No impact of fish oil supplements on bleeding risk: a systematic review

Katrine Munk Begtrup, Andreas Engel Krag & Anne-Mette Hvas

ABSTRACT

INTRODUCTION: Fish oil supplementation may inhibit platelet aggregation and can potentially increase the risk of bleeding. The aim of the present systematic review was to evaluate the effect of fish oil supplements on haemostasis and bleeding risk, and to provide recommendations on whether it is necessary to discontinue fish oil supplementation prior to surgery.

METHODS: Studies were identified through PubMed and Embase searches and by reviewing the reference lists of the included papers. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used. Included in the review were publications including a minimum of 20 healthy subjects and studies on patients who were undergoing surgery and who had fish oil exposure.

RESULTS: In total, 52 publications were included; 32 publications on healthy subjects and 20 publications on patients undergoing surgery. The majority of the included studies were randomised controlled trials or included a control group. Overall, fish oil supplements reduced platelet aggregation in healthy subjects. Fish oil exposure in surgical patients did not increase bleeding or blood transfusions either during or after surgery.

CONCLUSION: Fish oil supplements reduced platelet aggregation in healthy subjects. This biochemical effect was not reflected in increased bleeding risk during or after surgery evaluated in randomised controlled trials. Consequently, this systematic review does not support the need for discontinuation of fish oil supplements prior to surgery or other invasive procedures.

KEY POINTS

Clinicians have expressed concern about a potentially increased bleeding risk during surgery in patients who take fish oil supplements.

Fish oil supplements reduced primary haemostasis measured biochemically in healthy subjects.

Fish oil supplementation before or immediately after surgery did not increase intra- or postoperative bleeding in randomised controlled trials.

Based on this systematic review, discontinuation of fish oil supplements prior to surgery is not recommended.

SYSTEMATIC REVIEW

Centre for Haemophilia and Thrombosis, Department of Clinical Biochemistry, Aarhus University Hospital, Denmark

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Since the 1980s, fish oil has been investigated extensively for its protective effect in cardiovascular disease. Fish oil is now the second most commonly used dietary supplement in Denmark [1].

Dyerberg & Bang were the first to show that the bleeding times in the population of Greenlandic Inuit were significantly prolonged compared with those of the Danish population [2]. They found that the platelet membranes of the Greenlandic Inuit were markedly enriched with omega-3 polyunsaturated fatty acids; and they suggested that the Inuit's diet explained the low rate of cardiovascular disease in this population [2].

Since then, the impact of fish oil on haemostasis has been a subject of extensive debate.

Fish oil contains a high amount of the polyunsaturated omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). After ingestion, EPA substitutes arachidonic acid in the phospholipid layer of platelet cell membranes [3-5]. This EPA substitution reduces the level of plasma thromboxane B_2 [5], which is a stable metabolite of thromboxane A_2 [5]. Thromboxane A_2 induces platelet aggregation; hence, fish oil intake may inhibit platelet aggregation through reduced thromboxane A_2 synthesis [5, 6]. However, fish oil supplementation may affect platelets beyond thromboxane synthesis. A recent large randomised controlled trial (RCT) showed reduced coronary events in hypercholesterolaemic patients supplemented with EPA daily, but adverse bleeding events were significantly increased in patients with EPA supplementation [7]. Hence, some clinicians have expressed concern about the potential impact of fish oil supplementation on increased bleeding risk during surgery or other invasive procedures [8, 9].

This systematic review investigated the impact of fish oil supplements on haemostasis in healthy subjects, and the risk of bleeding in patients undergoing surgery or other invasive procedures. In conclusion, the present review does not support the need for discontinuation of fish oil supplements prior to surgery.

