Published in final edited form as:

J Card Surg. 2020 February ; 35(2): 405–412. doi:10.1111/jocs.14384.

Omega-3 and hemocompatibility-related adverse events

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Abstract

Background—Hemocompatibility-related clinical adverse events (HRAEs) are major causes of readmission in patients with left ventricular assist devices (LVADs). Omega-3 is an unsaturated fatty acid that possesses anti-inflammatory and antiangiogenic properties. We aimed to investigate the impact of omega-3 therapy on HRAEs during LVAD support.

Methods—Consecutive LVAD patients who were followed for 6 months were enrolled, and stratified by the use of omega-3. Freedom from any HRAEs and net burden of HRAEs, which was calculated by using a hemocompatibility score (using 4 escalating tiers of hierarchical severity to derive a total score for events), were compared between those with and without omega-3 therapy.

Results—Among 169 LVAD patients (57 years old and 124 males), 31 patients received 4 g/d of omega-3 therapy and 138 patients were in the control group. During the 6-month observational period, freedom from any HRAEs was 90% in the omega-3 group compared with 70% in the control group with a hazard ratio of 0.35 (95% confidence interval 0.11–0.87 and $P = .042$). The average hemocompatibility score in the omega-3 group was significantly lower compared with the control group (0.23 vs 0.91; $P = .042$), due to reduced Tier I scores (mild HRAE; $P = .003$) and Tier IIIB scores (severe HRAE; $P < .001$). The similar trends remained at propensity-matched populations.

Conclusions—Omega-3 therapy was associated with reduced HRAEs including both bleeding and thromboembolic events in LVAD patients.

Keywords

bleeding; LVAD; omega-3; stroke; unsaturated fatty acid

1 | INTRODUCTION

Despite an increase in survival in patients with advanced heart failure (HF) due to improvements in continuous-flow left ventricular assist device (LVAD) therapy,¹ device-related adverse events following LVAD implantation remain a challenge in the care of these patients.² In particular, hemocompatibility-related clinical adverse events (HRAEs) including gastrointestinal bleeding (GIB), pump thrombosis, and stroke, contribute greatly to the cost of care and reduce the quality of life.³ Unfortunately, there is no simple solution to this problem as HRAEs is a result of a complex interaction between preexisting factors, pump-related factors, and peri-pump factors that act in concert to produce clinical outcomes.³ The standard strategy for the treatment of HRAEs is to adjust antiplatelet and anticoagulation dosing as appropriate in response to either bleeding or thrombosis.⁴ It is a delicate balance that must be achieved and is likely unique to each patient, therefore more simple and novel preventative therapies continue to be sought after to overcome HRAEs.

We have recently demonstrated that omega-3, an unsaturated fatty acid,⁴ decreased the incidence of GIB during LVAD support, probably due to its suppressive effect on the development of arteriovenous malformation by inhibition of an angiogenesis-related signal cascade.⁵ Considering that the treatment of bleeding, in general, has a negative impact on thrombotic events, we investigated in this study the impact of omega-3 therapy on overall HRAEs including thrombotic events, as an expansion from our previous study, by using hemocompatibility score (HCS), which was originally proposed by Mehra⁶ and then used in the sub-study of MOMENTUM 3 trial³ and the optimized hemodynamic comparison study.⁷

2 | METHODS

2.1 | Patient selection

All consecutive patients who underwent LVAD implantation for the first time at our center between April 2014 and May 2017 were included in this retrospective analysis. Patients were divided into two groups based on treatment with omega-3. Omega-3 (Lovaza®; GlaxoSmithKline, Research Triangle Park, North Carolina) was administered at a dose of 4 g/d at the favor of the specific treating cardiologists. All patients treated with omega-3 (omega-3 group) were followed for 6 months from the time of omega-3 initiation (time zero). All other patients were followed for 6 months from the index admission discharge day (time zero) as a control group. The institutional review board of the University of Chicago approved this study.

