

*Determining if Omega 3 Fatty Acid
Supplements Reduce Cardiovascular
Outcomes in People with Dysglycemia:
the Ongoing ORIGIN Trial*



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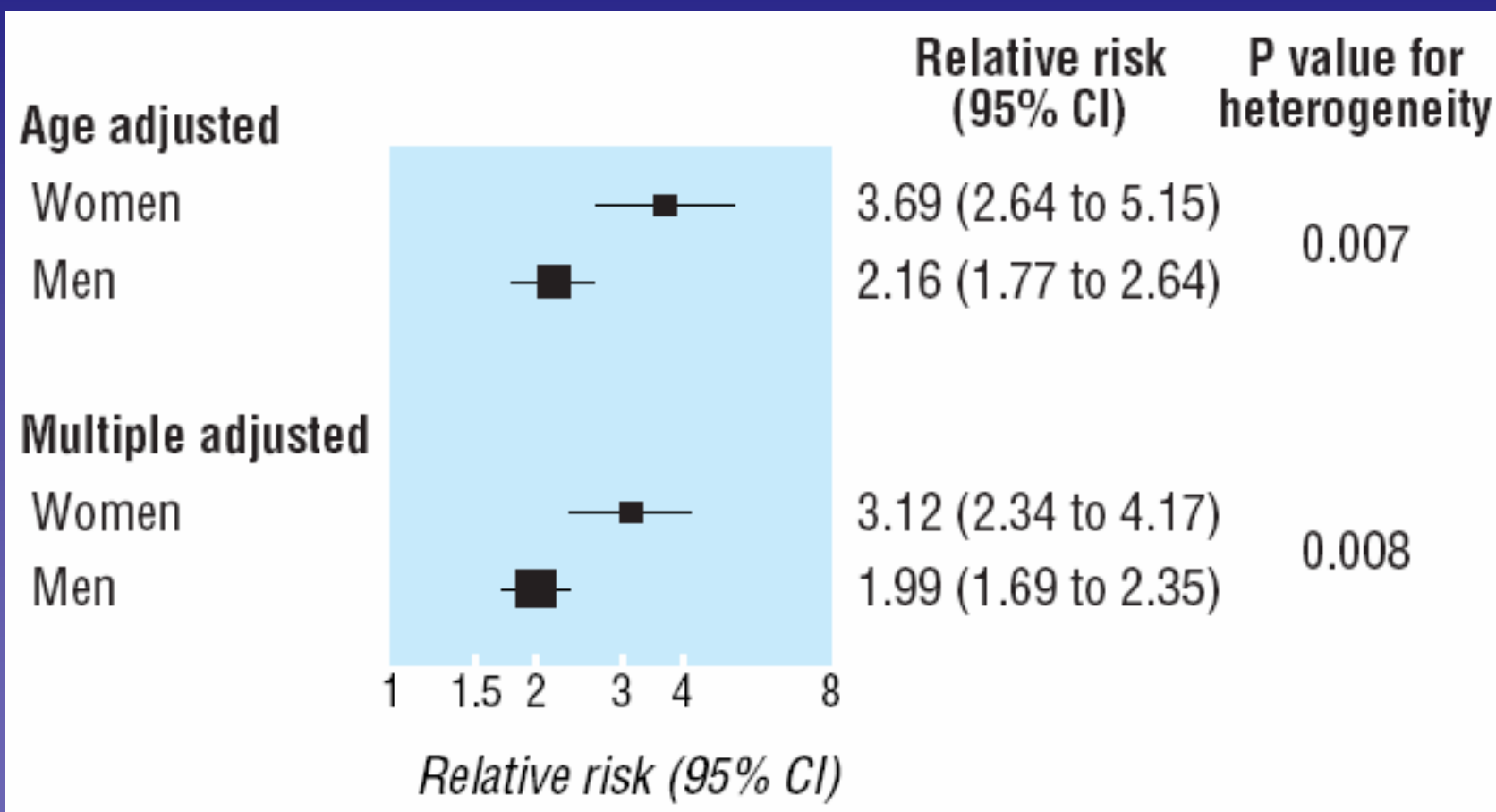
Outline

