

Coronary artery bypass graft surgeries:

Intravenous administration:

Intravenous administration of omega 3 PUFA makes it more bioavailable in the blood but shorter duration of intervention when compared with oral administration. The effect of intravenously administered omega 3 on hematological parameters and the activity of platelets was assessed by Miliü Veljoviüet al. [96] they infused 100 ml lipid emulsion of LCPUFA a day before surgery on 4 times intervals before cardiopulmonary bypass which is a surgical procedure that is known to induce inflammation. The intravenously administered n-3 in the interventional group didn't yield any significant effect when compared to the control group of 0.9% saline infusion on hematological parameters, transfusion requirements, and postoperative blood loss, allogenic red blood cells (RBCs), fresh frozen plasma (FFP), platelet units, postoperative blood loss, and post-operative platelet aggregation ADP test. While a significant reduction in post-operative platelet aggregation by the COL test was recorded in the n-3 group.

Mette M berger et al.[97] administered 0.2 g/kg of omega 3 intravenously. Two infusions were at 12 and 2 hrs pre-operatively and the last infusion was immediately after surgery. When compared to the saline group, patients with n-3 had a significant increase in the incorporation of EPA and DHA in platelet membranes. In atrial tissue, significant

incorporation of EPA was found, while no significant difference was observed in the DHA level. Furthermore, there was a significant improvement in inflammatory markers IL-6 and IL-8 and blood glucose levels. While no significant difference was observed between ICU severity score, ICU stays, and kidney function. Finally, Heidt et al.[98] found a significant beneficial effect of 100 mg fish oil infusion/ kg for 12 hrs preoperatively until ICU discharge and assessed the incidence of postoperative atrial fibrillation lasting more than 15 minutes.

Oral supplementation

For the effect of oral administration of omega 3 on surgical outcomes on patients undergoing coronary artery bypass graft surgery, six studies were summarized in table 1. Calò et. Al [99] ound that oral administration of 2 grams n-3 reduced the incidence of POAF >5 minutes (p=0.013) and hospital length of stay (p=0.017), while no effect was observed on the episodes of AF (p=0.889).

On the contrary 2g/day omega 3 orally administered did not lead to any improvement in Overall incidence of AF (P=0.28), Clinical AF (p=0.60), AF burden (p=0.49), hospital stay (p=0.49), and Length of stay in ICU/HDH 1 day (1 to 2 days) when provided on the time interval of 21-12 days preoperatively until discharge in saravanan study in 2010 [100]. Similarly in sandesara et al study[101], 4 g/day preoperatively and 2g/day post operatively and until the development of atrial fibrillation or until day 14 did not improve any of the following outcomes: AF (p=0.67), Legth of hospital stay (p=0.27), Congestive heart failure (p=0.68), Myocardial infarction (p=1.00), Bleeding requiring reoperation or transfusion (p=0.18), Infection (p=0.79), Renal failure (p=1.0), Respiratory failure (p=1.0) Stroke or transient ischemic attack (p=1.0), Rehospitalization for AF 1 (p=1.0), Readmission to intensive care unit (p=0.64), and Death within 30 d (p=1.0).

The effect of omega 3 supplementation on ECG atrial arrhythmic markers conducted by saravanan and colleagues on 2016 [100] did not yield any significant effect on ECG P-max duration, POAF (p=0.74), ECG P-wave duration (p=0.25), Cx 40 expression (p=0.40), Cx 43 expression (p=0.44), Incidence of AF (p=0.26), Total AF burden (p=0.62).

Omega 3 PUFA did have a significant reduction in the duration of atrial fibrillation (p=0.04), ICU stays (p=0.003), and hospital stays (p=0.04) in vasheghani farahani et al study[102]. Finally, the incidence of AF in the n-3 groups was reduced by 72%(OR 0.28 (p=0.013)), and AF was reduced in "on-pump" CABG surgery only. While the length of hospital stay didn't change significantly (p=0.75) in sorice, M et al study[103].

Liver surgeries

A meta-analysis of patients who underwent liver tumor surgery found that omega-3 fatty acids significantly reduced the incidence of postoperative infections, but only when given continuously during the perioperative period, not just before or after surgery. Omega-3 fatty acids did not affect mortality, liver failure, biliary leakage, bleeding, or ileus [41].

The largest and most recent randomized controlled trial (RCT) included in the meta-analysis found that intravenous omega-3 fatty acids (Omegaven) did not protect against postoperative complications. This suggests that reducing inflammation is not enough to prevent complications after liver surgery[43]. Another RCT found that omega-3 polyunsaturated fatty acid (PUFA)-based lipid emulsions were safe and effective in reducing inflammation, protecting liver function, and reducing the overall rate of complications and hospital stay in patients after hepatectomy[104]. Experimental studies have shown that omega-3 PUFAs can effectively reduce severe hepatic steatosis and protect the liver from ischemia-reperfusion injury[105].

Furthermore, omega 3 supplementation may be a better option than very low calorie diets for reducing liver steatosis prior to bariatric surgery in morbidly obese women. In a study by Bakker et al. (2019), omega-3 supplementation (2 g/day) for 4 weeks was found to reduce overall liver volume, left liver lobe volume, and visceral fat area to the same extent as a very low-calorie diet (800 kcal/day). However, the very low-calorie diet was associated with more complications [106]. The authors suggest that the beneficial effects of omega-3 supplementation may be due to its anti-inflammatory properties. Low-grade inflammation is associated with obesity and liver steatosis. Omega-3 fatty acids have been shown to reduce inflammation by a variety of mechanisms, including inhibiting the production of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines. Omega 3 supplementation is less restrictive and allows for more food consumption (2000 kcal/day) making it more likely that patients will be able to adhere to the diet and avoid the malnutrition that can occur with very low-calorie diets.

Omega 3 and deep vain thrombosis after femoral fracture

There are very scarce data about the effectiveness of omega 3 supplementation on post-surgical outcomes following femoral fracture surgeries. Omega-3 fatty acid supplementation may reduce the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) following femoral fracture surgery in the elderly. According to our knowledge, only one RCT (n=452 elderly participants (intervention-226 & control-226)) looked at the association between post-surgical risk of deep vein thrombosis and pulmonary embolism following proximal femoral fractures. The authors hypothesized that providing omega 3 supplements orally on regular basis can effectively lead to lowering the risk of post-surgical pulmonary embolism, venographic events as well as symptomatic deep vein thrombosis [38]. The possible mechanism of action could be due

to the anti-thrombotic effects of EPA.

A rat tail thrombosis model also showed that oral EPA intake significantly reduced the lesion area, demonstrating its antithrombotic effects[107]. Furthermore, two longitudinal studies found that higher intake of sea sources of omega-3 and higher serum omega-3 levels were negatively correlated with mortality and VTE rates in the elderly population [108,109].

Chapter 3: Methods

The current systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[110] provided in Appendix A. And registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the protocol number CRD42023318725. The review protocol was amended at the early stage of study screening as it was noticed that there were new and recently published systematic reviews and meta-analyses addressing the effect of omega 3 PUFA on post-operative atrial fibrillation (POAF) outcome. To avoid duplication, the research question became more concise to look at the effect only on ICU stay and length of hospitalization post CABG surgery as only one systematic review was previously published on this topic in 2017[27].

Search strategy

A comprehensive literature search strategy was conducted on five databases which are: Medline (Pubmed), EMBASE, PsychINFO, CINAHL, and the Cochrane Central. Register of Controlled Trial databases. The Health Databases Advanced Search (HDAS)[111] developed by the National Institute for Health and Care Excellence Databases search was used in collecting articles from the previously mentioned Databases. Furthermore, hand-searching of the supplementary search including reference lists of primary studies, review papers, and previous systematic reviews and meta-analyses was done.

The search initially covered papers up to 15th of March 2021 and then was updated on 12th of September 2023 to ensure an extensive and comprehensive search to include all

the recently published papers reporting on the effects of omega 3 PUFAs on ICU stay and length of hospital stay in patients undergoing CABG surgery. The initial search included concepts of exposure (omega-3 PUFA), population (CABG) and study designs (RCTs) to determine all outcomes studied in the literature. Then the second level of search was more precise and included all the concepts of population (CABG), intervention (Omega-3 PUFA), Control (usual care/placebo), Outcomes (total ICU stay and total hospital length of stay). Appropriate controlled vocabularies or syntax were used in search strategies (e.g. MeSH in pubmed, EMTREE in EMBASE) and free-text terms retrieved through previous systematic reviews search strategy and extra hand search of synonyms was done. Boolean operators "OR" and "AND" were used in creating the search strategy where the former was used for combining synonyms within the same concept and the later for combining different concepts. The following are examples of keywords employed in the search: "Omega-3" OR "Omega 3" OR "Fish oil" OR "Eicosapentaenoic Acid" OR "Eicosapentenoic Acid" OR "EPA" OR "Docosahexaenoic acid*" OR "Docosahexenoic acid*" in all-fields keywords AND "exp *Coronary artery bypass/" OR "aortocoronary Bypass" OR "coronary artery bypass" OR CABG in all-fields keywords. "intensive care unit"/exp OR "close attention unit" OR "combined medical and surgical icu" OR "length of hospital stay" OR "hospitalization"/exp OR "hospital stay" No filters of language, publication year, publication type, or publication status were applied when searching the keywords to ensure the collection of all possible research papers. Details on the search strategy used in the databases are included in Appendix B. And an example of detailed search strategy in one database (EMBASE) is provided in Appendix C.

Eligibility criteria

To structure the eligibility criteria, the PICO/TS framework (Patient/Population;

Intervention; Comparison; Outcome; Timing; Setting/Study design) was used. Included studies were *Population*: adult patients (>=18 years old) undergoing mainly coronary artery bypass graft (CABG) surgery, *Intervention*: only long chain omega-3 Poly-unsaturated fatty acid (PUFA) containing both EPA and DHA molecules. *Time:* provided in duration starting from preoperative until post-operative period. The method of administration was open to either oral supplementation or intravenous administration, *Control*: usual care or other non-fish oils, *Outcomes*: Length of intensive care unit (ICU) stay, and length of hospitalization post CABG surgery. *Setting/Study design*: Randomized controlled trails (RCTs).

The excluded studies were, all non-randomized trails, studies published in languages other than English, performed on other populations e.g., children, used combination of exposures with omega 3 such as vitamins and antioxidants cocktails, duration of supplementation was either pre-operative or post operative only, and looked at outcomes other than hospital length of stay, and ICU stay. Furthermore, studies that investigated the association of other open-heart surgeries, but did not included CABG, with omega 3 or fish oils.

Selection of the studies

The extracted studies were transferred to Rayyan platform [112]. Duplicates were also removed using the Rayyan platform prior to screening. By looking at the papers who had high percentage of similarity above 90% and comparing the abstracts, authors, journal. If they were identical, one paper is deleted. The screening was performed on two phases, the first phase was screening of only titles and abstracts of the retrieved papers, then the included papers were further screened for the full text following the inclusion criteria. The whole screening phase was performed by two independent reviewers to identify articles potentially eligible for inclusion in the systematic review.

Reason for exclusion was documented in case of exclusion of any study. The full texts of the screened studies were then critically reviewed separately for eligibility and data extraction. Any discrepancies in the evaluation between the two reviewers were proactively addressed through regular meetings and in-depth discussions. This collaborative approach aimed to reach a consensus on eligibility and data extraction. By employing these measures, we aimed to enhance the robustness and validity of our systematic review methodology

Data extraction

Data from each study were extracted by one reviewer and revised by another reviewer in Microsoft Excel® form and categorized as follows: first author, year of publication, sample size, number of patients in each study arm (intervention and control), type of trail (double-blind or open-label RCT), control used, omega 3 dose, method of administration (oral or intravenous), duration of supplementation, follow up duration. Outcomes and effects estimates from the intention to treat of the outcomes of interest were extracted. Authors were contacted to obtain missing and unclear information.

Assessment of articles quality

To assure the quality, reliability, and validity of the included studies and to have an insight to which extent are the results concluded in this systematic review and meta-analysis are applicable to the real-world scenarios internal validity through risk of bias assessment was performed. According to the Cochrane Handbook, the Risk of Bias is defined as the systematic error or deviation from the truth leading to under-estimation or over-estimation of the true intervention effect [113].