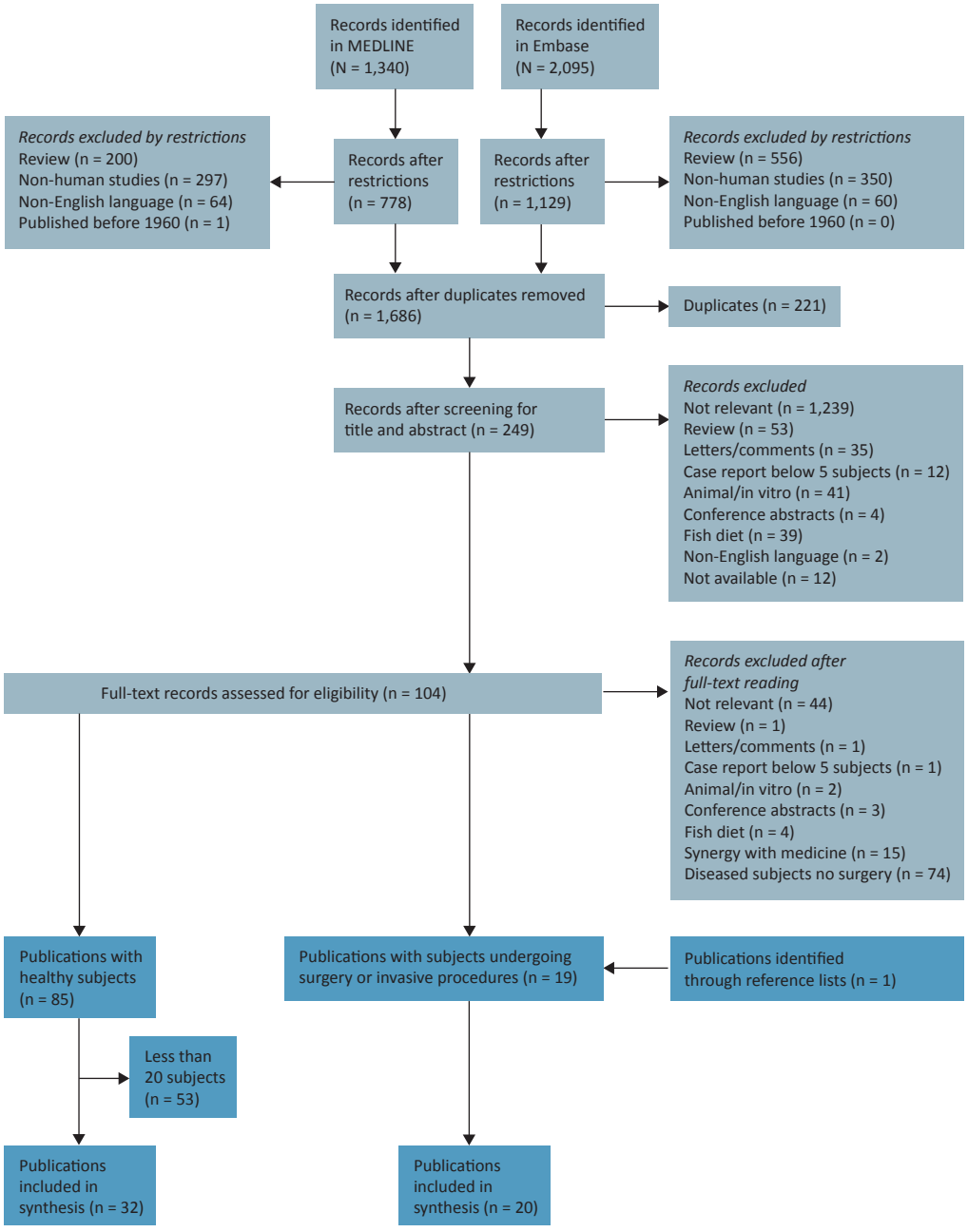
METHODS

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) guidelines [10]. The MEDLINE/PubMed and Embase databases were searched for relevant publications on 22 June 2016. The search terms used in MEDLINE/PubMed were ("Fish Oils"[Mesh] AND ("Surgical Procedures, Operative"[Mesh] OR "Hemorrhage"[Mesh] OR "Hemostasis"[Mesh])). In Embase, the search terms were ('fish oil'/exp AND ('bleeding'/exp OR 'blood clotting'/exp OR 'hemostasis'/exp OR 'thrombocyte function and characteristics'/exp OR 'invasive procedure'/exp OR 'surgery'/exp)). Manual searches in the reference lists identified additional publications. Filters were applied to each database search to omit studies fulfilling the following criteria: reviews, non-human studies, non-English-language publications and publication date before 1 January 1960. Publications were included if they were original studies of oral or intravenous fish oil supplementation evaluating biochemical data on primary haemostasis, secondary

FIGURE 1

Flow chart describing the systematic literature search and the inclusion and exclusion process.



haemostasis or fibrinolysis; and/or included objective clinical data on bleeding in healthy subjects or patients undergoing surgery or invasive procedures. The exclusion criteria were: reviews, conference abstracts, letters/comments without original data, case reports including less than five subjects, animal experiments, in vitro experiments, studies on fish diet and not supplementation, and studies investigating synergistic effects of fish oil in combination with medicine and guidelines. After duplicates had been removed, 1,686 records were screened by title and abstract. In this screening process, reviews and non-English-language records not removed by filters were excluded manually. In the next step, 249 full-text records were assessed for eligibility. **Figure 1** shows a flow chart outlining the screening and selection process.

The included publications were divided into two groups: Studies on healthy subjects and studies including patients undergoing surgery or invasive procedures. After the screening and inclusion process, it was decided to include only publications on healthy subjects including at least 20 subjects. There was no lower limit on the number of patients in publications including patients undergoing surgery.

RESULTS

Healthy subjects

Table 1 shows a summary of identified studies including at least 20 healthy individuals; in total 32 publications and 29 different study populations.

Compared with controls or baseline values, nine out of 16 studies, which were covered in 12 publications, demonstrated a reduced platelet aggregation by at least one agonist, reduced platelet adhesion and/or reduced thromboxane B2 [11-22]. In contrast, eight studies showed no statistically significant change in platelet aggregation or P-selectin after fish oil intake [23-30], and Cottin et al reported no influence on platelet-monocyte-aggregation [31]. Four studies reported a statistically significant reduction in thromboxane B2 after fish oil intake [19, 32-34], whereas one study did not report a significant change [27]. Bleeding time was statistically significantly increased in three out of the six studies after intake of fish oil [24, 26, 35], whereas the three remaining studies reported no effect on bleeding time [17, 28, 36].