- What is the risk of CV events with dysglycemia?
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 - in people with dysglycemia?
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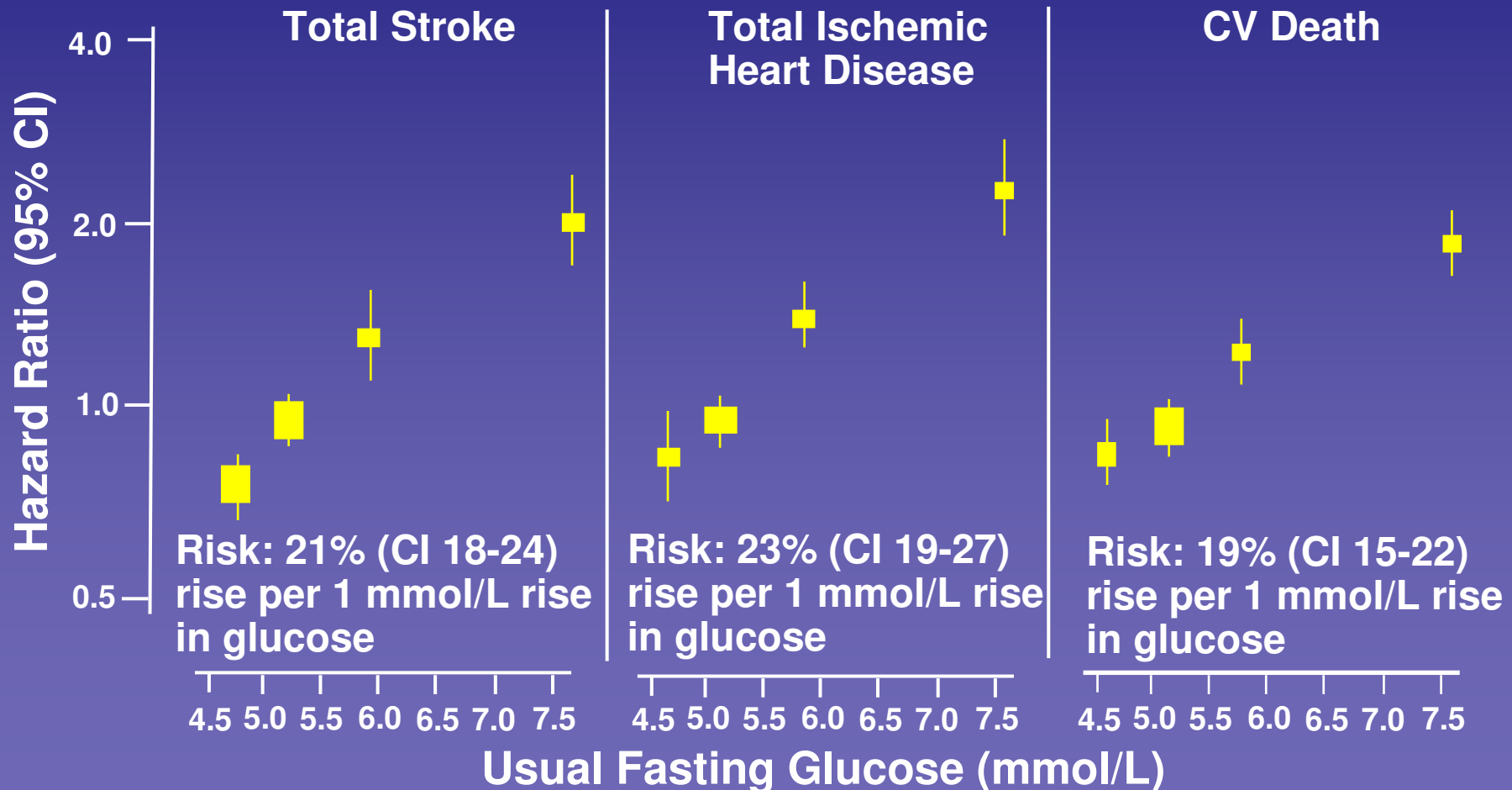
Risk of Fatal CHD with Diabetes