Since the aim of this systematic review is to collect only randomized controlled trials

addressing the research question, we used the revised Cochrane's risk of bias tool for randomized trials (RoB 2)[114]. The tool is structured into five main domains and signaling questions were answered to propose the judgement using a short version CRIBSHEET algorithm to determine the overall RoB for each study [115]. The quality of selected papers was defined based on 5 domains which are: bias rising from randomization, deviation from intended intervention, missing outcome data, risk of bias in measurement of the outcome, and risk of bias in selection of the reported result. During the assessment of the quality of studies, each study was independently assessed by two reviewers and conflicts were solved by meeting with a third reviewer. The completeness of reporting was assessed by checking if the studies had reported all of the outcomes specified in their protocols. Trial registries were also searched in Cochrane Central Register of Controlled Trial databases. Furthermore, assessment of external validity in terms of generalizability and applicability and source of funding and the presence of conflict of interest were done.

Statistical analysis

Since the outcomes in all studies were reported as continuous variables, the mean difference (MD) was calculated. The mean difference (MD) and 95% CIs were used as the effect size (ES) measure. All results were calculated on an intention-to-treat basis. I^2 statistics were used to test for heterogeneity between studies [28]. A fixed and random effects meta-analysis were used based on the level of heterogeneity of studies. Pooled therapy effect estimate was measured as a weighted average of the therapy effects MD < 0 favoring omega 3 over the control. In studies reporting the outcomes as median and interquartile ranges (IQR), a validated conversion equations were used to calculate mean and SD and they were considered for inclusion in Meta-analysis if the data were normally distributed [116]. Forest plots were used to summarize the clinical endpoints of

interest for each study. The presence of publication bias was assessed through the visual inspection of funnel plot and Egger bias test [117], when sufficient papers were collected for the outcome. If there was no publication bias, the funnel plot would look like a symmetrical and inverted funnel, with a few studies scattered at the bottom. To assess the robustness of the results of the meta-analysis, a sensitivity analysis was conducted by using different statistical models All analyses were performed using STATA SE software version 17 (STATA Corporation, College Station, TX, USA).

Chapter 4: Results

Results of the search:

The comprehensive literature search resulted in total of 878 records from the initial search and 141 from the second search which results in total of 1012 records. Where 871 citations were retrieved from databases and 7 of additional search results were being identified through google scholar, supplementary search of reference lists of included studies, reviews and previously published systematic reviews.

The 871 citations were retrieved from four databases which are: Medline (PubMed), Embase, CINAHL and Cochrane Central Register of Controlled Trail Library. Before screening, 45 duplicates were identified and thereby removed which then resulted in total of 826. Further 803 results were then excluded after screening titles and abstracts. A total number of 23 papers were consequently selected for full text articles screening and were assessed for eligibility. However, 12 records were excluded due to several reasons which are: different population (n=1), different study design (n= 4), outcomes other than the study aim (n= 6), and different exposure (n=1). A table of reasons for exclusions is provided in Appendix D. Furthermore, hand-searching of the supplementary search including reference lists of primary studies, review papers, and previous systematic reviews and meta-analyses was done to make sure a comprehensive literature search strategy. This yielded further 7 studies and 6 of them were excluded because they did not meet the research question, due to different study designs (n=4) and different exposures (n=2). A table of reasons of exclusions after full text is provided in Appendix E. Only 1 study ultimately met the inclusion criteria for the qualitative synthesis. This ended up by having a total of 12 papers included in the qualitative analysis. While the Quantitative analysis was done on 7 articles. The study flow diagram based on the PRISMA checklist is shown in Figure 2.

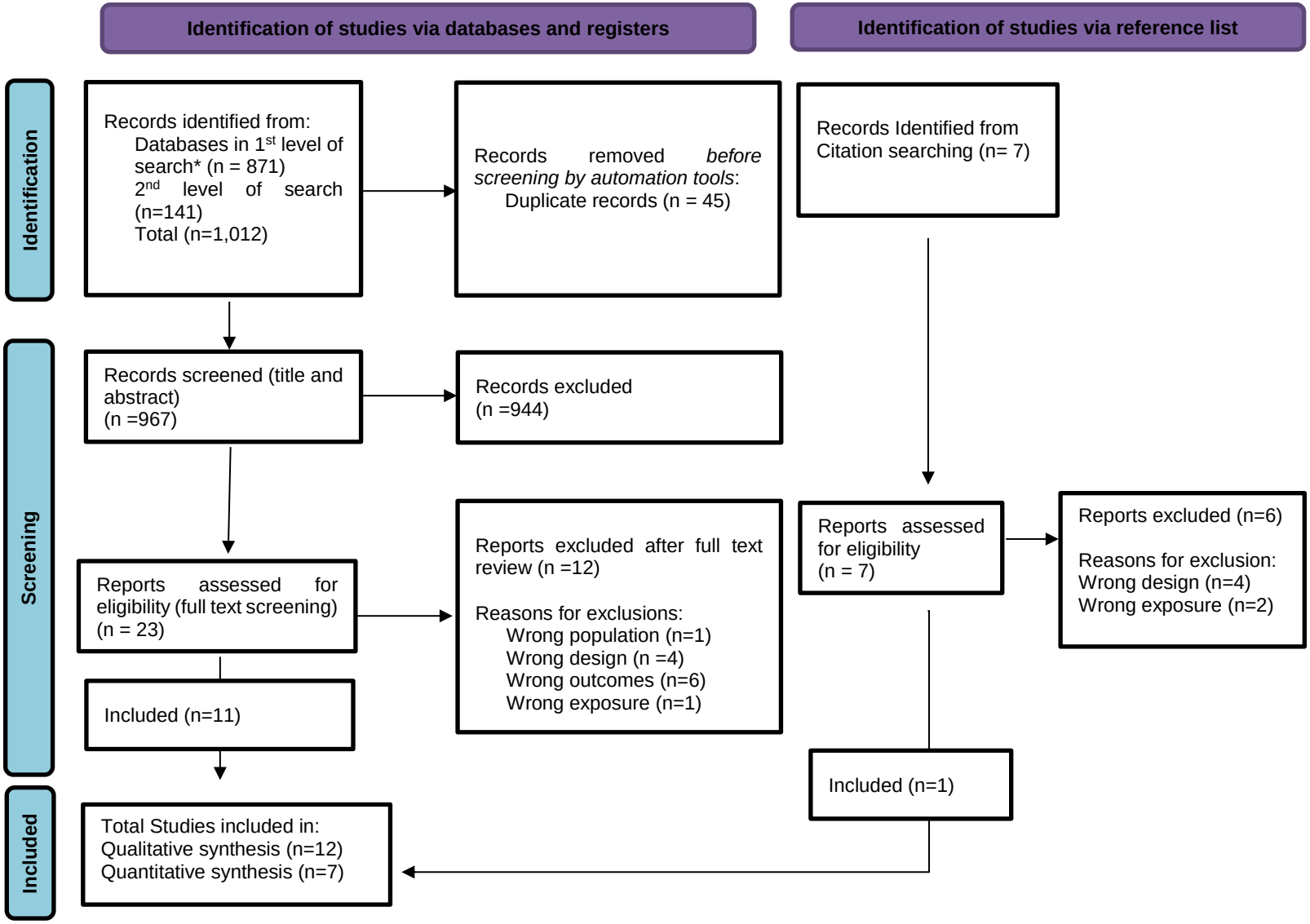


Figure 2. Study flowchart * Medline, Embase, PsychINFO, CINAHL and Cochrane Central Register of Controlled Trail Librar

Characteristics of included studies:

A total of 12 studies met the eligibility criteria for inclusion with a total sample size of (n= 3569) participants. The studies included varied in terms of key characteristics as shown in Table 1. Variation was observed in study design, sample size, types of surgeries, sample characteristics, omega 3 PUFA dose, EPA:DHA ratio, rout of administration, and duration of intervention.

The majority of the studies found on the omega 3 PUFA in relation to intensive care unit stay and length of hospitalization after CABG surgery were double blinded RCTs [98,100-103,118-122] except for two RCTs one of which was open label [99], while the second was single blinded study [97] . In terms of geographic distribution, the studies included were conducted across several regions. Specifically, two studies took place in Germany [97,98], two in Italy [99,103], and an additional two in the United States [101,121]. The remainder of the studies encompassed a variety of locations, including the United Kingdom [100], Australia [120], Iran [102], Mexico [122], and Russia [118]. One large study was conducted in 28 centers across Italy, the United States and Argentina [119]. Sample size varied between 28 - 1516 participants among the different study designs. Due to the nature of the surgery, the participants were older adults and elderly and the mean age of was above 58 years. Most studies had the majority of its participants males in both study arms, one had included only males in their study [122], and another one included only males in the intervention group [97]. Additionally, there were some discrepancies in the type of surgery, some assessed the effect of omega-3 supplementation on patients undergoing only CABG surgery [98,99,102,122]. One study specified the type of CABG and restricted inclusion to patients undergoing CABG by cardiopulmonary bypass (CPB) or "on-pump CABG"[97,100,118]. One compared the impact of CABG operative techniques "on-

pump" or "off-pump" in addition to omega 3 supplementation on surgical outcomes [103]. Four studies included patients undergoing CABG, valve replacement, valve repair or any combination of these surgeries, with the majority of participants undergoing CABG surgery [97,101,119-121]. The majority of studies used oral routes for perioperative omega 3 PUFA administration [99-103,119-122], while only three addressed the effect of short-term perioperative intravenous administration of omega-3 [97,98,118]. Regarding the studied outcomes, ICU length of stay was assessed by nine studies while total hospital length of stay was assessed by eleven papers.

IV administration

The I.V. administration of omega 3 was at 12 or 24 hrs pre-operatively – which is at very short time when compared to oral supplementation- and continued to the first post-operative day, or 2nd to 7th POD or until discharge [97,98,118]. The dose ranged from 100 mg/kg to 400 mg/kg. Ratio of EPA to DHA was not specified in studies.

Oral supplementation

Nine studies introduced omega 3 PUFA by oral supplementation. The lowest dose provided was 1.7 g/day provided by Calò [99]. Four studies provided dose of approximately 2 g/day of omega-3 capsules [100,102,103,121]. One administered 2.4g/day of omega 3 [122]. Two studies provided omega 3 loading of 6 g over 2 days pre-operatively and 10 g loading dose over 3-5 days pre-operatively [101,119]. One study provided the highest dose of omega 3 PUFA of 4.6 g/day in a liquid form of 15 ml/day [120]. The duration of supplementation ranged from a median of 17 days preoperatively to 4 weeks post-operatively or discharge. The most common duration of supplementation was 5 days preoperatively to discharge [99,102,103,119]. There were discrepancies regarding the

ratio of EPA to DHA among studies. Two studies used 1:2 ratios [99,103]. Two provided (1.2:1) [100,101]. While the rest provided (2:3)[121] and (1.5:1)[102] EPA to DHA ratios. Finally, three studies did not report the EPA to DHA ratio [119,120,122]

Table 1: Characteristics of Included Studies in Systematic Review

Study	Country	Design	Surgery	n (I/C)	Age (mean ± SD)	Men (%)	Dose	EPA: DHA ratio	Duration of supplementation	Outcomes Length of hospital stay Length of ICU stay
Berger, M.M 2013 [97]	Germany	RCT, SB	CABG ± valve surgery (CPB)	I: 14	64.7 ± 10.5	14 (100%)	400 mg FO/kg over 2 infusions of 200 mg FO/kg at 12 hrs + 2 hrs Pre-OD 200 mg FO/kg Post-OD	Not specified	Pre-OD 1 to Post-OD 1	(=) ICU stay (P= 0.118)
				C: 14	66.3 ± 9.5	11(78.5 %)	Saline			
Heidt, M.C 2009 [98]	Germany	RCT, DB	CABG	I: 52	M:61.2 ± 14.1 F: 74.4 ± 9.2	38 (73%)	100 mg FO /kg /day	Not specified	12 hrs Pre-OD to ICU discharge	Comparison between pts with AF to without AF (variance analysis) (=) ICU stays (P>0.05)* (=) Hospital stays (p>0.05)*
				C: 50	M: 66.6 ±10.7 F: 70.7 ± 8.2	32 (64%)	FFA 100 mg soya oil/kg/day containing 10 g soya oil			
Lomivorotov, V.V. [118]	Russia	RCT, DB	CABG (CPB)	I: 18	61	17 (94.4%)	<u>Pre-OD 1:</u> 200 mg/kg/day *<u>Post-OD 2 – 7:</u>* 100 mg/kg/day	Not specified	Pre-OD 1 to 2-7 Post- OD	(=) ICU stay (p=0.97) (=) Hospital Stay (p= 0.56)
				C: 21	58	20 (95%)	<u>Pre-OD 1:</u> 2 ml/kg/day *<u>Post-OD 2 –7:</u>* 1 ml/kg/day Intralipid			