Reduced fibrinogen or reduced thrombin generation was demonstrated in three studies after intake of fish oil [19, 37, 38], whereas three studies reported no statistically significant reduction [17, 33, 39]. No studies found any effect of fish oil intake on coagulation factor VII [16, 17, 21, 29, 33, 39]. Only one study investigated vitamin K-dependent coagulation factors and found no statistically significant change following a four-week intake of fish oil supplementation [38].

One RCT suggested an increased fibrinolysis indicated by increased tissue-plasminogen activator [40], whereas Schmidt et al reported a reduced fibrinolysis after fish oil intake [24]; moreover, an increased plasminogen activator inhibitor (PAI)-1 activity was found in two studies [20, 39]. The remaining six studies investigating markers of fibrinolysis found no statistically significant changes after intake of fish oil, [16, 17, 19, 21, 34, 41].

In the study by Prisco et al [18], healthy patients were exposed to fish oil for four months. Platelet aggregation was still reduced one month after discontinuation of fish oil; two months after discontinuation, platelet aggregation had returned to the baseline level. In the study by Freese & Mutanen [17], platelet aggregation was reduced following four weeks of fish oil supplementation, and had returned to normal levels 12 weeks after discontinuation of fish oil.

Patients undergoing surgery or invasive procedures

The effect of fish oil on clinical bleeding and/or biochemical haemostatic markers in patients undergoing surgery was reported in 20 publications on 19 different study populations (**Table 2**). Clinical bleeding was measured quantitatively in 12 studies, which were covered in 13 publications [8, 9, 42-52], and another four studies evaluated bleeding qualitatively [53-56]. Biochemical markers of haemostasis were reported in 13 out of 19 studies.

Preoperative fish oil exposure

Intraoperative bleeding and haemostasis

Clinical bleeding during a surgical procedure was reported in seven studies including patients exposed to fish oil preoperatively [8, 9, 43, 47, 49, 51, 56]. None of the seven studies found significantly increased clinical bleeding during surgery when comparing the fish oil group with the control group. Paradoxically, the double-blinded RCT by Mozaffarian et al reported that patients who were exposed to fish oil preoperatively received significantly fewer red blood cell transfusions than the control group during open-heart surgery [49]. One study estimated bleeding qualitatively as the surgeon noticed no difference in intraoperative bleeding [56]; furthermore, no difference in post-operative haematocrit level was measured in the same study on coronary angioplasty [56].

Post-operative bleeding and haemostasis

Post-operative bleeding was evaluated in four studies following only preoperative fish oil exposure. The four studies were covered in five publications [9, 43-45, 48]. None of the studies reported increased post-operative bleeding after preoperative fish oil exposure. One double-blinded RCT on open-heart surgery reported signifi-

TABLE 1

Summary of studies investigating the haemostatic effect of fish oil in healthy individuals including at least 20 subjects[a].