Usual Fasting Glucose vs. CVD

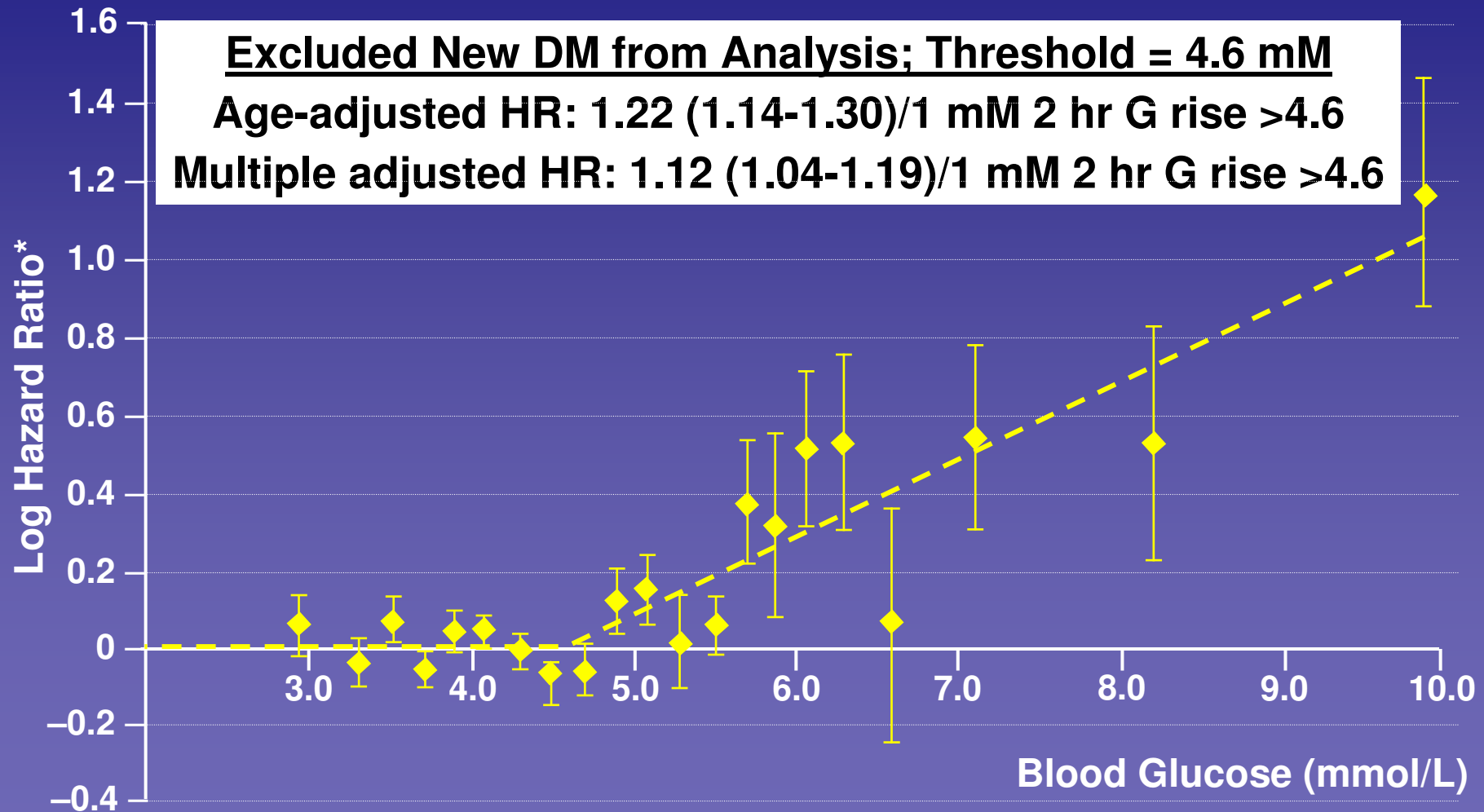
Sex & Study Stratified; Age-adjusted

N=237K; ~ 1.2 million person-years follow-up



2-hr Post 50g Blood G vs. CHD Death

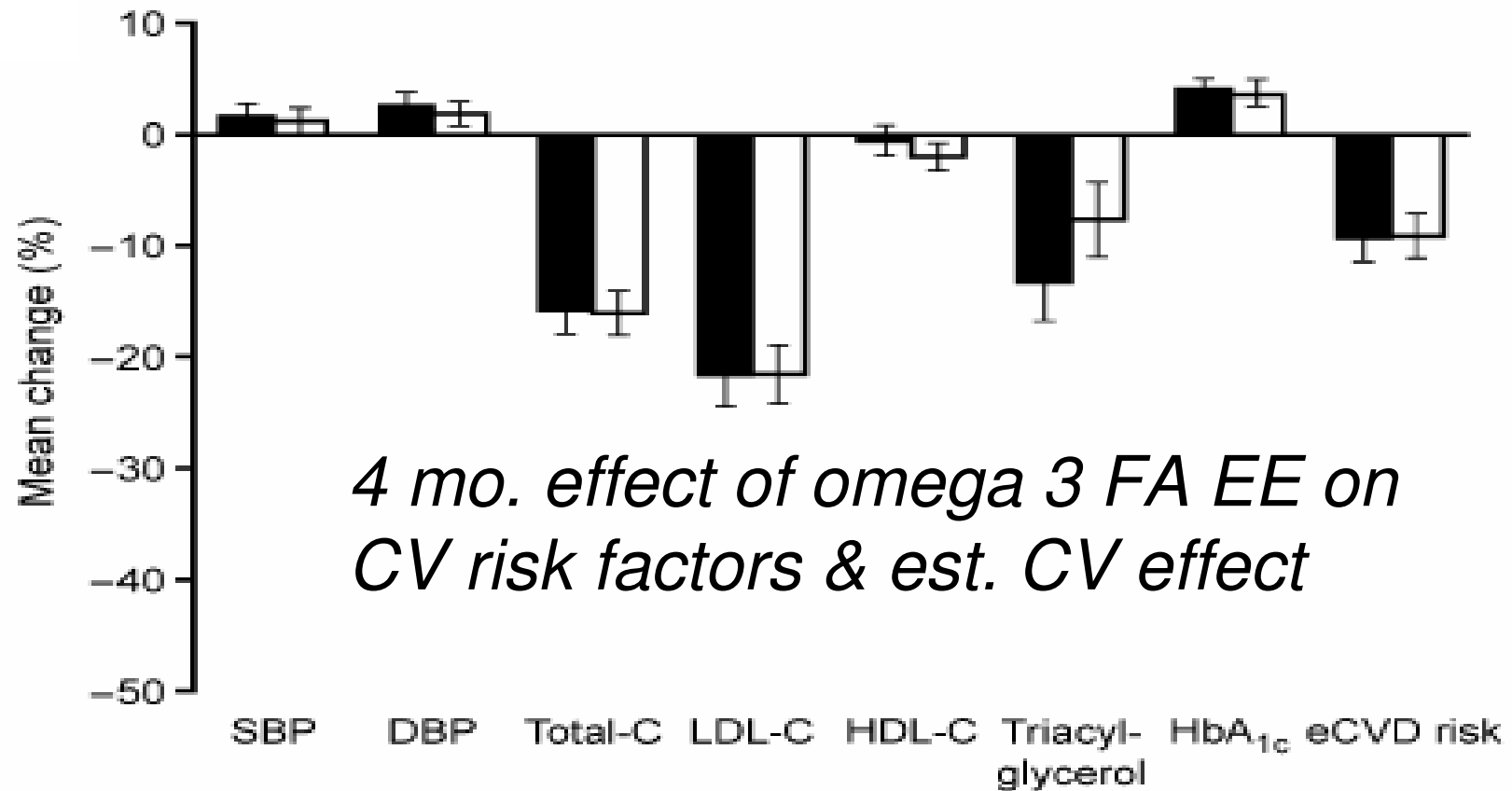
N=17, 869; 451,787 person-years of follow-up