2.2 | Follow-up protocol

All patients were followed from the time zero for 6 months and received guideline-directed medical therapy,⁸ including Antiplatelet therapy and warfarin with a target international normalized ratio (INR) between 2.0 and 3.0, unless recurrent HRAEs occurred. When patients were admitted to the hospital due to bleeding episodes, antiplatelet and anticoagulants were discontinued and standard management to treat bleeding was performed. After active bleeding resolved, anticoagulants were reintroduced using previous INR targets. Antiplatelet was held or reintroduced at a reduced dose. The aspirin dose, INR

level, mean artery pressure measured by Doppler, and LVAD speed data were collected at enrollment (time zero), and at the first and third months after enrollment.

2.3 | Definition of hemocompatibility-related clinical adverse event

Clinical adverse events attributable to LVAD-related bleeding or thrombosis were classified as HRAEs based on the ISHLT definition,³ which were adjudicated by two independent researchers (T.I. and D.R.): (a) Bleeding: gastrointestinal or other bleeding events that were not associated with surgical procedures and occurred at >30 days following LVAD implantation; (b) Neurological events: stroke or any other neurological events; (c) Thrombotic events: pump thrombosis that was medically or surgically treated or arterial thrombosis with or without organ involvement. All events defined above were counted from the time zero for 6 months.

2.4 | Hemocompatibility score

For each patient, a tiered hierarchal score was calculated, weighing each event by clinical relevance (Table 1). We then calculated an HCS as a summation of each score, to determine the aggregate net burden of HRAEs.³

2.5 | Statistical analyses

Variables with $P < .05$ were considered significant. Continuous data were described as mean $\pm$ standard deviation when normally distributed and compared between two groups using an unpaired t -test, or described as median (25% quartile, 75% quartile) when non-normally distributed and compared between two groups using the Mann-Whitney U test. Categorical data were compared between two groups by Fisher's exact test.

The six-month HRAEs-free rates from the time zero were analyzed by Kaplan–Meier analyses and compared between two groups using the log-rank test. Clinical events were expressed as patient-year and compared between the two groups. Univariate Cox proportional hazard ratio regression analyses were performed to investigate significantly associated factors for any HRAEs. Variables with $P < .20$ in these analyses were enrolled in the multivariate analyses model with the forced entry method.

We also performed a propensity score analysis, matching for age, device type, and the use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at the enrollment time to collect a ratio of 1:2 of the omega-3 group and control group, considering the impact of these three variables on HRAEs. A propensity score was calculated using logistic regression modeling including all three of the above variables, and paired participants were selected based on the propensity scoring.

3 | RESULTS

3.1 | Baseline characteristics

In total, 169 patients (101 HeartMate II and 68 HVAD) were enrolled. Patients were 57 (48, 66) years old, 124 were male, most patients received an LVAD as destination therapy (79%),

and 53 (31%) had an ischemic HF etiology (Table 2). No patients experienced any HRAEs before the follow-up.

Thirty-one patients received 4 g/d of omega-3, starting 26 (15, 63) days following LVAD implantation (time zero) and continued 4 g/d of omega-3 therapy for 6 months. None of them experienced any side effects such as diarrhea, fishy aftertaste, or burps.

In the control group, 138 patients who did not receive omega-3 were followed from the discharge of the index hospitalization (20 [9,28] days following LVAD implantation; time zero) and observed for 6 months. There were no statistical differences between the two groups in the LVAD duration before time zero ($P = 0.76$).

Patients in the omega-3 group were younger (49 [37,59] years old vs 58 [51,67] years old, $P < .001$), while other baseline characteristics were statistically identical between the groups ($P > .05$ for all). There were no statistical differences between the two groups in antithrombotic therapy, LVAD speed, or HF medications during the observational period ($P > .05$ for all; Table A1).