Reference	Study population, n, gender	Study design: fish oil exposure	Haemostasis		Fibrinolysis
			primary	secondary	
Cottin et al, 2016 [31]	48 M	RCT, placebo-controlled, single-blind, 2 wks: EPA 3.1 g daily Olive oil	→ platelet-monocyte-aggregation	-	-
McEwen et al, 2013 [11] (platelet) McEwen et al, 2015 [37] (secondary)	40	4 wks: 640 mg daily PUFA: 120 mg EPA + 520 mg DHA	↓ platelet aggregation	↓ fibrin generation ↓ peak thrombin	-
Phang et al, 2014 [12] Phang et al, 2013 [13]	94: 41 M + 53 F	RCT, double blind for 4 wks to a daily dose: Sunola oil EPA 500 mg + DHA 100 mg EPA 100 mg + DHA 500 mg	↓ platelet aggregation	-	-
Din et al, 2013 [40]	20 M	RCT, double blind, 6 wks, 2 g daily: Olive oil EPA + DHA, 1.2:1.0	-	-	↓ tPA
Phang et al, 2012 [14] Phang et al, 2012 [15]	30: 15 M + 15 F	RCT, placebo-controlled, 0, 2, 5 and 24 hours, single dose 2 × 1 g: Sunola oil EPA + DHA, 5:1 EPA + DHA, 1:5	*Prior to 24 hrs* EPA, males: ↓ platelet aggregation DHA, females: ↓ platelet aggregation *After 24 hrs* ↓ platelet aggregation ↓ platelet microparticles	-	-
Mann et al, 2010 [30]	30: 11 M + 19 F	RCT, 14 days: Sunola oil Tuna oil, rich in DHA, EPA, little of DPA Seal oil, EPA + DHA, rich in DPA	Seal oil: ↓ P-selcetin Fish oil: → P-selectin	-	-
Englyst et al, 2007 [61]	35 M	12 wks: 6 × 1 g fish oil daily	↑ platelet microparticles	↑ APC-resistance	-
Vanschoonbeek et al, 2004 [38]	25 M	4 wks: 3.0 g omega-3 daily		↓ fibrinogen ↓ factor V ↓ thrombin generation → vitamin K-dependent coagulation factors	-
Andrioli et al, 1999 [22]	60: 30 M + 30 F	RCT, 15 days: Fish oil, 4 g daily Soy lecithin, 2 g daily Usual diet	↓ platelet adhesion	-	-
Calzada et al, 1999 [32]	20	RCT, double-blind: 150 mg DHA + 30 mg EPA Sunflower oil 600 mg daily	↓ thromboxane B_2	-	-
Agren et al, 1997 [21]	55 M	15 wks: Fish oil, EPA + DHA Fish diet DHA oil, 1.68 g daily Control	↓ platelet aggregation	→ aPTT → F1 + F2 → fibrinogen → factor VII	→ tissue factor pathway inhibitor
Freese & Mutanen, 1997 [16]	30: 15 M + 15 F	4 wks: Fish oil, EPA 3.04 g + DHA 2.45 g Linseed oil	↓ platelet aggregation	→ factor VII	→ PAI-1
Freese & Mutanen, 1997 [17]	46: 17 + 29 F	2 groups, 4 wks: Linseed oil Fish oil BS: after 4 wks intake and again 12 wks after cessation	After 4 wks: ↓ platelet aggregation → bleeding time 12 weeks after cessation: → platelet aggregation → bleeding time	After 4 wks: → fibrinogen → factor VII 12 wks after cessation: → fibrinogen → factor VII	After 4 wks: → PAI-1 12 wks after cessation: → PAI-1
Osterud et al, 1995 [33]	134: 72 M + 62 F	5 groups, 10 wks: Harp seal blubber oil Cod liver oil Minke whale blubber oil Seal blubber oil/CLA No oil	Whale group: ↓ thromboxane B_2	→ fibrinogen → factor VII ↓ whale oil group: F1 + F2	-
Prisco et al, 1995 [18]	20 M	2 groups, 4 mo.s, 1 g daily: Fish oil Olive oil 3-mo. wash out BS: 1, 2 and 3 mo.s and after wash out	During fish oil: ↓ platelet aggregation Normal after 1 mo. Returned to baseline after 2 mo.s	-	-
Turini et al, 1994 [23]	20 M	2 groups, 42 days: Fish oil, EPA + DHA Vegetable oil	→ platelet aggregation	-	-

CONTINUES »

TABLE 1, CONTINUED

Summary of studies investigating the haemostatic effect of fish oil in healthy individuals including at least 20 subjects[a].

Reference	Study population, n, gender	Study design: fish oil exposure	Haemostasis		
			primary	secondary	Fibrinolysis
Prisco et al, 1994 [41]	20 M	RCT, double-blind, 4 mo.s: Fish oil 4 × 1 g PUFA daily Olive oil BS: 0, 2 and 4 mo.s after randomization 1, 2 and 3 mo.s after wash out		-	4 mo.s after randomization: → PAI-1 → F1 + F2
Hansen et al, 1993 [19]	31 M	RCT, double-blind, 7 wks: n-3 ethyl ester 4 g daily n-3 triglycerides 12 g daily Corn oil	↓ platelet aggregation ↓ thromboxane B_2 → vWF	↓ fibrinogen → factor VII	→ tPA
Lervang et al, 1993 [29]	24	RCT, 8 weeks: Fish oil, n-3 PUFA 0.6 g/day Control, mixture of fatty acids	→ platelet aggregation	→ fibrinogen → factor VII	-
Møller et al, 1992 [39]	40: 20 M + 20 F	RCT, single dose: 20 g n-3 PUFA 20 g n-6 PUFA, control group		→ fibrinogen → factor VII → TAT, d-dimer	↑ AI-1 activity ↓ tPA, control group
Schmidt et al, 1992 [24]	24: 10 M + 14 F	9 mo.s: 4 g n-3 PUFA daily	↑ bleeding time ↓ vWF → platelet aggregation	↑ fibrinogen	↓ fibrinolysis
Fumeron et al, 1991 [20]	36 M	2 groups, 3 wks: n-3 PUFA 6 g daily Usual diet	↓ platelet aggregation	-	↑ PAI-1 activity
Blonk et al, 1990 [36]	45 M	RCT, 12 wks: 1.5 g EPA + DHA 3 g EPA + DHA 6 g EPA + DHA	→ bleeding time	-	-
Bach et al, 1989 [25]	30: 16 M + 14 F	RCT, double-blind, 5 wks: Fish oil, 0.135 g EPA + 0.18 g DHA daily Placebo, neutral oil	→ platelet aggregation	-	-
Hansen et al, 1989 [34]	40: 20 M + 20 F	8 wks: 25 ml cod liver oil	↓ thromboxane B_2	→ fibrinogen → factor VII	→ clot lysis time → tPA
Simonsen et al, 1988 [26]	30 M	3 wks: 20 ml cod liver oil	↑ bleeding time → platelet aggregation	-	-
Salonen et al, 1987 [27]	44 M	RCT, 12 wks: Fish oil, 150 mg EPA + 120 mg DHA + 680 mg other fish oils Olive oil Intake discontinued 7 days before BS	→ platelet aggregation → thromboxane B_2	-	-
Rogers et al, 1987 [28]	60 M	RCT, 10-42 days, mean 32 days: Fish oil, 1.6-2.9 g EPA/day Olive oil	→ bleeding time → platelet aggregation	→ fibrinogen ↑ thrombin time	-
Mortensen et al, 1983 [35]	20 M	Double-blind, cross-over, 4 wks: Fish oil, 10 g Vegetable oil, 10 g	↑ bleeding time	↑ antithrombin → fibrinogen → aPTT	