Outline

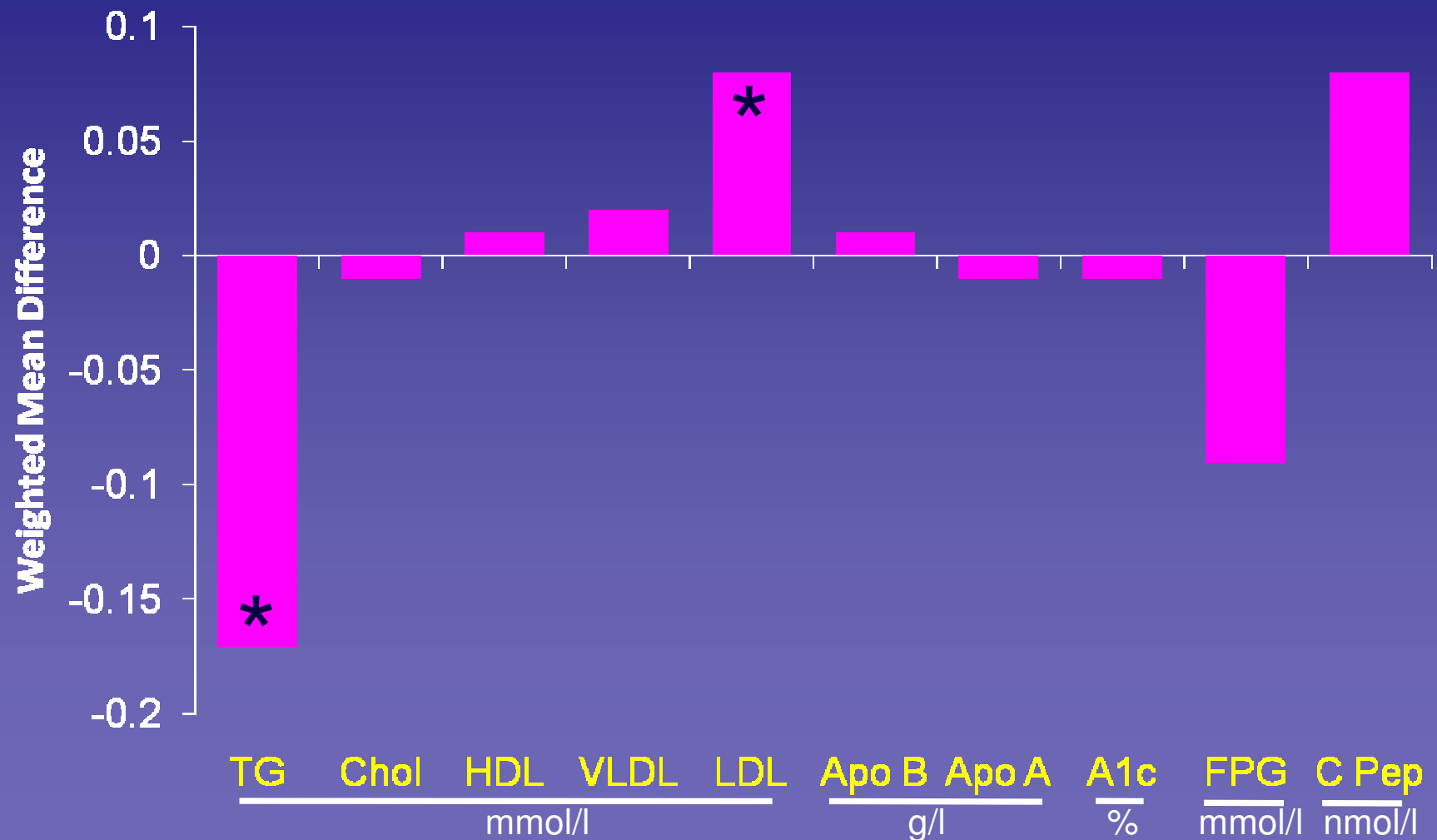
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AFORRD Trial