3.2 | Freedom from any HRAEs

Three patients in the omega-3 group and 42 patients in the control group experienced HRAEs from the time zero for 6 months. The omega-3 group had higher freedom from any HRAEs (90% vs 70%, $P = .023$; Figure 1), whereas survival was not significantly different between groups during the 6-month observational period (100% vs 90%, $P = .069$). Six-month freedom from any HRAEs was statistically not different between the HeartMate II cohort and HVAD cohort (71% vs 77%, $P = .51$).

3.3 | Comparison of the incidence of each HRAE

Of all 47 HRAEs, 17 events occurred in the same patients ($N = 7$). In other words, these 7 patients had multiple HRAEs (five patients had two-time GIBs; one patient had two-time GIB and one surgically managed pump thrombus; one patient had three-time GIB and one stroke). The rate of total HRAEs in the omega-3 group was lower compared with the control group (0.19 vs 0.83 events/patient-year, $P = .056$). The rates of GIB, stroke, and medically managed pump thrombosis were significantly lower in the omega-3 group compared with the control group ($P < .05$ for all; Figure 2); whereas the rate of surgically managed pump thrombosis was statistically comparable between the groups ($P = .36$).

As a sub-analysis, we performed similar analyses for each device cohort separately. Among the HeartMate II cohort ($N = 101$), the rates of GIB, medically managed pump thrombosis, and stroke were significantly lower in the omega-3 group ($P < .05$ for all), whereas the rate of surgically managed pump thrombosis was not different between the groups ($P = .34$). Among the HVAD cohort ($N = 68$), the GIB rate was significantly lower in the omega-3 group ($P = .048$) and the stroke rate was numerically lower in the omega-3 group ($P = .14$). No pump thromboses were observed in the HVAD cohort.

3.4 | Hemocompatibility score comparison

Net HCS in the omega-3 group was significantly lower than in the control group (0.23 vs 0.91 points/patient, $P = .018$; Figure 3), largely attributable to contributions from Tier I (mild HRAE) and Tier IIIB (severe HRAE). The average score of Tier I was significantly lower in the omega-3 group (0.03 vs 0.17 points/patient, $P = .003$), mostly due to lower incidence of bleeding events in the omega-3 group (0.03 vs 0.14 points/patient, $P = .018$). Nobody in the omega-3 group had a Tier IIIB score, whereas the average Tier IIIB score in the control group was 0.64 points/patient ($P < .001$).

3.5 | Risk factors associated with any HRAEs including omega-3 use

Univariate analyses demonstrated that age, administration of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and omega-3 use were significant factors associated with HRAEs ($P < .05$ for all; Table 3). A multivariate model found that age per 10 years (hazard ratio 1.34, 95% confidence interval 1.20–1.75, $P = .037$) and omega-3 use (hazard ratio 0.35, 95% confidence interval 0.11–0.87, $P = .042$) were independent factors associated with HRAEs.

3.6 | Comparison in background-matched populations

Twenty-five omega-3 group patients and 50 control group patients were selected by using propensity score matching analysis. There were no statistical differences in background characteristics between the two groups ($P > .05$ for all; Table A2). Standardized differences of all three matched variables were within 0.20. C-statistics were 0.738 before matching and 0.518 after matching.

Plasma samples were obtained from 16 patients in the omega-3 group and from 14 patients in the control group. Of nine biomarkers, angiopoietin-2 levels remained significantly lower in the omega-3 group compared to the control group (138 [93, 290] vs 176 [134, 314] pg/mL, $P = .047$); whereas other eight biomarkers remained not different between two groups ($P > .05$ for all). Six-month freedom from any HRAEs continued to be higher in the omega-3 group (92% vs 72%, $P = .048$; Figure A1).

4 | DISCUSSION

In this study, we investigated the prophylactic efficacy of omega-3 therapy on HRAEs during 6-months of LVAD support. The main findings are as follows: (a) Omega-3 group had a higher freedom from HRAEs than the control group during the 6-month observational period; (b) As a breakdown of HRAEs, bleeding and stroke rates were lower in the omega-3 group, and pump thrombosis rates in the omega-3 group was not inferior to the control group; (c) Net HCS was lower in the omega-3 group, primarily due to less tier I (mild HRAEs) and tier IIIB (severe HRAEs) contributions.