APC = activated protein C; aPTT = activated partial thromboplastin time; BS = blood samples; CLA = conjugated linoleic acid; DHA = docosahexaenoic acid (22:6 n-3); DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid (20:5 n-3); F = female; F1 + F2 = prothrombin fragment 1 + 2; M = male; PAI-1 = plasminogen activator inhibitor-1; PUFA = polyunsaturated fatty acid; RCT = randomized controlled trial; TAT = thrombin-antithrombin-complex; tPA = tissue plasminogen activator; vWF = von Willebrand factor.
↑) Statistically significant increase in fish oil group compared with baseline or controls, as regards to platelet aggregation this is for ≥ 1 agonist.
↓) Statistically significant reduction in fish oil group compared with baseline or controls, as regards to platelet aggregation this is for ≥ 1 agonist.
→) No statistically significant change in the fish oil group compared with baseline or controls.
a) Data published on the same study population are merged.

cantly fewer post-operative red blood cell transfusions in patients with preoperative fish oil exposure compared with the control group [48].

Biochemical markers were measured after surgery in two of the studies with patients who had been exposed to fish oil preoperatively. These studies were covered by three publications [9, 44, 45]. In patients undergoing coronary artery bypass grafting, the haematocrit level and markers of secondary haemostasis and fibrinolysis were not different [44, 45]. A retrospective case-control study on posterior spinal arthrodesis showed no difference in haemoglobin levels after surgery between patients who had been exposed to fish oil and other who had not [9].

TABLE 2

Summary of studies investigating clinical bleeding and haemostasis in patients undergoing surgery with fish oil exposure[a].

Reference	Procedure	Study design	Aim	Patients, n	Controls, n	Fish oil exposure per day
Cardiac surgery and interventional cardiology						
Mozaffarian et al, 2012 [49]	CABG and valve surgery	RCT, double-blinded	Fish oil on postop. atrial fibrillation	758	758	*Preop.* loading with 3.72-4.65 g EPA + 3-3.75 g DHA over 2-5 days *Postop.* 930 mg EPA + 750 mg DHA
Farquharson et al, 2011 [48]	CABG and valve surgery	RCT	Fish oil on postop. atrial fibrillation	97	97	2.7 g EPA + 1.9 g DHA
Heidarsdottir et al, 2010 [47]	CABG and valve surgery	RCT, double-blinded	Fish oil on postop. atrial fibrillation	83	85	1.24 g EPA + 1 g DHA
Eritsland et al, 1995 [46]	CABG	RCT, unblinded	Fish oil on coagulation and fibrinolysis	260: fish oil + ASA or warfarin	251: ASA or warfarin	2.04 g EPA + 1.28 g DHA
Eritsland et al, 1994 [59]	CABG	RCT, unblinded	Fish oil on fibrinolysis	29: fish oil + ASA or warfarin	29: ASA or warfarin	3.4 g EPA and DHA
Nilsen et al, 1993 [45] Nilsen et al, 1991 [44]	CABG	RCT, double blinded	Fish oil on lipids and coagulation	10	10	3.15 g EPA + 1.9 g DHA
DeCaterina et al, 1990 [43]	CABG	Case-control, prospective, open-label	Vascular and platelet effects of fish oil	15	15	3 g EPA + 1.3 g DHA
Ernst et al, 1989 [56]	Coronary angioplasty	RCT, unblinded	Not specified	20	20	4.5 g fish oil
Reis et al, 1989 [42]	Coronary angioplasty	RCT, double-blinded	Restenosis after angioplasty	150	72	6 g fish oil as ethyl esters or triglycerides
Dehmer et al, 1988 [53]	Coronary angioplasty	RCT, unblinded	Restenosis after angioplasty	43: fish oil + ASA + dipyridamole	39: ASA + dipyridamole	3.2 g EPA + 2.2 g DHA
Abdominal surgery						
Sorensen et al, 2014 [51]	Colorectal cancer surgery	RCT, double-blinded	Fish oil on clinical outcome	74	74	2.0 g EPA + 1.0 g DHA
Wang et al, 2012 [54]	Gastrointestinal surgery	RCT, double-blinded	Safety and efficacy of fish oil	32	31	20.8 mg EPA + 18.4 mg DHA per kg body weight
Aiko et al, 2005 [58]	Oesophageal cancer surgery	Case-control, retrospective	Fish oil on haemostasis and inflammatory response	17	11	Up to 2.25 g ω-3 fatty acids
Singer et al, 2004 [57]	Kidney transplantation	Case-control, prospective	Fish oil on coagulation in recipients	8	20	0.13 g fish oil per kg body weight
Heller et al, 2002 [50]	Gastrointestinal and pancreatic cancer surgery	RCT, double-blinded	Fish oil on haemostasis	24	20	EPA 25-56 mg + DHA 29-62 mg per kg body weight
Roulet et al, 1997 [55]	Total oesophagectomy	RCT	Fish oil on platelet function	10	9	2 g EPA + 2 g DHA approx.
Spine surgery						
Kepler et al, 2012 [8]	Spinal decompression	Case-control, retrospective	Fish oil on operative bleeding	16	79	Self-administered, unknown dose
Meredith et al, 2012 [9]	Posterior spinal arthrodesis	Case-control, retrospective	Fish oil on operative bleeding	28	56	Self-administered, unknown dose
Mixed surgery						
Swails et al, 1993 [52]	Mixed head and neck, cardiac, abdominal surgery	RCT	Fish oil on platelet aggregation	7	9	1.5 g EPA + 0.5 g DHA

aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid; CABG = coronary artery bypass grafting; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FPA = fibrinopeptide A; hb = haemoglobin; INR = international normalized ratio; LPS = lipopolysaccharide; PAI = plasminogen activator inhibitor; postop. = post-operatively; preop. = preoperatively; PT = prothrombin time; RCT = randomized controlled trial; t-PA = tissue-plasminogen activator; TAT = thrombin-antithrombin complex; TFPI = tissue factor pathway inhibitor; TXA_2 = thromboxane A_2; TXB_2 = thromboxane B_2.

CONTINUES »

TABLE 2, CONTINUED

Summary of studies investigating clinical bleeding and haemostasis in patients undergoing surgery with fish oil exposure[a].

	Results	
Length of exposure	**laboratory measurements**	**clinical endpoints**
2-5 days preop. + up to 10 days postop.	-	↓ red blood cell transfusions during and after surgery → chest tube output or other bleeding complications
	-	
3 wks preop.	-	↓ red blood cell transfusions → blood loss: drain, or major bleeding episodes
5-7 days preop. + up to 2 wcks postop.	-	→ estimated operative blood loss, drain blood volume, blood transfusions, or bleeding-related re-operations
9 mo.s postop.	↑ PAI-1 antigen ↓ platelet count → bleeding time, fibrinogen, factor VII, TAT, FPA, D-dimer and PAI-1 activity	→ bleeding episodes
6 mo.s postop.	↓ PAI-1 antigen → fibrinogen, D-dimer, PAI-1 activity, t-PA antigen and t-PA activity	-
2 mo.s preop.	*Preop.* → LPS-stimulated TXB_2 release from platelets *Preop.: and postop.* → fibrinogen, TFPI, TAT, or PAI-1, haematocrit	→ postop. bleeding: thoracic drain output, or blood transfusion requirements
28 days preop.	*Preop.* ↓ platelet adhesiveness, serum TXB_2, and platelet aggregation ↑ bleeding time	→ bleeding at or after surgery → postop. blood loss: drain, and transfusions
3 wks preop. + 3 days postop.	*Postop.* → haematocrit	"The surgeon noticed no differences in intraoperative bleeding"
5 days preop. + 6 mo.s postop.	-	→ bleeding side effects
7 days preop. + 6 mo.s postop.	→ bleeding time, prothrombin, aPTT ↓ platelet count	"No important bleeding complications in the treatment group" No blood transfusions in any group
7 days preop. + 7 days postop.	*Until the 4th postop. day* ↓ hb	→ blood loss during surgery → postop. blood transfusions or bleeding-related re-operations
5 days postop. from the 1st postop. day	*Postop. day 1-3* ↑ aPTT → plcatelet count and PT	Reports: "no bleeding event was observed in either group during the intervention period"
7 days postop. from 2 h after surgery	*2nd postop. day* ↓ D-dimer *Postop. day 2-4* ↑ platelet count → PT, aPTT, fibrinogen, fibrin/fibrinogen degradation products, TAT, TXB_2, or plasmin inhibcitor-plasmin complex	-
5 days postop. from the 1st postop. day	→ platelet count, PT and PTT	-
5 days postop. from the 1st postop. day	→ platelet count, platelet function, tromboplastin time, aPTT, fibrinogen, antithrombin, factor VIIa, or factor XIIa. → postop. hb drop	→ postop. transfusions, red blood cell, fresh frozen plasma transfusions and hydroxyethyl starch administration
7 days postop. from the 2nd postop. day	↓ platelet aggregation. → bleeding time and PT	"No increase in postoperative bleeding"
Within 14 days preop., discontinued at 2.3 days preop.	-	→ estimated operative blood loss
Within 14 days preop., discontinued at 5.2 days preop.	*Preop.* → INR, aPTT, platelet count *Postop.* → hb	→ operative estimated blood loss, transfused volume of cell saver, surgical drain output, and red blood cell transfusions
7 days postop.	*Preop.* → platelet aggregation	→ red blood cell transfusions