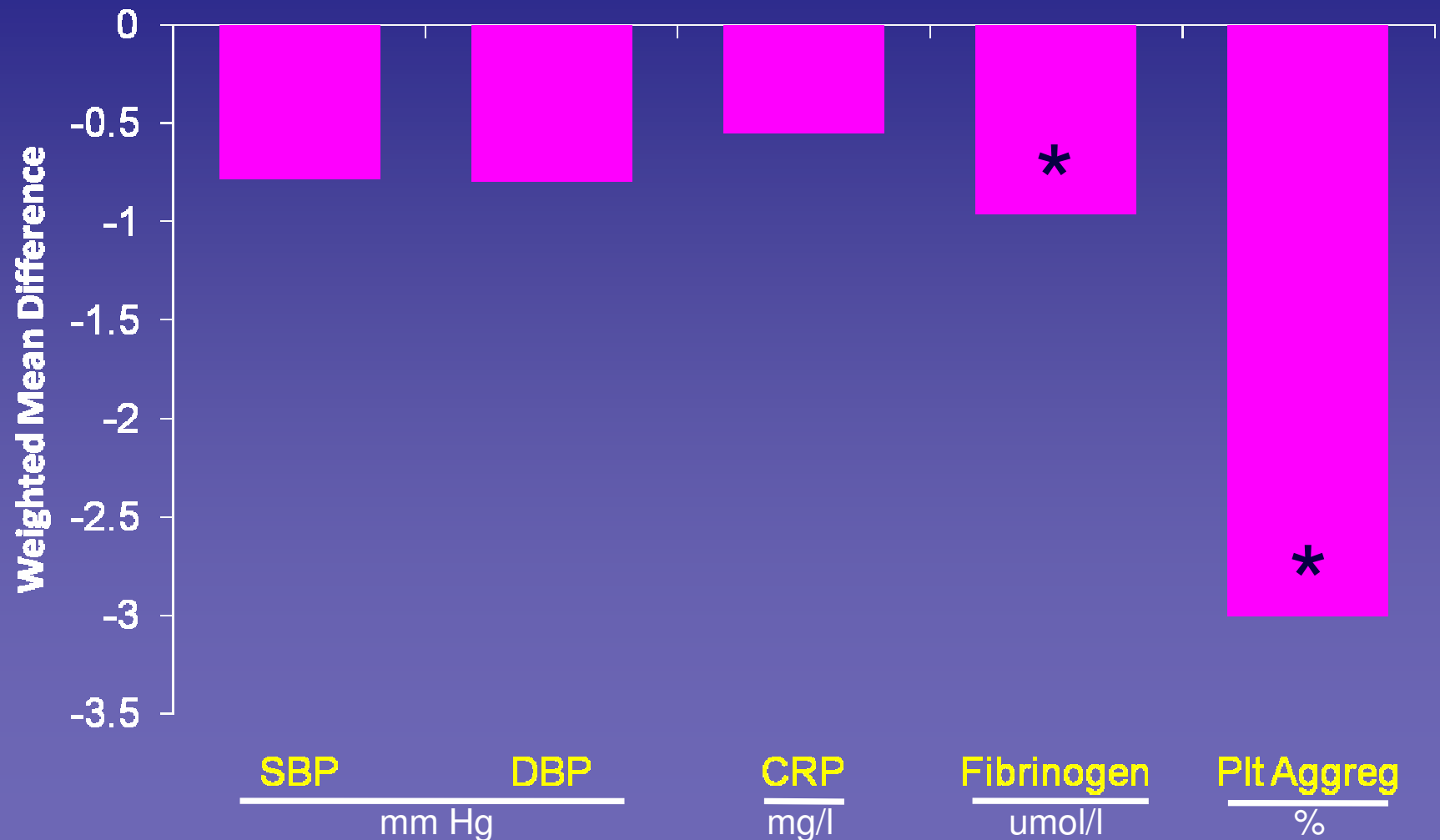
Meta-analysis of Type 2 DM Trials

Minor Effects on TG & LDL in up to 24 Trials



Meta-analysis of Type 2 DM Trials

Effects on Fibrinogen & Platelets in up to 3 Trials



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GISSI Prevenzione Trial

Participants

N = 11,324: 85% men; 15% diabetes; median age = 60; median time since MI = 16 days

Eligibility

Within 3 months of MI

Intervention

Random allocation of open addition of omega 3 FA EE90 1 g/d, or vitamin E 300 mg/d or both or neither

