

Fish Oil to Increase Graft Patency

Marisa Battistella, Pharm D

University Health Network-Toronto General Hospital

Toronto, On

Renal Pharmacists Day

Montreal

April 25, 2013

Effect of Fish Oil Supplementation on Graft Patency and Cardiovascular Events Among Patients With New Synthetic Arteriovenous Hemodialysis Grafts A Randomized Controlled Trial

Charmaine E. Lok, MD, MSc

Louise Moist, MD, MSc

Brenda R. Hemmelgarn, MD, PhD

Marcello Tonelli, MD, SM

Miguel A. Vazquez, MD

Marc Dorval, MD, MSc

Matthew Oliver, MD, MSc

Sandra Donnelly, MD, MSc

Michael Alton, MD

Kenneth Stanley, PhD

for the Fish Oil Inhibition of Stenosis in Hemodialysis Grafts (FISH)

Context: Synthetic arteriovenous grafts, an important option for hemodialysis vas-

cular fish o

with pat-

obje-

ency

Des-

alyt-

duct-

ber, 2

63%

Inte-

1-g

Main Outcome Measure: Proportion of participants experiencing graft thrombo-

sis or radiological or surgical intervention during 12 months' follow-up.

AKA
"FISH Study"

JAMA; 2012; 307(17):1809-16

Fish Oil: Basic Mechanisms

Benefits: ↓ endothelial dysfunction, intimal hyperplasia, thrombosis

- ↓ inflammatory cytokines, adhesion molecules
- ↓ platelet aggregation, serum viscosity
- ↑ release of NO, generation of PGI₂
- ↓ endothelin-1
- ↓ PDGF and smooth muscle proliferation
- Antioxidant effect in hemodialysis patients

Fish Oil

Omega-3 fatty acids

- Eicosapentanoic acid
 - ♦ (EPA; 20:5n-3)
- Docosahexanoic acid (DHA)
 - ♦ (DHA; 22:6n-3)
- Anti-proliferative, anti-oxidant, vasodilatory effects



FISH Study

Primary Objective:

- To compare the proportion of patients who experience a loss of native patency within 12 months after new graft creation in patients taking daily oral fish oil versus placebo supplementation

Secondary Outcomes

- **Graft Outcomes:**
 - The rate of and time to: thrombosis, radiological or surgical intervention to maintain patency
 - Bleeding episodes
- **Main Cardiovascular Outcomes:**
 - 1) BP
 - 2) Cardiovascular Composite of: MI, CHF, Stroke, PVD

Lok C.E. JAMA. 2012

Inclusion/Exclusion Criteria

Inclusion

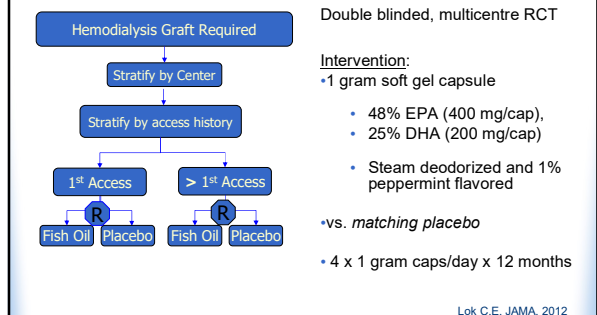
- ESRD requiring a new synthetic graft
- Age ≥ 18 years
- Must be able to provide informed consent

Exclusion

- Surgical revision of a prior access e.g. a jump graft (ie. must be new access)
- *major* bleed within 1 month of study
- Malignant hypertension
- Receiving >2 antiplatelet agents or anticoagulants (NOT ASA + warfarin)
- Ingestion of fish oil at randomization

Lok C.E. JAMA. 2012

FISH Study



Compliance Testing

- Participant serum was collected at baseline and 3 months and sent to the University of Guelph, Ontario, for analysis
 - A random 125 samples underwent gas-liquid chromatography to determine fatty acid composition (EPA) of total serum phospholipids
 - Compliance was determined by EPA incorporation into cells
- Lok C.E. JAMA, 2012

Statistical Analysis

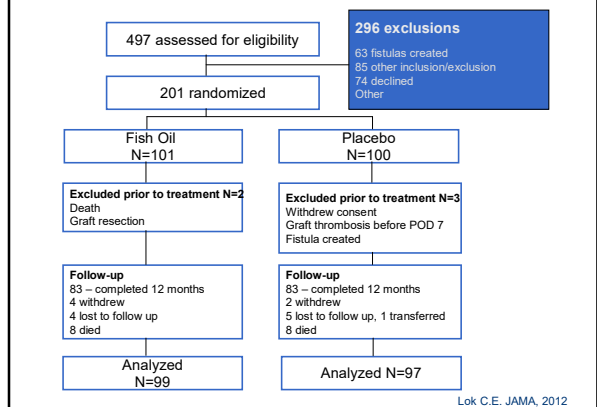
- Intention to treat analysis

Comparisons between groups of:

- Proportions: Fisher's exact test
 - Rates: exact binomial test
 - Quantitative values: Wilcoxon rank sum test or T-Test
 - Time to event: Kaplan-Meier survival curves
log-rank tests
- Lok C.E. JAMA, 2012