↑) Statistically significant increase in the fish oil group compared with baseline or controls, as regards to platelet aggregation this is for ≥ 1 agonist.
↓) Statistically significant reduction in the fish oil group compared with baseline or controls, as regards to platelet aggregation this is for ≥ 1 agonist.
→) No statistically significant change in the fish oil group compared with baseline or controls.
a) Data published on the same study population are merged.

Fish oil supplementation prior to surgery does not increase bleeding risk. Photo: Niels Age Skovbo, Fokus Foto.

Pre- and post-operative fish oil exposure

Post-operative bleeding and haemostasis

Five studies evaluated post-operative bleeding in patients who had been exposed to fish oil both before and after surgery [42, 47, 49, 51, 53]. None of the studies showed increased post-operative bleeding after fish oil exposure. Mozaffarian et al reported significantly fewer post-operative red blood cell transfusions in patients exposed to fish oil both pre- and post-operatively than in the control group, but no difference in chest tube output [49]. In the RCT by Sorensen et al, fish oil exposure did not increase post-operative bleeding, but haemoglobin was reduced immediately post-operatively in colorectal cancer patients [51]. Dehmer et al estimated bleeding qualitatively and found no difference in post-operative bleeding complications or bleeding time; however, the platelet count was reduced in the fish oil group [53].

Post-operative fish oil exposure

Post-operative bleeding and haemostasis

Five studies evaluated post-operative bleeding in patients who had been exposed to fish oil in the post-operative period [46, 50, 52, 54, 55]. In the RCT by Heller et al, patients undergoing gastrointestinal and pancreatic cancer surgery were exposed to fish oil supplementation from the first post-operative day [50], and no statistically significant difference in post-operative bleeding or laboratory measurements was found [50]. The RCT by Eritsland et al included coronary artery bypass grafting patients and reported no bleeding episodes post-operatively in either group; however, the time of initiation of fish oil supplementation post-operatively was not indicated [46]. Furthermore, the study found no difference in bleeding time, fibrinogen and secondary haemostasis [46], but post-operative fish oil exposure increased PAI-1 antigen, indicating reduced fibrinolysis [46]. Two studies evaluated bleeding qualitatively and reported no differences in post-operative bleeding [54, 55]. Roulet et al included patients undergoing total oesophagectomy and found reduced platelet aggregation in the fish oil group, but no difference in bleeding time and prothrombin time [55]. Wang et al included patients undergoing gastrointestinal surgery and reported significantly prolonged activated partial thromboplastin time in the fish oil group, but no difference in platelet count and prothrombin [54]. In an RCT on mixed surgical patients, no difference in red blood cell transfusions post-operatively was found [52].

Three studies with post-operative fish oil exposure measured biochemical markers, but not clinical bleeding [57-59]. One study with coronary artery bypass grafting patients found no difference in fibrinogen [59], but did find increased fibrinolysis shown by reduced PAI-1 antigen following fish oil exposure [59]. Aiko et al included oesophageal cancer patients and found reduced D-dimer and increased platelet count, but no difference in markers of primary and secondary haemostasis or fibrinolysis [58]. Finally, Singer et al found no difference in platelet count, prothrombin time, or partial thromboplastin time in kidney transplantation patients [57].

DISCUSSION

Fish oil supplementation reduced primary haemostasis in most studies including healthy subjects, but fish oil supplementation did not increase bleeding in patients undergoing surgery or invasive procedures. Overall, the influence of fish oil supplementation on secondary haemostasis was insignificant and contradictory, and only few studies included markers of fibrinolysis and no consistent impact of fish oil was demonstrated.

Clinical bleeding was investigated in 16 studies including patients undergoing surgery, which were covered in 17 publications [8, 9, 42-46, 48-56]; the majority of these studies were RCTs [42, 44-49, 51-54, 56]. No increase in intra- or post-operative bleeding was reported in patients exposed to fish oil supplementation preoperatively and/or post-operatively compared with controls [8, 9, 42-48, 51-54, 56]. Paradoxically, two studies demonstrated a reduced need for intraoperative red blood cell transfusions among patients in the fish oil

supplementation group [48, 49], and fish oil exposure was associated with significantly less operative bleeding in a meta-analysis on cardiac surgery [60]. Thus, it seems evident that fish oil supplementation did not increase the need for blood product transfusion. Our rationale for including studies measuring post-operative bleeding in patients with post-operative fish oil supplementation [46, 50, 52, 54, 55] was to investigate if fish oil induced clot degradation and caused post-operative haematomas. There was no evidence supporting that post-operative fish oil supplementation increased post-operative bleeding. Only one in four studies on surgery reported a prolonged bleeding time measured preoperatively after 28 days of fish oil exposure [43]. Notably, fish oil did not influence clinical bleeding in relation to surgery [43]. Bleeding time was measured in six studies including healthy subjects; three studies found a prolonged bleeding time, while the remaining three studies found no effect of fish oil on bleeding time.