4.1 | Current options to treat HRAEs

Antiplatelet and anticoagulation therapies are considered essential for LVAD therapy. However, the optimal dosing of these therapies that consider both bleeding and thrombotic events remains uncertain.⁸ The European TRACE study demonstrated that anticoagulation

therapy alone (without antiplatelet therapy) reduced the incidence of major bleeding without increasing the risk of thromboembolic events.⁹ The MAGENTUM 1 study showed that anticoagulation therapy with a reduced target INR goal of 1.5–1.9 along with standard antiplatelet therapy was safe without any thrombotic events during 6-months of HeartMate 3 support.¹⁰ In contrast, bleeding persisted even after the reduction in antithrombotic therapies (discontinuation of antiplatelet therapy, anticoagulation therapy, or both) in the US-TRACE trial.¹¹ Just adjusting the dosing of these therapies may be insufficient to overcome all HRAEs together.³

An implication to decrease LVAD speed and increase arterial pulsatility on the prevention of GIB events remains controversial. Partial LVAD support devices did not reduce the incidence of GIB despite sufficient preservation of arterial pulsatility. On the contrary, reduced arterial pulsatility (for example due to incremental LVAD speed) increased the level of angiotensin-2 in other studies,¹² which might result in the occurrence of GIB.

The device type may also have an impact on HRAEs. In the secondary analysis of the MOMENTUM 3 trial, HeartMate 3 LVAD demonstrated greater 6-month freedom from HRAEs in comparison with the HeartMate II LVAD.³ As a breakdown of HRAEs, the HeartMate 3 group experienced less pump thrombosis compared with the HeartMate II group, whereas the nonsurgical bleeding rates were comparable between the two groups.

4.2 | Omega-3 and bleeding events

One of the major causes of bleeding during LVAD support is GIB via arteriovenous malformation,^{13,14} which may dominantly result from activation of angiogenic and inflammatory signal cascades consisting of tumor necrosis factor- α and angiotensin-2.^{15,16}

Metabolism of omega-3 is complex. In a healthy population, omega-3 (mixture of eicosapentaenoic acid and docosahexaenoic acid) is metabolized into certain lipid mediators including cyclooxygenase-derived prostaglandin E₃, lipoxygenase-derived 4-hydroxy-docosahexaenoic acid, and cytochrome P450-derived epoxydocosapentaenoic acids, which suppress the progression of inflammation and angiogenesis.⁴ In LVAD patients, it is thus reasonable to postulate that omega-3-derived lipid mediators may block the upstream activation of angiotensin-2 and inhibit the formation of arteriovenous malformations, which would be a future concerns to be investigated.

4.3 | Omega-3 and stroke events

The great advantage of omega-3 therapy was that it suppressed not only bleeding events but also stroke, although the therapy of bleeding in general increases the risk of thrombosis. Omega-3 inhibits the aggregation of platelets, improves endothelial function, and stabilizes plaque in blood vessels.^{17,18} The JELIS trial demonstrated that administration of omega-3 reduced the risk of recurrent stroke by 20% in patients receiving low-dose statin therapy.¹⁹ They could not show the advantage of omega-3 therapy for the primary prevention of stroke, probably because of a low incidence rate of stroke in the control group also receiving statin therapy. The advantage of omega-3 therapy could be more easily seen among more high-risk populations, such as LVAD patients.

4.4 | Omega-3 and pump thrombosis

Despite the omega-3 has an anti-bleeding effect, it did not increase the risk of pump thrombosis (the incidence of surgically managed pump thrombosis was comparable between the two groups). Lower LVAD speed, device type, atrial fibrillation, and low antiplatelet dose are known as risk factors of pump thrombosis, and these variables were statistically compared between two groups in this study. Device malposition in HeartMate II and right ventricular failure are also major contributors to pump thrombosis that should be considered,^{20,21} although we do not have these data. These multifactorial factors instead of omega-3 use alone might also have had an impact on the development of pump thrombosis. Of note, no patients in the HVAD cohort experienced pump thrombosis in this study, and the impact of omega-3 therapy on preventing pump thrombosis in the HVAD cohort remains uninvestigated.

