

***Randomized Trial of
Omega – 3 Fatty Acids***



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for the OMEGA Study Group

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Inuit in Greenland **High consumption of fish oil**





Background



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- **Inconclusive clinical evidence on Ω 3**
Leon BMJ 2008
- **Benefit of Ω 3 in patients with:**
 - acute myocardial infarction
 - on top of optimized guideline therapy





Objectives



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Effect of **omega-3-acid ethylesters 90** (1g daily)
(460mg EPA + 380mg DHA) for 1 year

- **Primary Endpoint**
 - Sudden cardiac death
- **Secondary Endpoints**
 - Total mortality
 - Reinfarction
 - Stroke
 - Arrhythmic Events
 - Revascularization



Methods (1)



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Trial characteristics	- Prospective - Randomized - Double blind
Study centers	104 (Germany)
Enrollment period	Oct 2003 – June 2007
Patients	3,851 enrolled
DSMB	Yes
EPC	Yes



Methods (2)



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- **Inclusion criteria**
 - Patients 3-14 days after acute myocardial infarction
 - STEMI or NSTEMI
 - Male and female
 - Age ≥ 18 years
 - From April 2005: rule 6 of 8 pt: $\geq 70y$ or EF $< 40\%$ or Diabetes or no revasc
- **Exclusion criteria**
 - Women pregnant, nursing or without contraception
 - Hypersensitivity to study drugs
 - Taking other formulations of fish oil
 - Expected Non-compliance



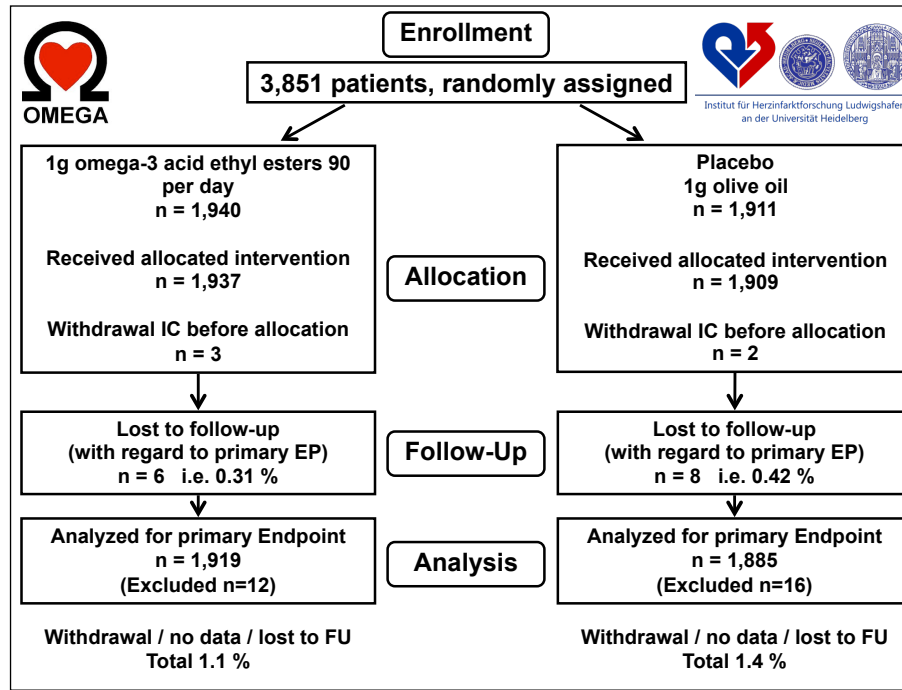
Methods (3)



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- **Assumption:**
 - **SCD Placebo:** 3.5 %
 - **SCD Ω 3:** 1.9 % (\downarrow 45 % RR GISSI-P)
 - Sample size 1,733 pt per group
 - 3,800 pt total (including 9 % expected Drop-outs)
- **Publication of study design:**

Rauch B et al.: „Highly Purified Omega-3 Fatty Acids for Secondary Prevention of Sudden Cardiac Death After Myocardial Infarction – Aims and Methods of the OMEGA-Study.“ *Cardiovasc Drugs Ther* (2006) 20:365-375.
- **ClinicalTrials.gov ID:** NCT00251134





Patient characteristics Admission



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	Total	Ω 3	Placebo	P-Value
Age	64 y	64 y	64 y	0.46
Male	74.4 %	75.1 %	73.7 %	0.35
Previous MI	16.2 %	17.2 %	15.2 %	0.09
Previous PCI	12.6 %	13.5 %	11.7 %	0.11
Diabetes mellitus	27.0 %	27.6 %	26.4 %	0.39
Renal failure	1.8 %	1.8 %	1.7 %	0.96
STEMI	59.0 %	59.2 %	58.8 %	0.82
NSTEMI	41.0 %	40.8 %	41.2 %	0.82
EF < 45 %	24.1 %	24.8 %	23.3 %	0.27