Study	Country	Design	Surgery	n (I/C)	Age (mean ± SD)	Men (%)	Dose	EPA:DHA ratio	Duration of supplementation	Outcomes Length of hospital stay Length of ICU stay
Calò 2005 [99]	Italy	OL, RCT, Parallel groups	CABG	I: 81	64.9 ± 9.1	68 (86%)	1.7 g/day 850 mg EPA, 882 mg DHA	1:2	Pre-OD 5 to discharge	(-) length of hospital stays after surgery (p= 0.017)
				C: 79	66.2 ± 8.0	68 (84%)	Usual care			
Saravanan, P., [100]	UK	SC, RCT, BD	CABG (CPB)	I: 52	64 ± 11	40 (77%)	2 g/day	1.2:1	17 days (Median) Pre-OD 12 to 21 until Discharge	(=) Hospital stay (p=0.49) (=) ICU stay (p>0.05)*
				C: 51	64 ± 10	42 (82%)	2 g/d Olive oil		16.5 (Median) (13-21 days)	
Farquharson, A.L. [120]	Australia	DB, RCT	CABG or Valve repair/ replacement	I: 97	64 ± 11	80 (82%)	4.6 g/day as Liquid oil 15 ml/day EPA: 2.7, DHA: 1.9 g/day)	Not specified	3 wk Pre-OP to Post-OD 6 or discharge 22 days (Median)	(-) Length of time in Cardiothoracic ICU (p = 0.006) (=)Total hospital length of stay (p= 0.24)
				C: 97	64 ± 10	62 (64%)	15 ml/day High monounsaturated sunflower oil		21 days (Median)	

Study	Country	Design	Surgery	n (I/C)	Age (mean ± SD)	Men (%)	Dose	EPA:DHA ratio	Duration of supplementation	Outcomes Length of hospital stay Length of ICU stay
Sandesara, 2012 [101] (The FISH trail)	US	MC, DB, RCT	CABG with or without valve surgery	I:120	63.4 ± 9.5	94 (78%)	*Pre-operative*: ≥4 g/day with minimum loading dose of 6 g over 2 days *Post-operative:* 2g/d 465 mg EPA 375 mg DHA	1.24:1	Pre-OD 2 unitl occurrence of AF or 14 days	(=) hospital stay (P=0.27) (=) ICU rehospitalization (p=0.64)
				C: 123	62 ± 11.4	102 (83%)	corn oil 2g/day			
Farahani 2017 [102]	Iran	SC, DB,RCT	CABG	I: 202	60.62 ±8.95	132 (65%)	2 g/day fish oil 300 mg EPA 200 DHA	1.5:1	Pre-OD 5 - Discharge	(-) ICU stay (p=0.003) (-) Hospital stay (p=0.04)
				C: 199	61.28 ± 10	127 (64%)	olive oil soft gelatin capsules			
Sorice M 2011[103]	Italy	DB, RCT	CABG "on-pump" and "off-pump"	I: 96	Off-pump 64±10 On-pump 63±10	Off-pump 37 (82%) On-pump: 39 (76%)	2 g/day	1:2	Pre-OD 5 to Discharge	(=) Length of hospital stay (p=0.75)
				C: 105	Off-pump (G1) 63±10 On-pump (G2) 63±9	(G1) 42 (87%) (G2) 46 (80%)	No intervention			

Study	Country	Design	Surgery	n (I/C)	Age (mean ± SD)	Men (%)	Dose	EPA:DHA ratio	Duration of supplementation	Outcomes Length of hospital stay Length of ICU stay
OPERA 2012 (Mozaffarian) [119]	US, Italy, Argentina (28 centers)	Multinational DB, RCT	CABG, valve repair or replacement, other open cardiac surgery	I: 758	63.8 SD(12.6)	551 (72.7%)	<u>Pre-operatively</u> 10 g loading over 3-5 days or 8 g over 2 days <u>Post-operatively</u> 2g ≥ 840 g/ capsule 465 mg EPA: 375 mg DHA	Not specified	Pre-OD 3-5 to Post-OD 10 or Discharge	(=) ICU stay (p=0.38) (=) Hospital stay (p=0.48)
				C: 758	63.6 SD(12.4)	543(71.6)	Olive oil			
Joss 2017 [121]	US	DB, RCT	CABG, valve replacement/ repair surgery	I: 284	66.6 ± 10.72	212 (74.7%)	2 g/day	2:3 DHA: EPA	Pre-OD 5 or 24 hrs Post-Operatively to Post-Operative week 4 75% of pts started and 25% post-OD1	(=) Length of hospital stay (p=0.834)
				C: 275	66.4 ± 10.72	199 (72.4%)	mineral oil with a trace amount of wheat germ oil			
Bernabe-Garcia 2013 [122]	Mexico	DB, RCT	CABG	I: 12	58.7 ± 2.7	100%	2.4 g/day omega 3 in 4 capsules (1.6g/day EPA + 0.8g DHA)	Not specified	Pre-OD 1 to Post-OD 6	(=) ICU stay, days (p= 0.440)

				C: 11	66.0 ± 2.5	100%	Corn starch			(-)Total hospital stays, days (P= 0.038)

Abbreviations: RCT: Randomized controlled trial, DB: Double-blind, PC: placebo-control, SB: Single-blind, OL: open-label, SC: single-center, MC: multicenter CABG: Coronary artery bypass graft, CPD: Cardiopulmonary bypass, F: female, M: male, Pre-OD: pre-operative day, Post-OD: post-operative day, FFA: free fatty acids, FO: fish oil, CCM: continuous cardiac monitor.

*p-value not present, significance is narratively reported

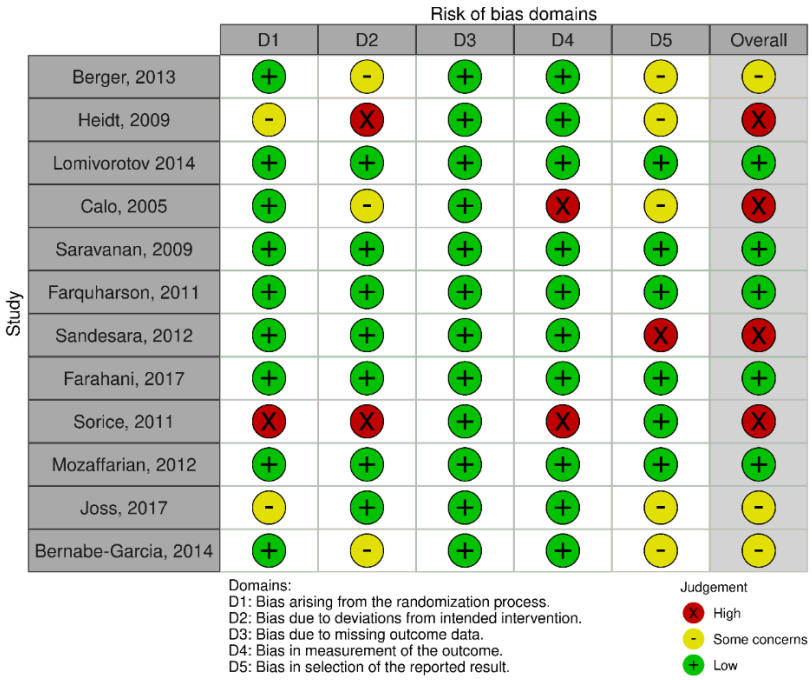
Internal validity (Risk of Bias Assessment):

The overall judgment of the twelve included studies was low risk of bias in five studies (41.6%) [100,102,118-120]. Some concerns in three (25%) [97,121,122] and high risk of bias was seen in four papers (33.3%) [98,99,101,103].

In the domain of bias due to randomization, most of the studies (75%) reported that it was randomized, or computer-generated randomization the risk was assessed as low [97,99-102,118-120,122]. One trial did not provide details about the randomization process [98] and another had significant difference in baseline characteristics table [121] giving them "some concerns" as a judgment. The allocation was not concealed in [103] study which increased the risk of bias in their paper.

Three papers had some concerns regarding bias arising from deviation from intended interventions [97,99-102,118-120,122]. While two had high risk of bias [98,103] in this domain. All of the papers had low risk of bias regarding missing outcomes data. In regards to bias due to measurement of the outcome, the outcome assessors were aware of the intervention received by study participants which might influence the assessment of the outcome in [99]and [103] studies giving them the judgment of high risk of bias. Finally, when we assessed the bias in selection of the reported result, 5 studies had some concerns [97-103,118-120,122] and one had high risk of bias [101]. Figures 2 and 3 summarize the risk of bias assessment of the included studies.

a)



b)

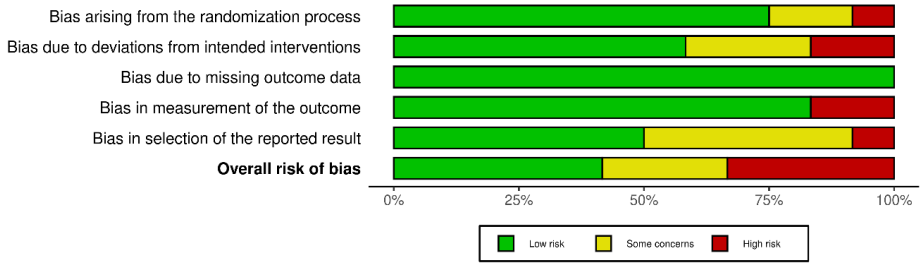


Figure 3. (a) Risk of bias summary of studies examining the effects of the omega 3 PUFA . (b) Risk of bias graph of studies examining the effects of the omega 3PUFA

External validity

In regard to the External validity, most of papers have small sample size. However, the OPERA trial is generalizable because it has large sample size of 1516 participants and is a multinational study. Furthermore, Bernabe et. al[122] included only men in their study

and Berger et al [97]included men only in the intervention arm which makes them not generalizable and nor representative to the population. Moreover, some trials limited inclusion to only patients undergoing only CABG by Cardiopulmonary bypass (CPB) [100,118]. Based on this, the samples are not representative to the target population which make them not generalizable to the population.

Source of funding and Conflict of interest

There was heterogeneity among the studies with respect to the sources of funding and conflict of interest disclosures. Five studies explicitly stated that authors had no conflict of interest [97,98,102,121,122] , In contrast, five studies did not provide any conflict of interest disclosure [99,101,103,118-120]. Notably, only one study acknowledged the presence of conflicts of interest [100].

Regarding funding sources, five studies received support from pharmaceutical companies [100-102,119,121]. Two studies declared no external funding [98,99] studies. While three studies provided no information regarding funding sources [103,118,120]. The findings are summarized in table 2

Table 2: Summary Of Conflict Of Interest And Funding Disclosures

Study	Conflict of interest	Funding
Berger, 2012 [97]	Disclosed no conflict of interest	Not reported
Heidt, 2009 [98]	Disclosed no conflict of interest	Disclosed no funding received
Lomivorotov, 2014 [118]	Not reported	Not reported
Calò, 2005 [99]	Not reported	Disclosed no funding received
Saravanan, 2009 [100]	One author has disclosed financial ties to two companies that sell Omacor, an omega-3 fatty acid supplement.	Funded by the British Heart Foundation, reported that it was not influenced by any pharmaceutical companies. free capsules of n-3 PUFA ethyl esters and placebo were provided

Sorice, 2011 [103]	Not reported	Not reported
Farquharson, 2011 [120]	Not reported	Not reported
Sandesara, 2012 [101]	Not reported	Disclosed being funded by Reliant Pharmaceuticals and GlaxoSmithKline.
Farahani, 2017 [102]	Disclosed no conflict of interest	Supported by grants from Tehran University of Medical Sciences. and Dana Pharmaceutical Company
Joss, 2017 [121]	Disclosed no conflict of interest	Funded by the Samaritan Foundation to purchase the study medication.
Mozafarrian, 2012 [119]	Not reported	Received funding from the National Heart, Lung, and Blood Institute, National Institutes of Health, GlaxoSmithKline, Sigma Tau, and Pronova BioPharma, which also provided the study drug. The organizations that provided the funding did not influence the design or conduct of the study
Bernabe-Garcia 2014 [122]	Disclosed no conflict of interest	Not reported

Meta-Analysis (Quantitative assessment)

Synthesis of Meta-analysis

For the construction of meta-analysis. Effect measures of all included studies were extracted and summarized in a table (Appendix F). Only studies that reported means and standard deviations, or that could be estimated from normally distributed data, were included in the meta-analysis. The study by Heidt et al. was excluded from the meta-analysis because it compared ICU and hospital stay between patients who developed atrial fibrillation and those who did not, without assessing the effect of omega-3 on these outcomes.