Primary Outcome

All cause death, nonfatal MI, nonfatal stroke

Follow-up

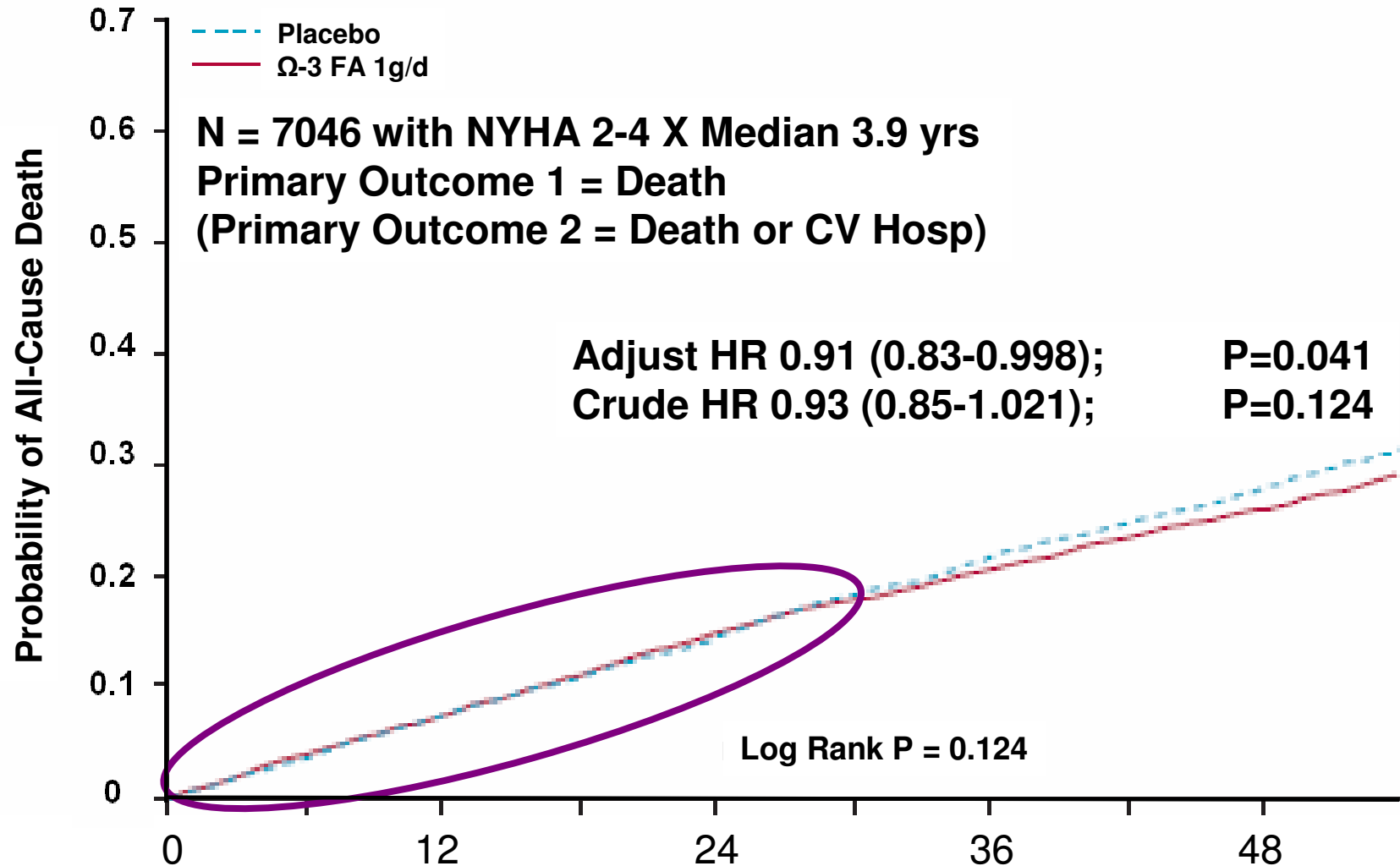
Mean Duration = 3.5 years; Extent = 99.9%

GISSI Prevenzione Trial

All Ω -3 vs. None (N=11324)



GISSI – HF Trial: Effect on Death



JELIS (Japan EPA Lipid Int'n Study)

Lancet 2007: 1090

Participants

N = 18,645, 31% men & 69% postmenopausal women; 16% diabetes

Eligibility

Age 40 – 75 (women had to be postmenopausal); Chol \geq 6.6;
No CV event (within 6 mo) or uncontrolled diabetes

Intervention

Stratified into primary and secondary prevention groups
All given statin (10-20 mg pravastatin or 5-10 mg simvastatin)
Open addition of EPA 600 mg tid vs. no EPA