Acute treatment



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	Total	Ω 3	Placebo	P-Value
PCI (primary / early)	77.8 %	77.9 %	77.6 %	0.87
Thrombolysis	8.4 %	8.3 %	8.4 %	0.92
No acute revasc	19.4 %	19.4 %	19.3 %	0.95
ASA	94.4 %	94.4 %	94.4 %	0.96
Clopidogrel	88.2 %	87.8 %	88.6 %	0.42
GP IIb/IIIa-Inhibitors	42.6 %	42.2 %	43.1 %	0.59
Betablocker	85.7 %	86.4 %	85.0 %	0.22
ACE-Inhibitors	69.5 %	69.2 %	69.7 %	0.72
Statins	81.5 %	81.1 %	81.9 %	0.53



Treatment at Hospital Discharge



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	Total	Ω 3	Placebo	P-Value
ASA	95.3 %	95.6 %	95.1 %	0.47
Clopidogrel	88.4 %	88.0 %	88.8 %	0.46
Statins	94.2 %	94.6 %	93.8 %	0.28
Betablocker	94.1 %	93.9 %	94.3 %	0.57
ACE-Inhibitors	83.3 %	82.9 %	83.7 %	0.50



The Omega-Trial



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Results

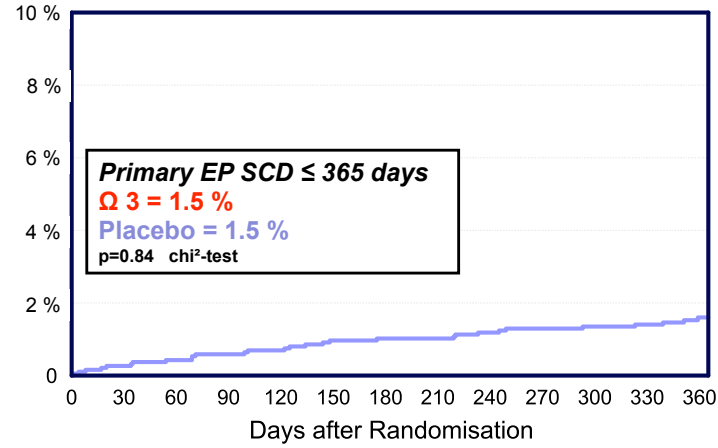


Primary Endpoint Sudden Cardiac Death



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Mortality Sudden Cardiac Death





Secondary Endpoints (1)

≤ 365 days



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	Total	Ω 3	Placebo	P-Value
Total death	4.2 %	4.6 %	3.7 %	0.18
Re-infarction	4.3 %	4.5 %	4.1 %	0.63
Stroke	1.1 %	1.4 %	0.7 %	0.07
MACCE (Total death, Re-MI, Stroke)	9.6 %	10.4 %	8.8 %	0.10
Arrhythmic events				
Total events	0.9 %	1.1 %	0.7 %	0.22
Resuscitation or DC-shock	0.6 %	0.6 %	0.6 %	0.98
ICD-terminated VT/VF	0.3 %	0.5 %	0.1 %	0.07



Secondary Endpoints (2) ≤ 365 days



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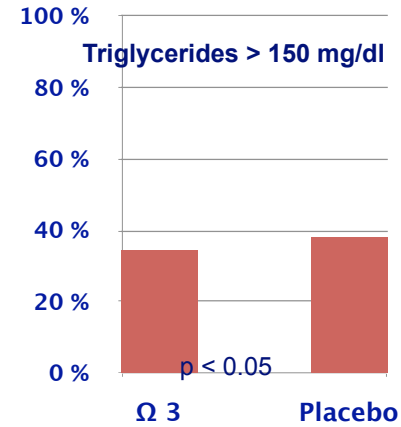
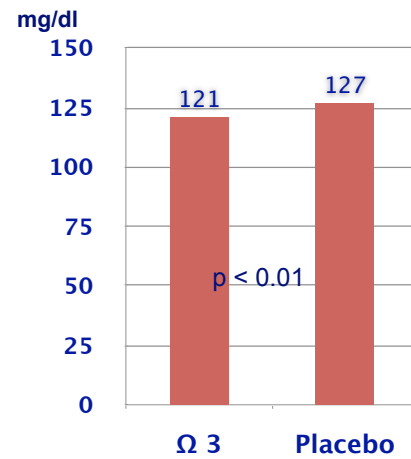
	Total	Ω 3	Placebo	P-Value
Progression of CAD (Re-MI / Revasc)	29.3 %	28.5 %	30.1 %	0.30
Revascularization	28.4 %	27.7 %	29.1 %	0.36
PCI	22.4 %	21.8 %	23.0 %	0.39
CABG	7.3 %	7.3 %	7.3 %	0.95
Rehospitalisation	48.1 %	48.9 %	47.2 %	0.34