Effect of perioperative omega-3 polyunsaturated fatty acids (PUFA) on intensive care unit (ICU) length of stay after coronary artery bypass graft (CABG) surgery

Seven studies analyzed ICU length of stay after CABG surgery. Four studies reported mean and standard deviation (SD) data and were directly included in the meta-analysis

[97,118,120,122]. Three studies reported ICU length of stay as median and interquartile range (IQR). Their mean with SD were predicted, only one of them was eligible for inclusion in the Meta-analysis [119]. Thus, the meta-analysis included five studies in total. It is important to note that there was heterogeneity in terms of sample size, omega-3 administration, dose, and duration. Table 3 summarizes included studies in Meta-analysis of ICU length of stay outcome.

Table 3: Summary Of Included Studies In Meta-Analysis Of The Impact Of Omega-3 PUFA On Intensive Care Unit Stay (ICU).

Study	Method of administration	Dose	Preoperative	Post operative	Mean difference	95% Confidence interval
Berger 2013	IV	400 mg	day 1	day 1	-0.71	[-1.54, 0.12]
Lomivorotov 2014	IV	Pre OP 200 mg -Post OP 100 mg	day 1	day 2-7	0.00	[-0.63, 0.63]
Farquharson 2011	Oral	4.6 g/d	3 weeks - 6	Day 6	-1.10	[-2.48, 0.28]
Bernabe-Garcia 2013	Oral	2.4 g/d	Day 1	Day 6	-2.30	[-5.32, 0.72]
Mozaffarian 2012	Oral	8 g over 2 d Pre PO - 2g post OP	Days 5 - 3	Day 10 or Discharge	0.00	[-0.15, 0.15]

Forest plot of the effect of omega 3 PUFA on ICU stay

The meta-analysis for the length of Intensive care unit stay for patients had coronary artery bypass graft surgery was developed using the random-effect model.

Overall, the administration of omega 3 long chain fatty acids resulted in a tendency

towards reduction in the length of stay in the intensive care unit compared to the control group but no statistical significant effect was observed mean difference and 95% confidence interval -0.25 [-0.68, 0.17].

Subgroup analysis based on method of administration was conducted and no effect was further seen on the duration of ICU stay, mean difference and 95% confidence intervals -0.30 [-0.99,0.39] and -0.59 [-1.7, 0.52] for intravenous and oral supplementation respectively.

The intravenous administration of omega 3 PUFA subgroup analysis included only 2 studies. There was a moderate heterogeneity between the 2 studies as per the I^2 test equal to 43.79% . The dose administered was 200 mg/kg/day and 400 mg/kg/day of omega 3 in pre-operative day 1, and the post-operative duration was different between the studies. Both studies had small sample size which make the power very small. In regard to the oral administration, there was a substantial heterogeneity between the studies (I^2 =56.71%. The study conducted by Mozaffarian et. al had almost half the weight of the observed effect with 48.66%. Figure 4 shows the meta-analysis and sub-group analysis of the impact of perioperative administration of omega 3 PUFA on post-surgical intensive care unit stay in patients undergoing CABG surgery.

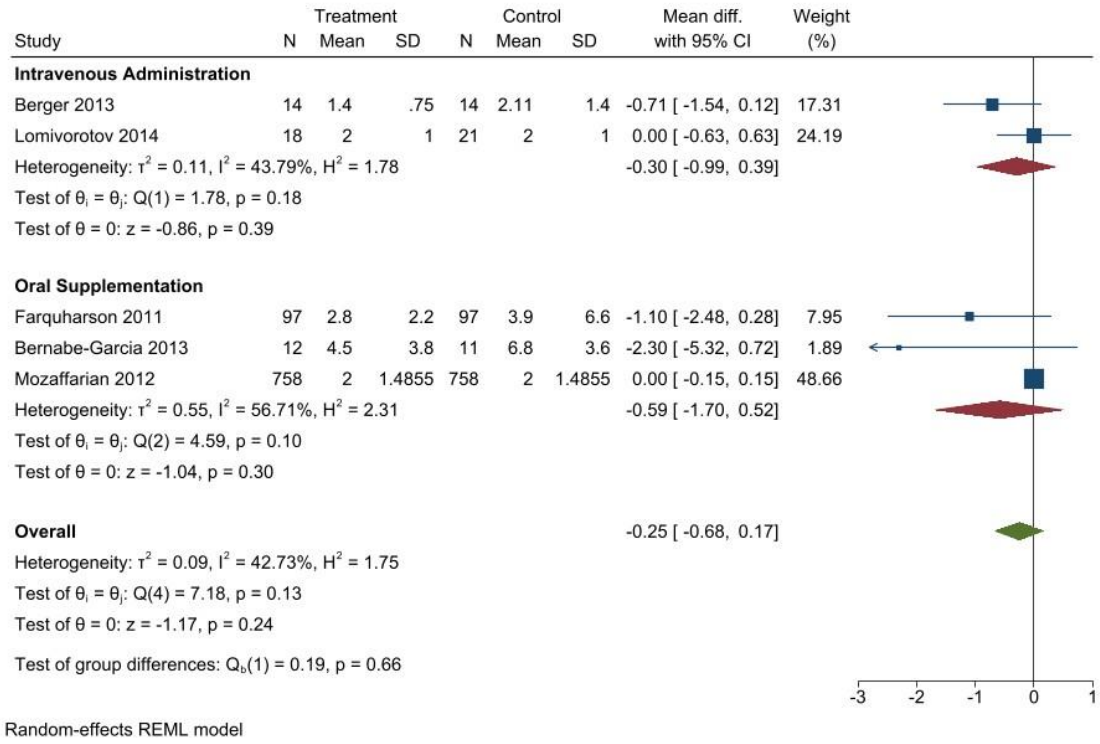


Figure 4. Meta-analysis and sub-group analysis of the impact of perioperative administration of omega 3 PUFA (intravenous and oral), compared to control (usual care or non-fish oils) on post-surgical intensive care unit stay in patients undergoing CABG surgery.

Assessment of publication bias:

Publication bias was not assessed as the number of included studies in the meta-analysis was small.

Effect of omega-3 polyunsaturated fatty acids (PUFA) on hospital length of stay after coronary artery bypass graft (CABG) surgery

Eleven studies analyzed hospital length of stay after CABG surgery, but only six studies were eligible for inclusion in the meta-analysis. Five studies reported mean and standard deviation (SD) data and were directly included in the meta-analysis [97,99,103,118,122]. The study by Sorice et al. (2011) reported results in a subgroup based on

the type of CABG surgery, so it was divided into two for constructing the meta-analysis. None of the studies that reported hospital length of hospital as median and interquartile range (IQR) were eligible for inclusion in the meta-analysis after the prediction of their mean and standard deviation[100-102,119]. Other studies were also excluded as they were reported as adjusted mean ratio[120] and median and SD [121]. It is important to note that there was heterogeneity in terms of sample size, omega-3 administration, dose, and duration. Table 4 summarizes included studies in Meta-analysis of hospital length of stay outcome.

Table 4: Summary Of Included Studies In Meta-Analysis Of The Impact Of Omega-3 PUFA On Hospital Length Of Stay After CABG Surgery.

Study	Method of administration	Dose	Preoperative	Post operative	Mean difference	95% Confidence interval
Berger 2013	IV	400 mg	day 1	day 1	0.5	[-2.65, 3.65]
Lomivorotov 2014	IV	Pre OP 200 mg - Post OP 100 mg	day 1	day 2-7	-1	[-4.19, 2.19]
Sorice 2011 "on-pump CABG"	Oral	2 g/d	day 5	Discharge	-0.1	[-1.16, 0.96]
Sorice 2011 "Off-pump CABG"	Oral	2 g/d	day 5	Discharge	0.2	[-1.59, 1.99]
Bernabe-Garcia 2013	Oral	2.4 g/d	Day 1	day 6	-2	[-5.02, 1.02]
Calò 2005	Oral	1.7 g/d	day 5	Discharge	-0.9	[-1.63, -0.17]

Forest plot of the effect of omega 3 PUFA on length of hospital stay

Overall, the meta-analysis showed that perioperative administration of omega-3 PUFA resulted in a significant reduction in length of hospital stay for patients who underwent CABG surgery, with a mean difference (MD) of -0.58 days (95% confidence interval -1.13, -0.04).

Subgroup analysis based on method of administration revealed that intravenous administration of omega 3 PUFA did not result in any statistically significant difference in length of hospitalization (MD: -0.24 days; 95% CI: -2.48, 2.00). However, significant reduction in length of hospitalization was found in oral supplementation of omega 3 PUFA subgroup (MD: -0.6 days; 95% CI: -1.17, -0.04). The study by Calò et al. (2005) had the largest weight (55.1%), indicating that it had the greatest impact on the overall results. There was no significant heterogeneity between studies (I2 = 0%). Figure 5 shows the meta-analysis and sub-group analysis of the impact of perioperative administration of omega 3 PUFA on hospital length of stay for patients undergoing CABG surgery.

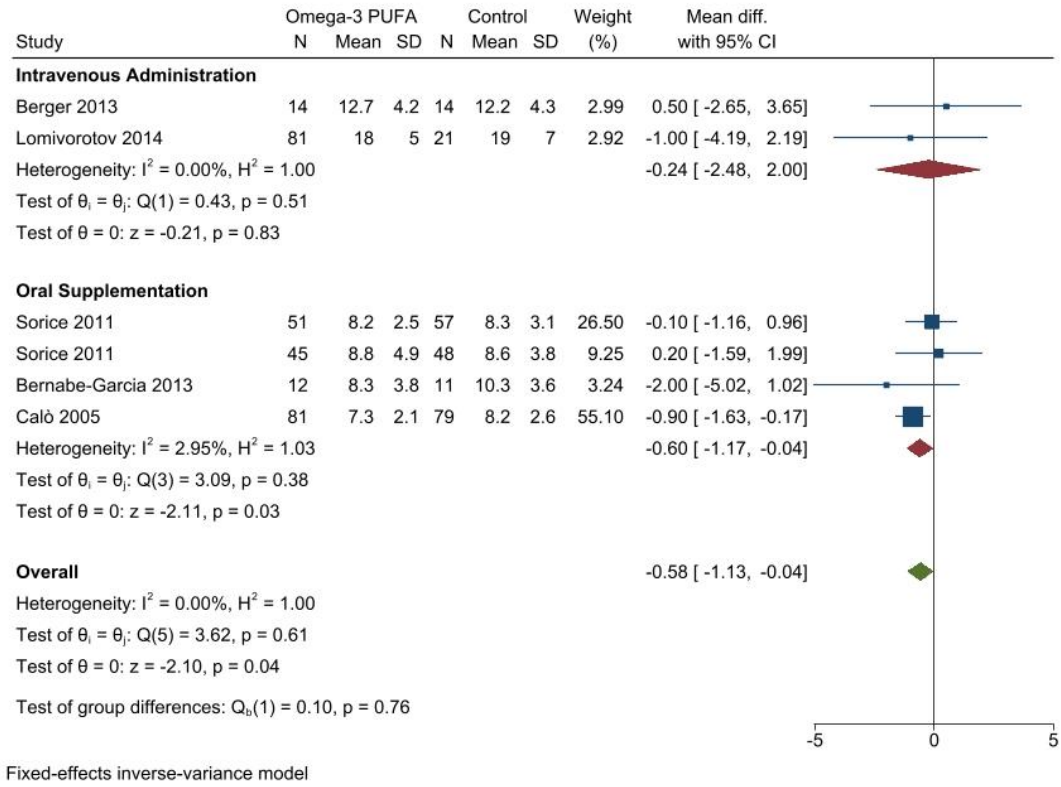


Figure 5. Meta-analysis and sub-group analysis of the impact of perioperative administration of omega 3 PUFA compared to control on hospital length of stay for patients undergoing CABG surgery.