4.5 | Future direction and limitations

Our study showed that omega-3 therapy reduced not only bleeding but also stroke event rates, preserving a comparable pump thrombosis rate. As a result, we could demonstrate these various favorable effects of omega-3 therapy on overall HRAEs by using the HCS, a net burden of HRAEs. In addition, omega-3 is noninvasive (oral administration) and has few associated side effects. Angiotensin-converting enzyme inhibitors, hemodynamic optimization, and antiplatelet and anticoagulation therapies are also significantly associated with HRAEs (bleeding, thrombosis, or both).^{3,22,23} The combination strategy of these therapies with omega-3 at an optimal dose should be explored. Particularly, HeartMate 3 LVAD, which has an advantage over HeartMate II LVAD in preventing pump thrombosis but not bleeding, may have synergistic outcomes in combination with omega-3. A prospective randomized control trial for primary or secondary prevention using omega-3 is now ongoing given our findings.

We should recognize that this study is a proof of concept and just an observational analysis without randomization among the moderate size of the cohort. The indication for omega-3 therapy was determined by the attending physician and inclusion bias may exist. Particularly, there was a significant difference in age, which was also an independent risk factor of HRAE. We performed a propensity score matching analysis to manage these biases, although we used only three variables for statistical matching considering sample size. After propensity score matching, the impact of omega-3 diminished, although the statistical impact remained significant. We should emphasize that there are various factors that impact on HRAE, including omega-3. Also, we should state that the patients on omega-3 were relatively younger (median 49 years old). In other words, we lack the data of efficacy of omega-3 therapy in the elderly population, who might rather be good candidates of omega-3 therapy to prevent HRAE given their higher vascular burden. Furthermore, we may not completely exclude the impact of other confounders including medicinal uses.

The timing of omega-3 initiation varied among patients, although the duration between LVAD implantation and enrollment timing were statistically comparable between the two groups. The observational period was 6 months, and the effect of longer-term omega-3

therapy should be validated. A prospective randomized control study is warranted to demonstrate the impact of omega-3 therapy on preventing HRAEs during LVAD supports.

5 | CONCLUSION

Omega-3 therapy was associated with reduced HRAEs in LVAD patients, particularly due to reduced bleeding and stroke rates. A randomized control trial is warranted to establish the use of omega-3 as prophylactic therapy for HRAEs in LVAD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

CONFLICT OF INTERESTS

NU receives consultant fee and grants support from Abbott and Medtronic; GS receives consultant fees from Medtronic; VJ receives consultant fees from Abbott.

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FIGURE 1.

Comparison of freedom from HRAE between the omega-3 group and control group. * $P < .05$ by log-rank test. HRAE, hemocompatibility-related clinical adverse events

FIGURE 2.

Comparison of each HRAE incidence rate between the omega-3 group and control group. * $P < .05$. Variables between groups were compared by using negative binomial regression analyses. GIB, gastrointestinal bleeding; HRAE, hemocompatibility-related clinical adverse events; PT, pump thrombosis

FIGURE 3.

Comparison on average of each Tier of HCS and net HCS between the omega-3 group and control group. * $P < .05$. Variables between groups were compared by using the Mann-Whitney test. HCS, hemocompatibility score

TABLE 1

Calculations of hemocompatibility score

Intensity	Clinical components	Score
Tier I: mild	2 gastrointestinal or other nonsurgical bleeding episodes Suspected pump thrombosis (medically treated) Non-stroke-related neurological events	1 point each
Tier II: moderate	>2 gastrointestinal or other nonsurgical bleeding episodes Nondisabling stroke	2 points each
Tier III		
IIIA: moderate to severe	Pump malfunction attributable to pump thrombosis leading to reoperation for removal or replacement	3 points each
IIIB: severe	Disabling stroke Death attributable to a hemocompatibility etiology or inconclusive	4 points each