Triglycerides 1y Follow Up Guideline indication for $\Omega 3$

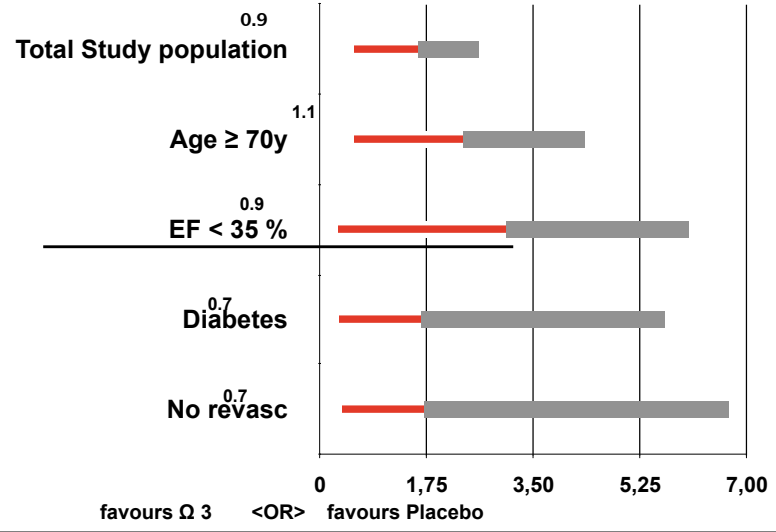


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SCD in predefined high risk Subgroups





Conclusions



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- **In moderate/high risk AMI patients, strict guideline treatment is associated with a very low rate of sudden cardiac death: 1.5 % / first year**

1g Ω 3 vs Placebo for 1 year

- **No significant difference in Primary Endpoint:**
 - Sudden cardiac death: 1.5 % Ω / 1.5 % Placebo
- **No significant difference in Secondary Endpoints:**
 - Total death, reinfarction, stroke
 - Progression CAD, arrhythmic events



Limitation



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- **Low rate of sudden cardiac death 1.5 %**
→ calculated sample size too small (*power*)!
- **A-posteriori power calculation**
→ calculated power 80 %
→ realized power ~50 %
- **No trend favouring $\Omega 3$**



The OMEGA – Trial



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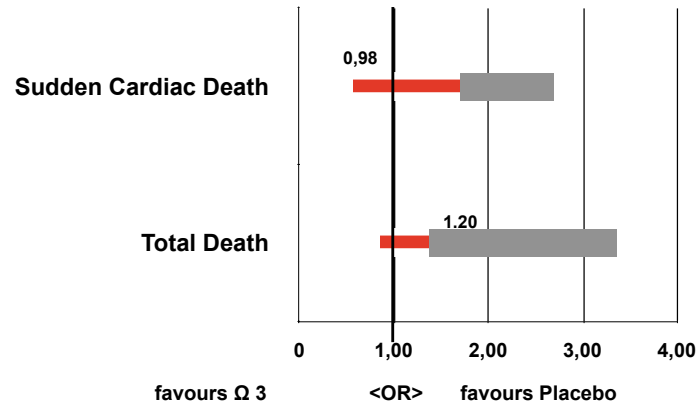
The End



Per Protocol Analysis



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Lost to follow-up



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- **Lost to Follow-Up (6 patients Ω 3, 8 Placebo)**
- **Worst-case-scenario:**
 - Ω 3: 6 patients SCD, Placebo: none \rightarrow $p=0.56$
 - Placebo: 8 patients SCD, Ω 3: none \rightarrow $p=0.23$



Reasons for Exclusion from Analysis



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	Ω 3	Placebo
No information because of Withdrawal IC	n=5	n=3
Only randomization information, CRF not available	n=7	n=13
<hr/>		
Lost to Follow Up	n=6	n=8



Not predefined Events **≤ 365 days**



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	Total	Ω 3	Placebo	P-Value
Cardiac death	3.1 %	3.5 %	2.7 %	0.16
Non-cardiac death	1.1 %	1.1 %	1.0 %	0.79
Heart Failure	25.2 %	24.3 %	26.1 %	0.21
Major Bleeding	1.8 %	1.8%	1.8 %	0.93
Patients with ICD	1.5 %	1.5 %	1.5 %	0.84



Follow Up 1 year Adherence to Treatment



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	Total	Ω 3	Placebo	P-Value
Study medication				
Intake: Protocol violation	8.0 %	8.1 %	8.0 %	0.89
Current medication				
ASA	88.7 %	88.9 %	88.6 %	0.78
Clopidogrel	26.1 %	25.8 %	26.3 %	0.76
Statins	87.4 %	88.2 %	86.6 %	0.15
Betablocker	89.0 %	88.0 %	90.0 %	0.06
ACE-Inhibitors	72.6 %	72.0 %	73.2 %	0.43

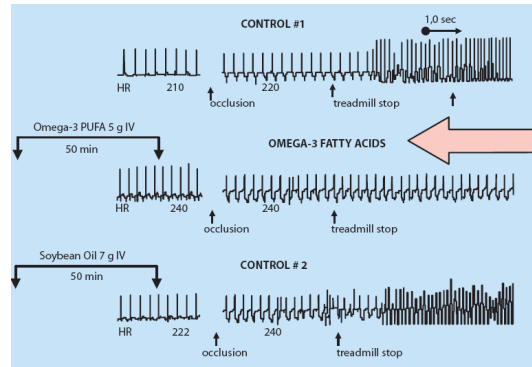


Antiarrhythmic effect of Ω 3 in dogs



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Ischemia induced VTs



Kang: Circulation 94, 1996