Assessment of publication Bias:

Publication bias was assessed using Egger's test and funnel plot analysis. Egger's test showed no significant publication bias ($p = 0.7531$). Additionally, the funnel plot was symmetrical, indicating no evidence of publication bias. Figure 6 shows Funnel plot to assess publication bias for studies of length of hospital stay outcome

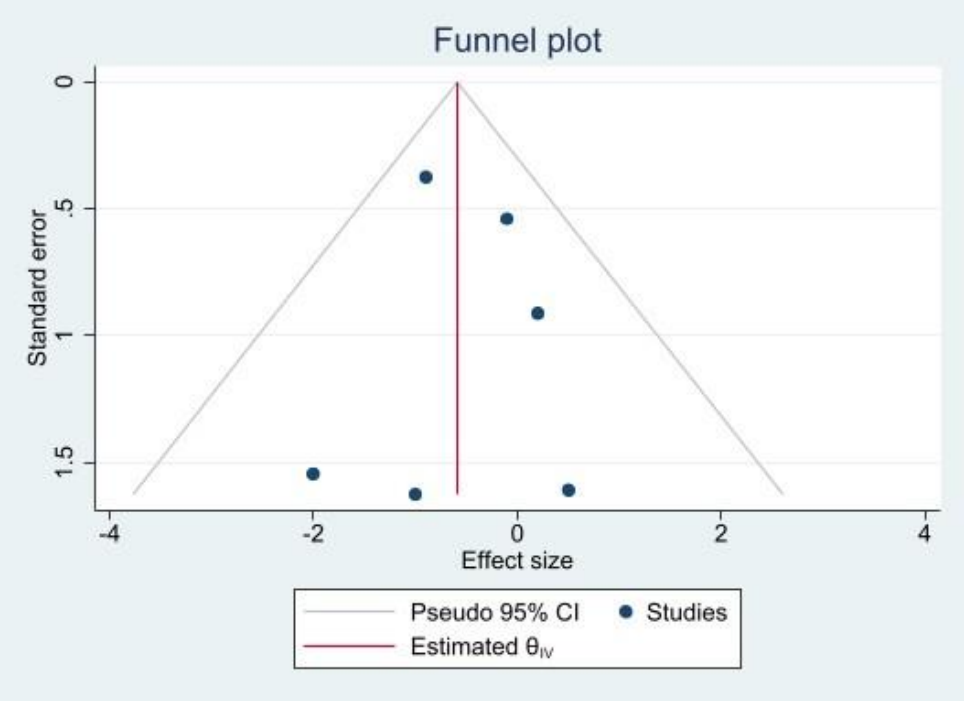


Figure 6. Funnel plot to assess publication bias for studies of length of hospital stay outcome

Chapter 5: Discussion

This systematic review provides update of the current knowledge in regard to the effect of omega 3 PUFA supplementation on ICU stay and length of hospitalization post CABG surgery. The systematic review is more concise to the effect of only omega 3 long chain fatty acid (EPA + DHA) administration on clinical outcomes post-CABG surgery. Twelve studies have been identified for the qualitative synthesis and seven of them were eligible for inclusion in the meta-analysis.

The overall pooled mean difference between the omega 3 PUFA group and the control group regarding ICU stay after CABG surgery showed no statistical difference between the groups but a tendency towards reduction was observed -0.25 (95% CI -0.68, 0.17). Subgroup analysis in terms of method of administration did not show any further significant effect -0.30 (-0.99,0.39) and -0.59 (-1.7, 0.52) for intravenous and oral supplementation, respectively.

Moreover, omega-3 PUFA was associated with significant reduction in days of hospital stay -0.58 (95% CI -1.13, -0.04). Furthermore, subgroup analysis showed that oral supplementation resulted in a statistically significant reduction in length of hospitalization with MD -0.6 (95% CI -1.17, -0.04). However, no statistically significant difference in length of hospitalization was observed when omega-3 was administered intravenously -0.24 (95% CI -2.48, 2.00).

The effect of omega-3 PUFA on ICU length of stay post CABG surgery

On average, there was no difference in the length of ICU stay between patients who received omega-3 polyunsaturated fatty acids (PUFAs) and those who did not after coronary artery bypass grafting (CABG) surgery -0.25 (95% CI -0.68, 0.17).

This finding is consistent with a previous systematic review, which found no effect of omega-3 PUFAs or combined with other vitamins on ICU length of stay in patients undergoing different cardiac surgeries (weighted mean difference -2.95 days, (95% CI -10.28, 4.39)[27] . However, it is not consistent with another systematic review found that administration of mainly antioxidant vitamin therapy, some of them with omega-3 PUFA resulted in improvement in all clinical outcomes including intensive care unit length of stay (MD -0.21, 95% CI -0.30, -0.12, P < 0.00001) [28]. Possible explanation for the lack of effect on ICU stay could be that the anti-inflammatory effects are not potent enough to immediately reduce the post-operative inflammatory response after surgery but when combined with other vitamins will produce stronger effect and reduces ICU stay.

Omega 3 and hospital length of stay post CABG surgery

Omega-3 PUFA was associated with significant reduction in days of hospital stay -0.58 (95% CI -1.13, -0.04). A meta-analysis showed a significant effect of perioperative omega 3 PUFA on length of hospitalization post cardiac surgeries [27]. Moreover, the perioperative use of antioxidant vitamin therapy resulted in a significant reduction of hospital stay duration (MD -0.68, 95% CI -0.98, -0.39, P < 0.00001). These findings are essentially consistent with the results of the current study. Reduction in length of hospitalization in response to perioperative omega 3 PUFA administration may be explained by several mechanisms.

First, the anti-inflammatory and pro-resolving effects of omega-3 PUFAs are likely to play a major role. One way that omega-3 PUFAs reduce inflammation is by competing with arachidonic acid for the production of eicosanoids [123] . Eicosanoids are signaling molecules that play a role in a variety of physiological processes, including inflammation[79]. Therefore, omega-3 PUFAs, on the other hand, are converted to less pro-inflammatory eicosanoids.

Another way that omega-3 PUFAs reduce inflammation is by promoting the production of specialized pro-resolving mediators (SPMs) [79]. SPMs are a class of lipid mediators that are derived from EPA and DHA including are resolvins, protectins and docosatrienes and have potent anti-inflammatory and pro-resolving effects[80,81]. Enzymatic conversion of omega-3 polyunsaturated fatty acids into SPMs actively disrupts inflammatory circuits and skews the immune response toward repair and homeostasis [19,83,86,87].

The anti-inflammatory and pro-resolving effects of omega-3 PUFAs are likely to be particularly beneficial for patients who are at high risk for developing complications after surgery. For example, patients who undergo coronary artery bypass grafting (CABG) surgery are at high risk for developing postoperative inflammation, which can lead to a number of complications, such as arrhythmias, heart failure, and infection and increasing length of hospitalization.

Furthermore, the antiarrhythmic effects of omega-3 PUFAs are likely to play a major role in reducing post-operative atrial fibrillation (POAF) and are thought to be mediated through a number of mechanisms, including: Modulation of ion channels and alteration of membrane phospholipid composition [89,124,125]. Omega-3 PUFAs can also alter the membrane phospholipid composition of cardiac cells [126]. This can lead to changes in the fluidity and permeability of the cell membrane, which can also affect the electrical

activity of the heart and reduce the risk of arrhythmias [124].

Subgroup analysis showed that oral supplementation resulted in a statistically significant reduction in length of with MD -0.6 (95% CI -1.17, -0.04). However, no statistically significant difference in length of hospitalization was observed when omega-3 was administered intravenously -0.24 (95% CI -2.48, 2.00). The observed effect might be due to the fact that oral supplementation has longer duration compared to the intravenously administered omega 3 PUFA resulting in accumulation of more omega 3 PUFA in the body and better anti-inflammatory functions.

Regarding the risk of bias and external validity, the studies differed in terms of bias and most of the papers have small sample size and some trials limited inclusion to only patients undergoing only CABG by Cardiopulmonary bypass (CPB). Based on this, the samples for some trials are not representative to the target population which make them not generalizable to the population.

Implications for practice and research

The findings of this systematic review and meta-analysis suggest that omega-3 PUFA supplementation, particularly oral administration, may be an effective intervention for reducing the length of hospitalization following CABG surgery. The potential benefits of omega-3 PUFAs are likely mediated by their anti-inflammatory, pro-resolving, and antiarrhythmic properties. Further research is warranted to optimize the dose, duration, and formulation of omega-3 PUFA supplementation for maximizing clinical benefits in the perioperative setting.

Strengths:

The current systematic review and meta-analysis is an update of all available evidence on the effect of omega 3 PUFA on post CABG clinical outcomes as the last published systematic review was on 2017 [27]. Furthermore, the current review is more concise to

CABG surgery and addressed only the effect of omega 3 to observe its sole effect on post-surgical clinical outcomes and included two new papers not previously analyzed. Relevant and key bibliographic databases were searched using a comprehensive list of key terms until 12th of September 2023. The studies included in the systematic review are all randomized controlled trials and most of them were double blinded. Additionally, the references list of relevant studies were searched. Furthermore, two reviewers independently screened studies for inclusion and assessed the risk of bias in included studies.

Limitations

The current systematic review has also several limitations. The evidence provided by this review was based on relatively small sample size for most papers (<100 participants) which might affect overall power and restrict the generalizability of the studies. Furthermore, the included studies were not all with good methodological quality and there was heterogeneity between studies and two open-label trials were added to the review, which may weaken the strength of the conclusion. The studies were old and the most recent one was published in 2017 which means 6 years have passed. Furthermore, the heterogeneity between studies in their populations, omega 3 dose, and duration of supplementation makes it difficult to compare results and to detect the true effect. Finally, not all studies are included in the meta-analysis due to heterogeneity in effect measures and largest study was not included in length of hospital stay meta-analysis.

Conclusion:

This updated systematic review and meta-analysis, demonstrates that perioperative omega 3 PUFA administered orally is correlated with significant improvement in length of hospitalization due to its anti-inflammatory and anti-arrhythmic effects. Omega 3

PUFA did not exert beneficial effects on reducing length of ICU stay. Due to heterogeneity and low quality of included studies, the results should be interpreted with caution. There are some concerns regarding the external validity. Further well designed and large studies are warranted to confirm these findings.

Chapter 6: References**:**

1. Sekhri T, Kanwar R, Wilfred R, et al. Prevalence of risk factors for coronary artery disease in an urban Indian population. *BMJ open* 2014; **4**(12): e005346.

2. Indicators O. Health at a Glance 2009. *Health workers: Psychiatrists Retrieved from website: http://www oecd-ilibrary org/docserver/download/fulltext/8109111ec030 pdf* 2009.

3. Weiss AJ, Elixhauser A. Trends in operating room procedures in US hospitals, 2001–2011: Statistical Brief# 171. 2014.

4. NIH. What Is Coronary Artery Bypass Grafting? 2022.

5. Montrief T, Koyfman A, Long B. Coronary artery bypass graft surgery complications: A review for emergency clinicians. *The American Journal of Emergency Medicine* 2018; **36**(12): 2289-97.

6. Pryor DB, Shaw L, Harrell FE, Jr., et al. Estimating the likelihood of severe coronary artery disease. *Am J Med* 1991; **90**(5): 553-62.

7. Matsuzawa Y, Nakamura T, Shimomura I, Kotani K. Visceral fat accumulation and cardiovascular disease. *Obes Res* 1995; **3 Suppl 5**: 645s-7s.

8. Han SY, Kim NH, Kim DH, Kim YH, Park YK, Kim SM. Associations between Body Mass Index, Waist Circumference, and Myocardial Infarction in Older Adults Aged over 75 Years: A Population-Based Cohort Study. *Medicina (Kaunas)* 2022; **58**(12).