Primary Outcome

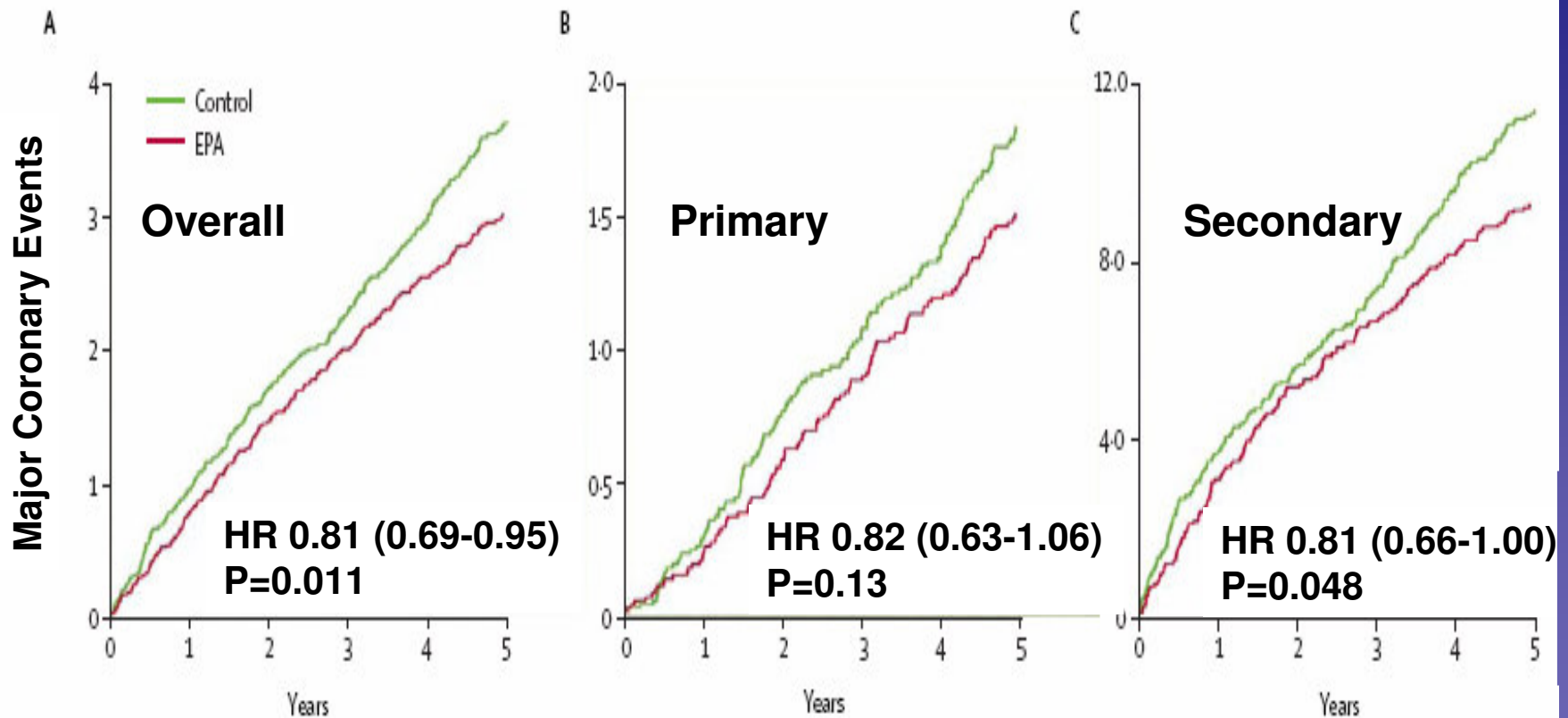
Sudden cardiac death, any MI, unstable angina, angioplasty, stenting, or CABG

Follow-up

Mean Duration = 4.6 years; Extent = 91%

JELIS (Japan EPA Lipid Int'n Study)

Lancet 2007: 1090



Numbers at risk

Control group	9319	8931	8671	8433	8192	7958	7478	7204	7103	6841	6678	6508	1841	1727	1658	1592	1514	1450
Treatment group	9326	8929	8658	8389	8153	7924	7503	7210	7020	6823	6649	6482	1823	1719	1638	1566	1504	1442

JELIS (Japan EPA Lipid Int'n Study)