TABLE 2

Comparison of baseline characteristics

	Total (N = 169)	Omega-3 (+) (N = 31)	Omega-3 (-) (N = 138)	P value
Demographics				
Age, y	57 (48, 66)	49 (37, 59)	58 (51, 67)	<.001*
Body mass index	29.9 (25.3, 35.7)	31.6 (24.6, 35.4)	29.8 (25.3, 35.9)	.62
Male	124 (73%)	25 (81%)	99 (72%)	.22
Destination therapy	134 (79%)	28 (90%)	106 (77%)	.07
Device				
HeartMate II	101 (60%)	17 (55%)	84 (61%)	.34
HVAD	68 (40%)	14 (45%)	54 (39%)	.34
INTERMACS profile 1–3	110 (65%)	21 (68%)	89 (64%)	.45
INTERMACS profile 4–6	59 (35%)	10 (32%)	49 (36%)	.45
Comorbidity				
Ischemic etiology	53 (31%)	7 (23%)	46 (33%)	.17
Diabetes mellitus	58 (34%)	7 (23%)	51 (37%)	.09
Atrial fibrillation	62 (37%)	9 (29%)	53 (38%)	.22
History of stroke	30 (18%)	3 (10%)	27 (20%)	.15
History of ventricular tachyarrhythmia	61 (36%)	9 (29%)	52 (38%)	.25
Postoperative right ventricular failure	22 (13%)	4 (13%)	18 (13%)	.98
Length of index hospitalization, d	20 (15, 29)	20 (17, 29)	220 (14, 28)	.80

Note: Continuous variables were compared between groups by using the Mann-Whitney U test. Categorical variables were compared between groups by using Fisher's exact test.

* $P < 0.05$.

TABLE 3

Variables associating with any HRAEs among baseline characteristics

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Demographics				
Age, per 10 y	1.40 (1.08–1.81)	.010 *	1.34 (1.02–1.75)	.037 *
Body mass index	0.99 (0.95–1.04)	.72		
Female	1.01 (0.52–1.96)	.97		
Destination therapy	1.80 (0.76–4.25)	.18	1.76 (0.72–4.76)	.24
HeartMate II vs. HVAD	1.23 (0.67–2.27)	.51		
Omega-3 administration	0.28 (0.09–0.90)	.033 *	0.35 (0.11–0.87)	.042 *
Comorbidity				
Ischemic etiology	1.26 (0.68–2.32)	.46		
Diabetes mellitus	0.91 (0.49–1.69)	.77		
Atrial fibrillation	1.27 (0.70–2.30)	.43		
History of stroke	0.81 (0.36–1.81)	.61		
History of ventricular tachyarrhythmia	1.49 (0.82–2.69)	.22		
Baseline therapeutic parameters				
PT-INR	1.07 (0.57–1.98)	.84		
PT-INR >3.0	2.08 (0.75–5.83)	.26		
PT-INR <1.5	1.60 (0.50–5.16)	.43		
Aspirin dose, per 100 mg	0.89 (0.64–1.22)	.46		
Aspirin administration	0.66 (0.33–1.29)	.22		
ACE or ARB	0.48 (0.25–0.93)	.030 *	0.52 (0.32–1.21)	.12
Beta-blocker	0.63 (0.33–1.22)	.21		
Aldosterone antagonist	0.67 (0.36–1.26)	.21		
Digoxin	2.91 (0.95–8.17)	.23		
Mean arterial pressure	1.14 (0.93–1.05)	.65		

Note: All variables were analyzed by the Cox proportional hazard ratio regression analyses. Variables with $P < 0.20$ in the univariate analyses were enrolled in the multivariate analyses with the forced injection method. Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PT-INR, prothrombin time with international normalized ratio.

* $P < 0.05$.