9. Kuhail M, Shab-Bidar S, Yaseri M, Djafarian K. Major Dietary Patterns Relationship with Severity of Coronary Artery Disease in Gaza-Strip, Palestine: A Cross-Sectional Study. *Ethiop J Health Sci* 2021; **31**(3): 599-610.

10. Malhotra A, Redberg RF, Meier P. Saturated fat does not clog the arteries: coronary heart disease is a chronic inflammatory condition, the risk of which can be

effectively reduced from healthy lifestyle interventions. BMJ Publishing Group Ltd and British Association of Sport and Exercise Medicine; 2017. p. 1111-2.

11. Kishimoto Y, Saita E, Taguchi C, et al. Associations between Green Tea Consumption and Coffee Consumption and the Prevalence of Coronary Artery Disease. *J Nutr Sci Vitaminol (Tokyo)* 2020; **66**(3): 237-45.

12. Delgado-Lista J, Alcala-Diaz JF, Torres-Peña JD, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. *Lancet* 2022; **399**(10338): 1876-85.

13. Hu EA, Steffen LM, Coresh J, Appel LJ, Rebholz CM. Adherence to the Healthy Eating Index-2015 and Other Dietary Patterns May Reduce Risk of Cardiovascular Disease, Cardiovascular Mortality, and All-Cause Mortality. *J Nutr* 2020; **150**(2): 312-21.

14. Yang ZQ, Yang Z, Duan ML. Dietary approach to stop hypertension diet and risk of coronary artery disease: a meta-analysis of prospective cohort studies. *Int J Food Sci Nutr* 2019; **70**(6): 668-74.

15. Yuan Q, Xie F, Huang W, et al. The review of alpha-linolenic acid: Sources, metabolism, and pharmacology. *Phytother Res* 2022; **36**(1): 164-88.

16. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am J Clin Nutr* 2006; **83**(6 Suppl): 1467S-76S.

17. Cholewski M, Tomczykowa M, Tomczyk M. A Comprehensive Review of Chemistry, Sources and Bioavailability of Omega-3 Fatty Acids. *Nutrients* 2018; **10**(11).

18. Pradelli L, Mayer K, Klek S, et al. omega-3 Fatty-Acid Enriched Parenteral Nutrition in Hospitalized Patients: Systematic Review With Meta-Analysis and Trial Sequential Analysis. *JPEN J Parenter Enteral Nutr* 2020; **44**(1): 44-57.

19. Serhan CN, Petasis NA. Resolvins and protectins in inflammation resolution. *Chem Rev* 2011; **111**(10): 5922-43.

20. Hjorth E, Zhu M, Toro VC, et al. Omega-3 fatty acids enhance phagocytosis of Alzheimer's disease-related amyloid-beta42 by human microglia and decrease inflammatory markers. *J Alzheimers Dis* 2013; **35**(4): 697-713.

21. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002; **346**(15): 1113-8.

22. Berger MM, Delodder F, Liaudet L, et al. Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial. *Am J Clin Nutr* 2013; **97**(2): 246-54.

23. Lombardi M, Carbone S, Del Buono MG, et al. Omega-3 fatty acids supplementation and risk of atrial fibrillation: an updated meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother* 2021; **7**(4): e69-e70.

24. Gencer B, Djousse L, Al-Ramady OT, Cook NR, Manson JE, Albert CM. Effect of Long-Term Marine ω-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. *Circulation* 2021; **144**(25): 1981-90.

25. Mozaffarian D, Wu JHY, de Oliveira Otto MC, et al. Fish Oil and Post-Operative Atrial Fibrillation: A Meta-Analysis of Randomized Controlled Trials. *Journal of the American College of Cardiology* 2013; **61**(21): 2194-6.

26. Zhang B, Zhen Y, Tao A, Bao Z, Zhang G. Polyunsaturated fatty acids for the prevention of atrial fibrillation after cardiac surgery: An updated meta-analysis of randomized controlled trials. *Journal of Cardiology* 2014; **63**(1): 53-9.

27. Langlois PL, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in cardiac surgery patients: An updated systematic review and meta-analysis. *Clin Nutr*

2017; **36**(3): 737-46.

28. Geng J, Qian J, Si W, Cheng H, Ji F, Shen Z. The clinical benefits of perioperative antioxidant vitamin therapy in patients undergoing cardiac surgery: a meta-analysis. *Interact Cardiovasc Thorac Surg* 2017; **25**(6): 966-74.

29. Ni Choileain N, Redmond HP. Cell response to surgery. *Arch Surg* 2006; **141**(11): 1132-40.

30. Desborough JP. The stress response to trauma and surgery. *British Journal of Anaesthesia* 2000; **85**(1): 109-17.

31. CUTHBERTSON DP. OBSERVATIONS ON THE DISTURBANCE OF METABOLISM PRODUCED BY INJURY TO THE LIMBS. *QJM: An International Journal of Medicine* 1932; **1**(2): 233-46.

32. Angele MK, Chaudry IH. Surgical trauma and immunosuppression: pathophysiology and potential immunomodulatory approaches. *Langenbecks Arch Surg* 2005; **390**(4): 333-41.

33. Okada A, Takagi Y, Nezu R, Lee S. Zinc in clinical surgery--a research review. *Jpn J Surg* 1990; **20**(6): 635-44.

34. Li X, Tang L, Lin YF, Xie GF. Role of vitamin C in wound healing after dental implant surgery in patients treated with bone grafts and patients with chronic periodontitis. *Clin Implant Dent Relat Res* 2018; **20**(5): 793-8.

35. Yu J, Liu L, Zhang Y, Wei J, Yang F. Effects of omega-3 fatty acids on patients undergoing surgery for gastrointestinal malignancy: a systematic review and meta-analysis. *BMC Cancer* 2017; **17**(1): 271.

36. Ma C, Tsai H, Su W, Sun L, Shih Y, Wang J. Combination of arginine, glutamine, and omega-3 fatty acid supplements for perioperative enteral nutrition in surgical patients with gastric adenocarcinoma or gastrointestinal stromal tumor (GIST):

A prospective, randomized, double-blind study. *J Postgrad Med* 2018; **64**(3): 155-63.

37. Langlois PL, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in cardiac surgery patients: An updated systematic review and meta-analysis. *Clin Nutr* 2017; **36**(3): 737-46.

38. Zheng X, Jia R, Li Y, Liu T, Wang Z. Omega-3 fatty acids reduce post-operative risk of deep vein thrombosis and pulmonary embolism after surgery for elderly patients with proximal femoral fractures: a randomized placebo-controlled, double-blind clinical trial. *Int Orthop* 2020; **44**(10): 2089-93.

39. Jackson JC, Mozaffarian D, Graves AJ, et al. Fish Oil Supplementation Does Not Affect Cognitive Outcomes in Cardiac Surgery Patients in the Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation (OPERA) Trial. *J Nutr* 2018; **148**(3): 472-9.

40. Bakker N, Schoorl M, Stoutjesdijk E, Houdijk APJ. Erythrocyte deformability and aggregability in patients undergoing colon cancer surgery and effects of two infusions with omega-3 fatty acids. *Clin Hemorheol Microcirc* 2020; **74**(3): 287-97.

41. Xiao F, Han W, Yue Q, Ke J, Jia B, Fu X. Perioperative omega-3 fatty acids for liver surgery: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2021; **100**(27): e25743.

42. Villareal RP, Hariharan R, Liu BC, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol* 2004; **43**(5): 742-8.

43. Linecker M, Botea F, Aristotele Raptis D, et al. Perioperative omega-3 fatty acids fail to confer protection in liver surgery: Results of a multicentric, double-blind, randomized controlled trial. *J Hepatol* 2020; **72**(3): 498-505.

44. Chiang N, Serhan CN. Specialized pro-resolving mediator network: an update on production and actions. *Essays Biochem* 2020; **64**(3): 443-62.

45. Arnardottir H, Pawelzik SC, Ohlund Wistbacka U, et al. Stimulating the Resolution of Inflammation Through Omega-3 Polyunsaturated Fatty Acids in COVID-19: Rationale for the COVID-Omega-F Trial. *Front Physiol* 2020; **11**: 624657.

46. Naghavi M, Wang, H., Lozano, R., Davis, A., Liang, X., Zhou, M., . Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**(9963): 117-71.

47. Gupta R, Guptha S, Sharma KK, Gupta A, Deedwania P. Regional variations in cardiovascular risk factors in India: India heart watch. *World J Cardiol* 2012; **4**(4): 112-20.

48. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation* 2023; **147**(8): e93-e621.

49. Statistics NCfH. Multiple Cause of Death 2018–2021 on CDC WONDER Database. 2023. https://wonder.cdc.gov/mcd.html (accessed 28 October 2023 2023).

50. World Health Organization. Global atlas on cardiovascular disease prevention and control. 2011. https://www.who.int/publications/i/item/9789241564373 (accessed 28 October 2023 2023).

51. Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *Eur Heart J Acute Cardiovasc Care* 2012; **1**(1): 60-74.

52. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. *J Cell Physiol* 2019; **234**(10): 16812-23.

53. Chen S, Yang F, Xu T, et al. Smoking and coronary artery disease risk in patients with diabetes: A Mendelian randomization study. *Front Immunol* 2023; **14**:

891947.

54. Yang RF, Zhang H, Wang Z, Liu XY, Lin Z. A study on the relationship between waist phenotype, hypertriglyceridemia, coronary artery lesions and serum free fatty acids in adult and elderly patients with coronary diseases. *Immun Ageing* 2018; **15**: 14.

55. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; **39**(33): 3021-104.

56. Haffner SM. Diabetes, hyperlipidemia, and coronary artery disease. *Am J Cardiol* 1999; **83**(9b): 17f-21f.

57. Zhuang Z, Gao M, Yang R, et al. Association of physical activity, sedentary behaviours and sleep duration with cardiovascular diseases and lipid profiles: a Mendelian randomization analysis. *Lipids Health Dis* 2020; **19**(1): 86.

58. Trakarnwijitr I, Li B, Adams H, Layland J, Garlick J, Wilson A. Age modulates the relationship between platelet-to-lymphocyte ratio and coronary artery disease. *Int J Cardiol* 2017; **248**: 349-54.

59. Waheed N, Elias-Smale S, Malas W, et al. Sex differences in non-obstructive coronary artery disease. *Cardiovasc Res* 2020; **116**(4): 829-40.

60. Amin AP, Nathan S, Evans AT, et al. The effect of ethnicity on the relationship between premature coronary artery disease and traditional cardiac risk factors among uninsured young adults. *Prev Cardiol* 2009; **12**(3): 128-35.

61. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol* 2018; **72**(23 Pt A): 2915-31.

62. Ziff OJ, Samra M, Howard JP, et al. Beta-blocker efficacy across different cardiovascular indications: an umbrella review and meta-analytic assessment. *BMC*

Med 2020; **18**(1): 103.

63. Al-Lamee RK, Nowbar AN, Francis DP. Percutaneous coronary intervention for stable coronary artery disease. *Heart* 2019; **105**(1): 11-9.

64. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021; **42**(14): 1289-367.

65. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022; **145**(3): e4-e17.

66. Riley RF, Don CW, Powell W, Maynard C, Dean LS. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circ Cardiovasc Qual Outcomes* 2011; **4**(2): 193-7.

67. Lazar HL, Fitzgerald CA, Ahmad T, et al. Early discharge after coronary artery bypass graft surgery: are patients really going home earlier? *The Journal of thoracic and cardiovascular surgery* 2001; **121**(5): 943-50.

68. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; **124**(23): e652-735.

69. Hannan EL, Zhong Y, Lahey SJ, et al. 30-day readmissions after coronary artery bypass graft surgery in New York State. *JACC Cardiovasc Interv* 2011; **4**(5): 569-76.

70. Li Z, Armstrong EJ, Parker JP, Danielsen B, Romano PS. Hospital variation in readmission after coronary artery bypass surgery in California. *Circ Cardiovasc Qual*

Outcomes 2012; **5**(5): 729-37.

71. Montrief T, Koyfman A, Long B. Coronary artery bypass graft surgery complications: A review for emergency clinicians. *Am J Emerg Med* 2018; **36**(12): 2289-97.

72. Das UN. Essential Fatty Acids—Biochemistry, Physiology and Clinical Significance. Molecular Basis of Health and Disease. Dordrecht: Springer Netherlands; 2011: 101-51.