Due to the demonstrated effect of fish oil on platelets reported by Dyerberg & Bang [2], most studies obviously investigated primary haemostasis. In studies including healthy subjects, the majority found reduced platelet aggregation following fish oil intake [11-19, 21]. Paradoxically, one study on healthy subjects showed an increase in platelet microparticles following fish oil intake which suggested a prothrombotic state [61]. In studies including healthy subjects, four out of five studies investigating thromboxane B_2 levels found that thromboxane B_2 levels were reduced after fish oil exposure [19, 32-34]. Two studies showed that platelet aggregation was normalised two months [18] and 12 weeks [17] after discontinuation of fish oil. This suggests that primary haemostasis is affected by fish oil exposure beyond ten days, which is the average lifespan of platelets, after discontinuation.

In contrast to studies on healthy subjects, studies on patients with cardiovascular disease taking fish oil supplements consistently showed no reduced primary haemostasis [6, 62-67]. This indicates that the platelets of these patients are less responsive to fish oil treatment, or that the effects of fish oil supplements on primary haemostasis were masked by concomitant antithrombotic medication.

Secondary haemostasis was sparsely investigated. The theoretical rationale for investigating secondary haemostasis following fish oil exposure is the potential anti-inflammatory effects of fish oil. Fish oil may reduce fibrinogen synthesis in the acute phase response [58]. The same pattern of no consistent effect on secondary haemostasis was found both in the studies including healthy subjects and in patients undergoing surgery. These results indicate that fish oil has no substantial systematic effect on secondary haemostasis.

Fibrinolysis is impaired in patients with hypertriglyceridemia and hypercholesterolemia, which may be due to an increased level of the fibrinolysis inhibitor PAI-1 [68]. Fish oil seems to reduce blood levels of triglycerides and cholesterol; this effect may theoretically increase fibrinolysis by reducing PAI-1 [68]. The fibrinolytic system was very sparsely investigated, with PAI-1 as the most commonly investigated marker. The studies included in the present review showed no consistent effect on PAI-1 or other markers of fibrinolysis [16, 17, 19-21, 24, 34, 39-41, 44-46, 58, 59, 68]. Only very few studies investigated fibrinolysis, but the studies included in this review indicated that fish oil had no significant effect on fibrinolysis.

Due to the inhibitory effect of fish oil supplementation demonstrated by platelet aggregometry, some concern might exist on the concomitant use of antithrombotic treatment and fish oil supplementation prior to surgery. Our literature search was not designed to specifically address this question, but several studies were identified investigating the effect of aspirin in combination with fish oil supplementation [69-78]. Any additional effect of fish oil was either absent or very discreet. Larson et al found that fish oil might improve the ability of aspirin to inhibit platelet function, but without increasing the risk of bleeding [73]. The assumption of no increased clinically significant bleeding risk is corroborated by the findings by Wachira et al [79] and Harris [80], who performed extensive reviews on the effect of fish oil supplementation in combination with antithrombotic medication in various clinical settings, including surgery. In summary, the combination of fish oil and antithrombotic therapy including antiplatelet therapy did not cause increased clinically significant bleeding [79, 80]. Thus, the need for discontinuation of fish oil supplementation in combination with antithrombotic treatment prior to surgery is not supported.

The major strength of this review is the systematic and comprehensive literature search performed in two large databases with a comprehensive and transparent presentation of the designs used and results found in the included studies. We included all literature published since 1960; thus, even old studies were not excluded. We excluded small studies with fewer than 20 individuals to improve the strength of the results discussed.

Some limitations have to be considered. Doses and duration of fish oil supplementation varied among studies, which might weaken our conclusion. This systematic review did not include a meta-analysis with quantitative estimation of the bleeding risk because only two of the included studies investigating patients undergoing surgery had bleeding as their primary endpoint, and both were retrospective. We cannot exclude reporting bias (e.g. no systematic registration and reporting of

bleeding) and thereby the bleeding risk would be underestimated in the present review.

In conclusion, the present systematic review showed no increased bleeding risk during or after surgery in patients exposed to fish oil supplementation. However, fish oil supplementation distinctly reduced primary haemostasis in healthy subjects. Overall, fish oil supplementation had no effect on secondary haemostasis or fibrinolysis. As the biochemical effect of fish oil supplements in healthy subjects was not reflected in an increased bleeding risk during surgery, this systematic review does not support the need for discontinuation of fish oil supplements prior to surgery or other invasive procedures.

CORRESPONDENCE: *Anne-Mette Hvas.* E-mail: am.hvas@dadlnet.dk
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