Results

Patient Flow

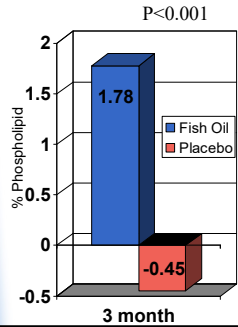


Baseline Characteristics

Characteristic	Fish Oil (N=99)	Placebo (N=97)
Mean age (yrs)[range]	62.5 [28-88]	63.4 [27-87]
Male sex	47	51
Caucasian	64	59
ESRD Etiology: Diabetes	49	39
Comorbidities: Coronary heart disease	32	34
Congestive heart failure *	26	13
Peripheral vascular disease	17	12
Hemodialysis Vintage (mean yrs)	2.76	2.84
Number prior accesses (mean)	1.1	1.2
Graft location: forearm	62	51
Aspirin/Warfarin/Other anti-platelet	57/26/11	51/20/14
Statins	68	57
Total Cholesterol (mmol/L)	3.76	3.66

Lok C.E. JAMA, 2012

Compliance and Safety

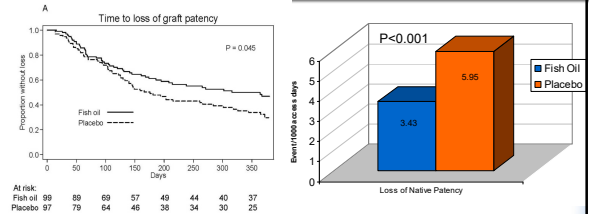


Safety:

- No difference in bleeding events
 - 9 in fish oil
 - 8 in placebo; (p=1.00)

Lok C.E. JAMA, 2012

Loss of Native Patency

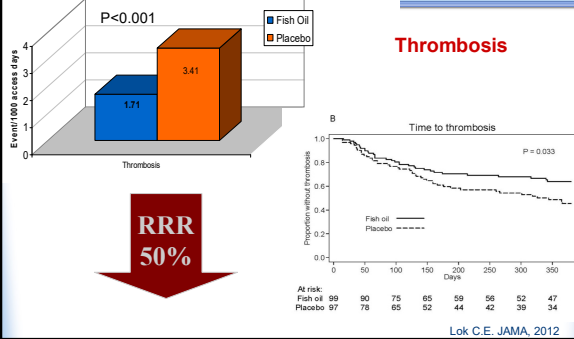


Primary Outcome= Proportion with Loss of Native Patency

- 48 (48%) in fish oil group
- 60 (62%) in placebo group
- P=0.06

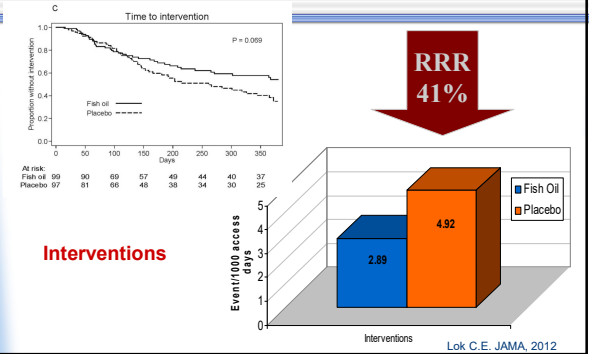
Lok C.E. JAMA, 2012

Clinically Important Endpoints



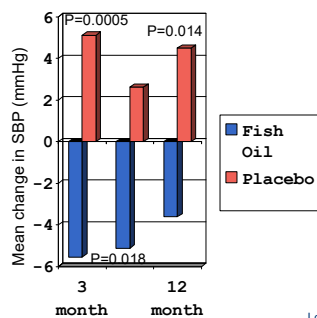
Lok C.E. JAMA, 2012

Clinically Important Endpoints



Lok C.E. JAMA, 2012

Mean Change in Systolic Blood Pressure



Lok C.E. JAMA, 2012

Blood Pressure

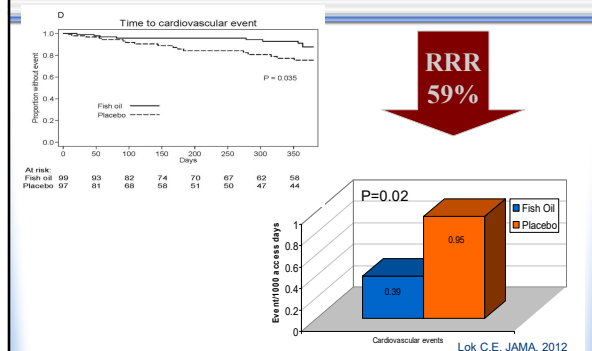
- Reduction in the mean number of BP medications/patient
 - 1.68 (fish oil)
 - 0.61 (placebo)

P<0.001
- Proportion of patients who had at least 1 reduction in dose or frequency of BP meds
 - 64% (fish oil)
 - 42% (placebo)

P=0.004

Lok C.E. JAMA, 2012

Cardiovascular Outcomes



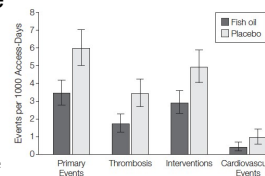
Limitations

- Enrolment goal not reached
- No difference in primary endpoint found
 - ♦ The choice of primary outcome measure as a proportion may not have been optimal

Lok C.E. JAMA, 2012

Interpretation of FISH Study Result

- Statistically “negative”
- Clinically “positive”
- What to do....
 - ♦ Look at trend
 - ♦ Why was it “negative”
- Make your decision:
 - ♦ What does your patient have to gain or lose?



Conclusions

- Daily fish oil ingestion in hemodialysis patients with newly created grafts:
 - ♦ Prolongs the time to loss of native graft patency (unassisted primary patency)
 - ♦ Reduces the rate of thrombosis by half and reduces the frequency of needed radiological or surgical interventions to maintain patency
 - ♦ Improves blood pressure and cardiovascular events

Lok C.E. JAMA, 2012

Stay Tuned

- **PISCES**
 - ♦ Study in HD pts with Fish Oil looking only at CV outcomes.....