73. Singh M. Essential fatty acids, DHA and human brain. *Indian J Pediatr* 2005; **72**(3): 239-42.

74. Parrish CC. Essential fatty acids in aquatic food webs. In: Kainz M, Brett MT, Arts MT, eds. Lipids in Aquatic Ecosystems. New York, NY: Springer New York; 2009: 309-26.

75. Brenna JT. Efficiency of conversion of alpha-linolenic acid to long chain n-3 fatty acids in man. *Curr Opin Clin Nutr Metab Care* 2002; **5**(2): 127-32.

76. Greupner T, Kutzner L, Nolte F, et al. Effects of a 12-week high-alpha-linolenic acid intervention on EPA and DHA concentrations in red blood cells and plasma oxylipin pattern in subjects with a low EPA and DHA status. *Food Funct* 2018; **9**(3): 1587-600.

77. Lin YH, Llanos A, Mena P, Uauy R, Salem N, Jr., Pawlosky RJ. Compartmental analyses of 2H5-alpha-linolenic acid and C-U-eicosapentaenoic acid toward synthesis of plasma labeled 22:6n-3 in newborn term infants. *Am J Clin Nutr* 2010; **92**(2): 284-93.

78. Committee USDGA. Dietary guidelines for Americans, 2010: US Department of Health and Human Services, US Department of Agriculture; 2010.

79. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-

inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008; **8**(5): 349-61.

80. Kohli P, Levy BD. Resolvins and protectins: mediating solutions to inflammation. *Br J Pharmacol* 2009; **158**(4): 960-71.

81. Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. *J Exp Med* 2000; **192**(8): 1197-204.

82. Kwon Y. Immuno-Resolving Ability of Resolvins, Protectins, and Maresins Derived from Omega-3 Fatty Acids in Metabolic Syndrome. *Mol Nutr Food Res* 2020; **64**(4): e1900824.

83. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 2014; **510**(7503): 92-101.

84. Morita M, Kuba K, Ichikawa A, et al. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. *Cell* 2013; **153**(1): 112-25.

85. Duvall MG, Levy BD. DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation. *Eur J Pharmacol* 2016; **785**: 144-55.

86. Bazan NG, Calandria JM, Serhan CN. Rescue and repair during photoreceptor cell renewal mediated by docosahexaenoic acid-derived neuroprotectin D1. *J Lipid Res* 2010; **51**(8): 2018-31.

87. Abdulkhaleq LA, Assi MA, Abdullah R, Zamri-Saad M, Taufiq-Yap YH, Hezmee MNM. The crucial roles of inflammatory mediators in inflammation: A review. *Vet World* 2018; **11**(5): 627-35.

88. Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* 2010; **142**(5): 687-98.

89. Wong SW, Kwon MJ, Choi AM, Kim HP, Nakahira K, Hwang DH. Fatty acids modulate Toll-like receptor 4 activation through regulation of receptor dimerization and recruitment into lipid rafts in a reactive oxygen species-dependent manner. *J Biol Chem* 2009; **284**(40): 27384-92.

90. Stillwell W, Shaikh SR, Zerouga M, Siddiqui R, Wassall SR. Docosahexaenoic acid affects cell signaling by altering lipid rafts. *Reprod Nutr Dev* 2005; **45**(5): 559-79.

91. Breznock EM. The Systemic Response of the Traumatized Patient: An Overview. *Veterinary Clinics of North America: Small Animal Practice* 1980; **10**(3): 523-32.

92. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Co mmittee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*; **101**(6): 1644-55.

93. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. *JPEN J Parenter Enteral Nutr* 2013; **37**(5 Suppl): 21s-9s.

94. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammati on. *The New England journal of medicine*; **332**(20): 1351-62.

95. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *Jama* 2000; **283**(8): 1038-45.

96. Veljović M, Popadić A, Vukić Z, et al. Myocardial protection during elective coronary artery bypasses grafting by pretreatment with omega-3 polyunsaturated fatty acids. *Vojnosanit Pregl* 2013; **70**(5): 484-92.

97. Berger MM, Delodder F, Liaudet L, et al. Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery:

a randomized controlled trial. *The American Journal of Clinical Nutrition* 2012; **97**(2): 246-54.

98. Heidt MC, Vician M, Stracke SK, et al. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thoracic and cardiovascular surgeon* 2009; **57**(5): 276-80.

99. Calò L, Bianconi L, Colivicchi F, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *Journal of the American College of Cardiology* 2005; **45**(10): 1723-8.

100. Saravanan P, O'Neill SC, Bridgewater B, Davidson NC. Fish oils supplementation does not reduce risk of atrial fibrillation following coronary artery bypass surgery. *Heart Rhythm* 2009; **6**(5).

101. Sandesara CM, Chung MK, Van Wagoner DR, et al. A Randomized, Placebo-Controlled Trial of Omega-3 Fatty Acids for Inhibition of Supraventricular Arrhythmias After Cardiac Surgery: The FISH Trial. *Journal of the American Heart Association* 2012; **1**(3): e000547.

102. Vasheghani Farahani A, Yousefi Azar A, Goodarzynejad HR, et al. Fish oil supplementation for primary prevention of atrial fibrillation after coronary artery bypass graft surgery: a randomized clinical trial. *International journal of surgery (London, England)* 2017; **42**: 41-8.

103. Sorice M, Tritto FP, Sordelli C, Gregorio R, Piazza L. N-3 polyunsaturated fatty acids reduces post-operative atrial fibrillation incidence in patients undergoing "on-pump" coronary artery bypass graft surgery. *Monaldi archives for chest disease = archivio monaldi per LE malattie del torace* 2011; **76**(2): 93-8.

104. Gong Y, Liu Z, Liao Y, et al. Effectiveness of omega-3 Polyunsaturated Fatty

Acids Based Lipid Emulsions for Treatment of Patients after Hepatectomy: A Prospective Clinical Trial. *Nutrients* 2016; **8**(6).

105. Marsman HA, de Graaf W, Heger M, et al. Hepatic regeneration and functional recovery following partial liver resection in an experimental model of hepatic steatosis treated with omega-3 fatty acids. *Br J Surg* 2013; **100**(5): 674-83.

106. Bakker N, van den Helder RS, Geenen RWF, et al. Four Weeks of Preoperative Omega-3 Fatty Acids Reduce Liver Volume: a Randomised Controlled Trial. *Obes Surg* 2019; **29**(7): 2037-44.

107. Kuma H, Nagashima R, Hatae H, Tsuda T, Hamasaki N. Beneficial effect of EPA (20:5 n-3 PUFA) on preventing venous thromboembolism: a rat tail thrombosis model experiment. *Thromb Res* 2013; **131**(1): 107-8.

108. Reiner MF, Stivala S, Limacher A, et al. Omega-3 fatty acids predict recurrent venous thromboembolism or total mortality in elderly patients with acute venous thromboembolism. *J Thromb Haemost* 2017; **15**(1): 47-56.

109. Isaksen T, Evensen LH, Johnsen SH, et al. Dietary intake of marine n-3 polyunsaturated fatty acids and future risk of venous thromboembolism. *Res Pract Thromb Haemost* 2019; **3**(1): 59-69.

110. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.

111. National Health Service (NHS). Resources for advanced searching. 2023. https://library.nhs.uk/knowledgehub/resources-for-advanced-searching/.

112. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; **5**(1): 210.

113. The Cochrane Collaboration. Chapter 7: Considering bias and conflicts of interest among the included studies. 2023.

https://training.cochrane.org/handbook/current/chapter-07 (accessed 23 September 2023.

114. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.

115. The Cochrane Collaboration. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. 2023. https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials (accessed 23 September 2023.

116. Hong Kong Baptist University. Estimating the sample mean and standard deviation (SD) from the five-number summary and its application in meta-analysis. 2023. https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html (accessed 18 september 2023.

117. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**(7109): 629-34.

118. Lomivorotov VV, Efremov SM, Pokushalov EA, et al. Randomized trial of fish oil infusion to prevent atrial fibrillation after cardiac surgery: data from an implantable continuous cardiac monitor. *Journal of cardiothoracic and vascular anesthesia* 2014; **28**(5): 1278-84.

119. Mozaffarian D, Marchioli R, Macchia A, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. *JAMA* 2012; **308**(19): 2001-11.

120. Farquharson AL, Metcalf RG, Sanders P, et al. Effect of dietary fish oil on atrial fibrillation after cardiac surgery. *American journal of cardiology* 2011; **108**(6): 851-6.

121. Joss JD, Hernan J, Collier R, Cardenas A. Perioperative supplementation of polyunsaturated omega-3 fatty acid for the prevention of atrial fibrillation after cardiothoracic surgery. *American journal of health-system pharmacy* 2017; **74**(1): e17-

e23.

122. Bernabe-Garcia M, Lopez-Alarcon M, Mansilla-Olivares A, et al. Oral administration of n-3 long-chain fatty acids reduce inflammatory response and improve clinical outcomes in patients with cardiovascular surgery. *Experimental and Clinical Cardiology* 2014; **20**(6): 145-60.

123. Bistrian BR. Clinical aspects of essential fatty acid metabolism: Jonathan Rhoads Lecture. *JPEN J Parenter Enteral Nutr* 2003; **27**(3): 168-75.

124. Westphal C, Konkel A, Schunck WH. CYP-eicosanoids--a new link between omega-3 fatty acids and cardiac disease? *Prostaglandins Other Lipid Mediat* 2011; **96**(1-4): 99-108.

125. Kacik M, Oliván-Viguera A, Köhler R. Modulation of K(Ca)3.1 channels by eicosanoids, omega-3 fatty acids, and molecular determinants. *PLoS One* 2014; **9**(11): e112081.

126. Ip WTK, Chandramouli C, Smith JA, McLennan PL, Pepe S, Delbridge LMD. A Small Cohort Omega-3 PUFA Supplement Study: Implications of Stratifying According to Lipid Membrane Incorporation in Cardiac Surgical Patients. *Heart Lung Circ* 2017; **26**(8): 846-55.

Appendix

Appendix A. Prisma 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	iv
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	iv
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1- 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	17
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	15-16
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	16. Appendix B&C
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	17
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	18
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	18
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	18
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	18
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	20

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	19
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	19
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	19
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	20
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	19
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	19
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	18
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	21-22
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix D&E
Study characteristics	17	Cite each included study and present its characteristics.	26-30
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	32
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	35,38
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	23-25, 31
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	37-40
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	38,39
	20d	Present results of all sensitivity analyses conducted to assess	37-40

Section and Topic	Item #	Checklist item	Location where item is reported
		the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not Reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not Reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	42
	23b	Discuss any limitations of the evidence included in the review.	46
	23c	Discuss any limitations of the review processes used.	46
	23d	Discuss implications of the results for practice, policy, and future research.	45
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	15
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	15
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	15
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix. B. Search strategy table from Medine, EMBASE, CINAHL, PsycINFO and Cochrane Central Register of Controlled Trial

Database	Fatty Acids	Coronary Artery Bypass	ICU Stay	Length of Hospital Stay
Medline	exp *Fatty Acids, Omega-3/ “Omega-3” “Omega 3” “Fish oil” "Eicosapentaenoic Acid" "Eicosapentenoic Acid" EPA "Docosahexaenoic acid*" "Docosahexenoic acid*" DHA n3 n-3 “Alphalinolen* acid” “Alpha-linolen* acid”	exp *Coronary artery bypass/ “aortocoronary Bypass” “coronary artery bypass” CABG	Intensive care unit/ “Intensive Care Unit” “Unit, Intensive Care” “ICU Intensive Care Units”	Length of stay/ “Stay Length” “Stay Lengths” “Hospital Stay” “Hospital Stays” “Stay, Hospital” “Stays, Hospital”
EMBASE	omega 3 fatty acid/ “Omega-3” “Omega 3” “Fish oil” "Eicosapentaenoic Acid" "Eicosapentenoic Acid" EPA "Docosahexaenoic acid*" "Docosahexenoic acid*" DHA n3	exp *coronary artery bypass graft/ “aortocoronary Bypass” “coronary artery bypass” CABG	Exp *intensive care unit/ “close attention unit” “combined medical and surgical icu” “intensive care” “cardiovascular icu” “coronary care units” “coronary intensive care unit”	exp *hospitalization/ ”’length of hospital stay” “hospital stay” “hospitalization” “short stay” hospitalization”

	n-3 “Alphalinolen* acid” “Alpha-linolen* acid”			
PsychINFO	Not relevant	Not relevant	Not relevant	Not relevant
CINAHL	exp *Fatty Acids, Omega-3/ “Omega-3” “Omega 3” “Fish oil” "Eicosapentaenoic Acid" "Eicosapentenoic Acid" EPA "Docosahexaenoic acid*" "Docosahexenoic acid*" DHA n3 n-3 “Alphalinolen* acid” “Alpha-linolen* acid”	exp *Coronary artery bypass/ “aortocoronary Bypass” “coronary artery bypass” CABG	Exp *intensive care unit/ “close attention unit” “"medical/surgical icus” “mixed medical and surgical icu” “mixed surgical and medical icu” “respiratory care unit” “respiratory care units” “special care unit”	exp *hospitalization/ ”’length of hospital stay” “hospital stay” “hospitalization” “short stay” hospitalization”
Cochrane Central Register of Controlled Trial	exp *Fatty Acids, Omega-3/ “Omega-3” “Omega 3” “Fish oil” "Eicosapentaenoic Acid" "Eicosapentenoic Acid" EPA "Docosahexaenoic acid*" "Docosahexenoic acid*" DHA	exp *Coronary artery bypass/ “aortocoronary Bypass” “coronary artery bypass” CABG	Exp *intensive care unit/ “ICU stay” “Intensive care unit stay” “close attention unit” “intensive care” “mixed surgical and medical icu” “coronary care units” “coronary intensive care unit”	exp *hospitalization/ “ Hospitalization duration” ”length of hospital stay” “hospital stay” “hospitalization”

	n3 n-3 “Alphalinolen* acid” “Alpha-linolen* acid”			

Appendix C. Detailed search strategy for EMBASE database

('coronary artery bypass graft'/exp OR 'aorta coronary artery bypass' OR 'aorta coronary bypass' OR 'aorta coronary bypass graft' OR 'aorta coronary vein bypass' OR 'aorta coronary vein bypass graft' OR 'aorta coronary vein shunt' OR 'aortic coronary artery bypass' OR 'aortic coronary bypass' OR 'aorticocoronary anastomosis' OR 'aorto coronary artery bypass' OR 'aorto coronary bypass graft' OR 'aorto coronary vein bypass' OR 'aortocoronary anastomosis' OR 'aortocoronary artery bypass' OR 'aortocoronary artery bypass graft' OR 'aortocoronary bypass' OR 'aortocoronary bypass graft' OR 'aortocoronary shunt' OR 'aortocoronary vein bypass' OR 'aortocoronary vein bypass graft' OR 'aortocoronary venous bypass' OR 'aortocoronary venous bypass graft' OR 'coronary artery bypass' OR 'coronary artery bypass graft' OR 'coronary artery bypass grafting' OR 'coronary artery graft' OR 'coronary bypass' OR 'coronary bypass graft' OR 'coronary bypass grafting' OR 'coronary vein bypass graft' OR 'coronary venous bypass graft' OR 'heart surgery'/exp OR 'cardiac surgery' OR 'cardiac surgical procedures' OR 'cardiosurgery' OR 'heart operation' OR 'heart surgery' OR 'myocardial resection' OR 'surgery, heart' OR 'open heart surgery'/exp OR 'heart surgery, open' OR 'intracardiac surgery' OR 'open cardiac surgery' OR 'open heart surgery' OR cabg OR 'cabg surgery') AND ('omega 3 fatty acid'/exp OR 'bilantin omega' OR 'conchol 36' OR 'eicosa e' OR 'eicosapen' OR 'fatty acids, omega 3' OR 'fatty acids, omega-3' OR 'n 3 fatty acid' OR 'n 3 polyunsaturated fatty acid' OR 'omega 3' OR 'omega 3 carboxylic acid' OR 'omega 3 carboxylic acids' OR 'omega 3 fatty acid' OR 'omega 3 feingold' OR 'omega 3 plus' OR 'omega 3 polyunsaturated fatty acid' OR 'omega forte' OR 'omega-3-carboxylic acids' OR 'omega3 polyunsaturated fatty acid' OR 'sanhelios omega 3' OR 'fish oil'/exp OR 'fish oil' OR 'fish oils' OR 'omegaven' OR 'optimepa' OR 'tuna oil' OR 'marine oil'/exp OR 'eicosapentanoic acid'/exp OR 'lipid emulsion'/exp OR 'emulsion, fat' OR 'emulsion, lipid' OR 'fat emulsion' OR 'fat emulsions, intravenous' OR 'lipid emulsion' OR 'icosapentaenoic acid'/exp OR '5, 8, 11, 14, 17 eicosapentaenoic acid' OR '5, 8, 11, 14, 17 icosapentaenoic acid' OR '5, 8, 11, 14, 17-eicosapentaenoic acid' OR 'eicosa 5, 8, 11, 14, 17 pentaene carboxylic acid' OR 'eicosa 5, 8, 11, 14, 17 pentaenoic acid' OR 'eicosapentaenoate' OR 'eicosapentaenoic acid' OR 'eicosapentenoic acid' OR 'epaspire' OR 'icosa 5, 8, 11, 14, 17 pentaenoic acid' OR 'icosapent' OR 'icosapentaenoate' OR 'icosapentaenoic acid' OR 'omega 3 eicosapentaenoic acid' OR 'timnodonate' OR 'timnodonic acid' OR 'docosahexaenoic acid'/exp OR 'dhasco' OR 'docosahexaenoate' OR 'docosahexaenoic acid' OR 'docosahexaenoic acids' OR 'docosahexenoic acid' OR 'n 3'/exp) AND ('length of hospital stay' OR 'hospitalization'/exp OR 'hospital stay' OR 'hospitalization' OR 'short stay hospitalization' OR 'intensive care unit'/exp OR 'gicu' OR 'gicus' OR 'icu`s' OR 'close attention unit' OR 'combined medical and surgical icu' OR 'combined surgical and medical icu' OR 'critical care unit' OR 'general icu' OR 'intensive care department' OR 'intensive care unit' OR 'intensive care units' OR 'intensive therapy unit' OR 'intensive treatment unit' OR 'medical-surgery icu' OR 'medical/surgical icu' OR 'medical/surgical icus' OR 'medico-surgical icu' OR 'mixed medical and surgical icu' OR 'mixed surgical and medical icu' OR 'respiratory care unit' OR 'respiratory care units' OR 'special care unit' OR 'surgery/medical icu' OR 'surgical-medical icus' OR 'surgical/medical icu' OR 'unit, intensive care' OR 'cardiac surgery intensive care unit'/exp OR 'surgical intensive care unit'/exp OR

'hospitalization length of stay' OR 'coronary care unit'/exp OR 'cardiac icu' OR 'cardiac icus' OR 'cardiac intensive care unit' OR 'cardiovascular intensive care unit' OR 'cardiologic unit' OR 'cardiology icu' OR 'cardiology intensive care unit' OR 'cardiology unit' OR 'cardiovascular icu' OR 'cardiovascular intensive care unit' OR 'coronary icu' OR 'coronary care unit' OR 'coronary care units' OR 'coronary intensive care unit' OR 'coronary resuscitation unit' OR 'coronary unit')

Appendix D. Table of Excluded studies after full text-screening from electronic databases

Title	Reason for exclusion
Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery?	population
Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency	Outcome
Antioxidant Supplementation Attenuates Oxidative Stress in Patients Undergoing Coronary Artery Bypass Graft Surgery	Outcome
Effect of pretreatment with omega-3 polyunsaturated fatty acids (PUfas) on hematological parameters and platelets aggregation in patients during elective coronary artery bypass grafting	outcome
Myocardial protection during elective coronary artery bypasses grafting by pretreatment with omega-3 polyunsaturated fatty acids	Outcome
Plasma n-3 and n-6 fatty acids and the incidence of atrial fibrillation following coronary artery bypass graft surgery	Study design
Omega-3 fatty acids do not alter P-wave parameters in electrocardiogram or expression of atrial connexins in patients undergoing coronary artery bypass surgery	Outcome
Vascular prostacyclin is increased in patients ingesting omega-3 polyunsaturated fatty acids before coronary artery bypass graft surgery	Outcome
Preoperative carbohydrate load and intraoperatively infused omega-3 polyunsaturated fatty acids positively impact nosocomial morbidity after coronary artery bypass grafting: a double-blind controlled randomized trial	Exposure
Prevention The effect of omega-3 polyunsaturated fatty acids in prevention of postoperative atrial fibrillation development in patients undergoing coronary artery bypass graft surgery	study design
Marine n-3 fatty acids are incorporated into atrial tissue but do not correlate with postoperative atrial fibrillation in cardiac surgery	study design
A small cohort omega-3 PUFA supplement study: implications of stratifying according to lipid membrane incorporation in cardiac surgical patients	study design

Appendix E. Table of Excluded studies after full text-screening from Supplementary Search

Title	Reason for exclusion
A small cohort omega-3 PUFA supplement study: implications of stratifying according to lipid membrane incorporation in cardiac surgical patients	Study design
Preoperative n-3 polyunsaturated fatty acids are associated with a decrease in the incidence of early atrial fibrillation following cardiac surgery.	Study design
Prevention of new-onset atrial fibrillation after direct myocardial revascularization surgery: randomized comparative study	Time of exposure-only post-operative period
Omega-3 poly-unsaturated fatty acids reduce the incidence of postoperative atrial fibrillation in patients with history of prior myocardial infarction undergoing isolated coronary artery bypass grafting.	Study design
Protective effect of Eicosapentaenoic acid on insulin resistance in hyperlipidemic patients and on the postoperative course of cardiac surgery patients: the possible involvement of adiponectin.	Exposure: only EPA molecule
Effect of omega-3 polyunsaturated fatty acid on the prevention of atrial fibrillation after Off-pump coronary artery bypass grafting	Study design

Appendix F. Summary table of all effect measures extracted from included studies for the construction of Meta-analysis

Outcome	*Study*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*comment*
ICU stay (days)	Berger, M.M 2013	14	1.4	0.75	14	2.11	1.4	Included in MA
	farquharson 2011	97	2.8	2.2	97	3.9	6.6	
	Bernabe 2013	12	4.5	3.8	11	6.8	3.6	
	Lomivorotov 2014	18	2	1	21	2	1	
	Mozaffarian	758	7	2.9	758	6.6	2.2	Included in MA after calculation of mean and SD with sample normally distributed
	Study	n	Median	IQR	n	Median	IQR	
	Farahani 2017	202	2.4	(2.25-3)	199	1.54	(0.52-3.9)	Data are significantly skewed away from normality
	Mozaffarian	758	2	(1-3)	758	2	(1-3)	Included in MA, no significant evidence to show that the data are skewed
	saravanan	52	1	(1-2)	51	1	(1-2)	Data are significantly skewed away from normality

Outcome	*Study*	*n*	*Mean*	*SD*	*n*	*Mean*	*SD*	*Comment*

Hospital Stay	Berger, M.M 2013	14	12.7	4.2	14	12.2	4.3	Included in MA
	Calò 2005	81	7.3	2.1	79	8.2	2.6	
	Sorice (G2 n3, G4) on-pump	51	8.2	2.5	57	8.3	3.1	
	Sorice (G1 n3, G3) off-pump	45	8.8	4.9	48	8.6	3.8	
	Lomivorotov 2014	18	18	5	21	19	7	
	Bernabe 2013	12	8.3	3.8	11	10.3	3.6	
	Study	n	Adjusted mean ratio	SD	n	Adjusted mean ratio	SD	
	Farquharson 2011	97	8.6	7.1	97	9.9	10.2	Not included in MA
	Study	n	Median	IQR	n	Median	IQR	
	Farahani 2017(days)	202	14	(12-18)	199	14	(12-18)	the data are significantly skewed away from normality
	Mazaffarian (days)	758	7	(5-9)	758	7	(5-8)	the data are significantly skewed away from normality in intervention group
	Sandesara, 2012 (Days)	120	6	(5-8)	123	5	(4-7)	the data are significantly skewed away from normality.
	saravanan (days)	52	8.5	(6-12)	51	7	(6-10)	the data are significantly skewed away from normality in control group
	Study	n	Median	SD	n	Median	SD	
	Joss 2017 (days)	284	6	3.4	275	6	5	Not included in MA