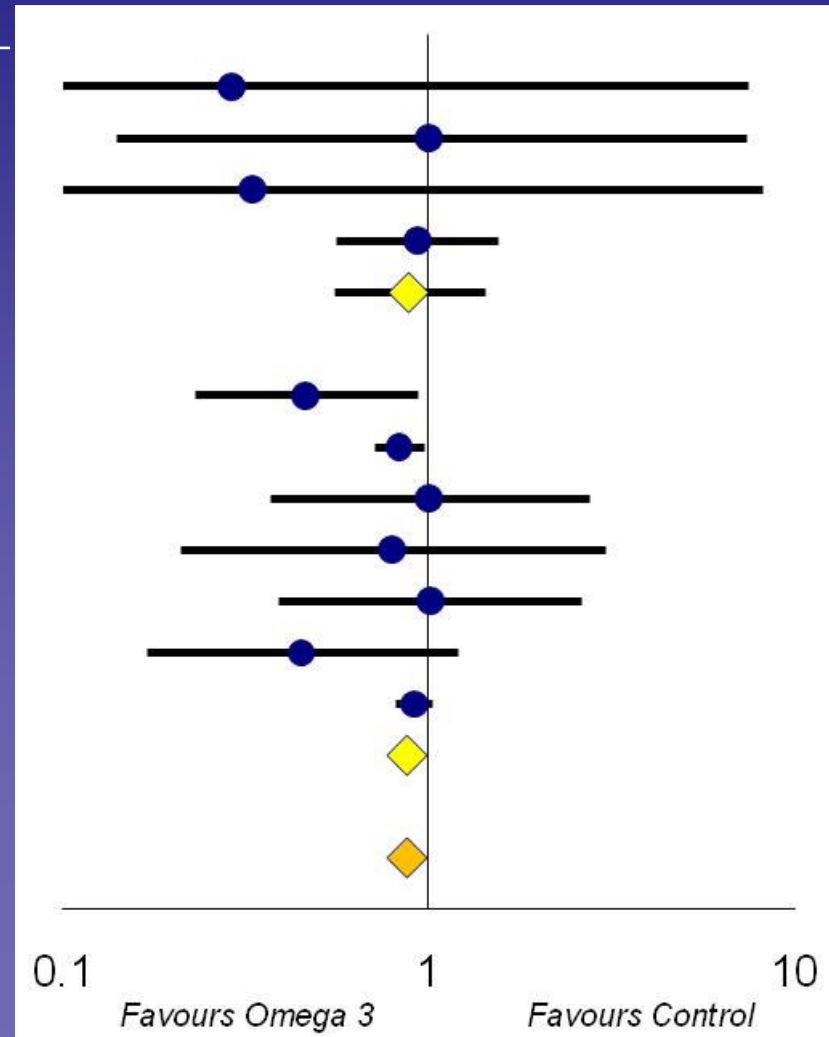
Components of Primary Outcome

Event	Number (%) of patients		p value	Hazard ratio (95 %CI)	
	Control	EPA			
All patients					
Major coronary events	324 (3.5)	262 (2.8)	0.011	0.81 (0.69-0.95)	
Items of account					
Sudden cardiac death	17 (0.2)	18 (0.2)	0.854	1.06 (0.55-2.07)	
Fatal MI	14 (0.2)	11 (0.1)	0.557	0.79 (0.36-1.74)	
Non-fatal MI	83 (0.9)	62 (0.7)	0.086	0.75 (0.54-1.04)	
Unstable angina	193 (2.1)	147 (1.6)	0.014	0.76 (0.62-0.95)	
CABG or PTCA	222 (2.4)	191 (2.1)	0.135	0.86 (0.71-1.05)	
Combined endpoint					
Coronary death or MI	113 (1.2)	88 (0.9)	0.083	0.78 (0.59-1.03)	
Fatal MI or nonfatal MI	93 (1.0)	71 (0.8)	0.091	0.77 (0.56-1.05)	
Coronary death	31 (0.3)	29 (0.3)	0.812	0.94 (0.57-1.56)	
Non-fatal coronary events	297 (3.2)	240 (2.6)	0.015	0.81 (0.68-0.96)	

Ω-3 FA & CV Death

Systematic Review of Trials ≥ 1 Year

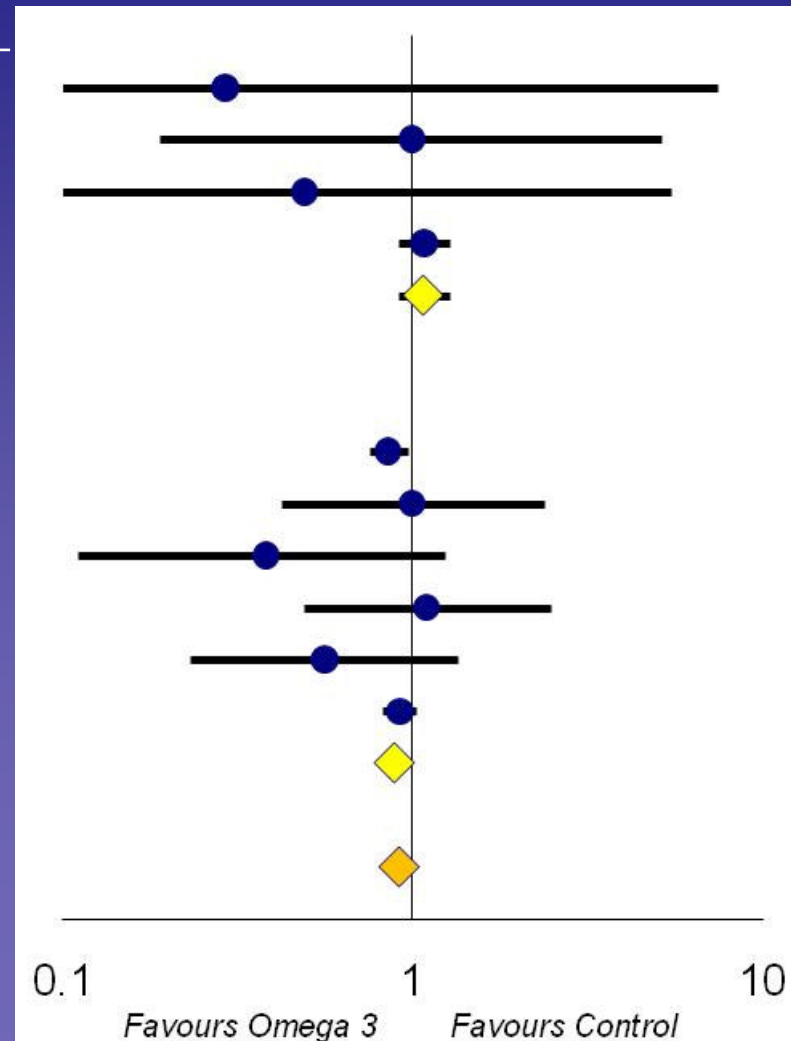
Trial	Total Events	OR (95%CI)
Sacks 1995	1	0.29 (0.01-7.44)
Leng 1998	4	1.00 (0.14-7.34)
Von Schacky 1999	1	0.33 (0.01-8.12)
JELIS 2007	60	0.93 (0.56-1.55)
MODERATE RISK	66	0.88 (0.55-1.43)
Singh 1997	40	0.46 (0.23-0.93)
GISSI – P 1999	639	0.83 (0.71-0.97)
Nilson 2001	16	1.00 (0.37-2.74)
Raitt 2005	9	0.79 (0.21-3.04)
Leaf 2005	18	1.01 (0.39-2.60)
Brouwer 2006	19	0.45 (0.17-1.20)
GISSI – HF 2008	1477	0.91 (0.81-1.02)
HIGH RISK	2218	0.87 (0.79-0.95)
ALL TRIALS	2278	0.87 (0.79-0.95)



Ω-3 FA & All Death

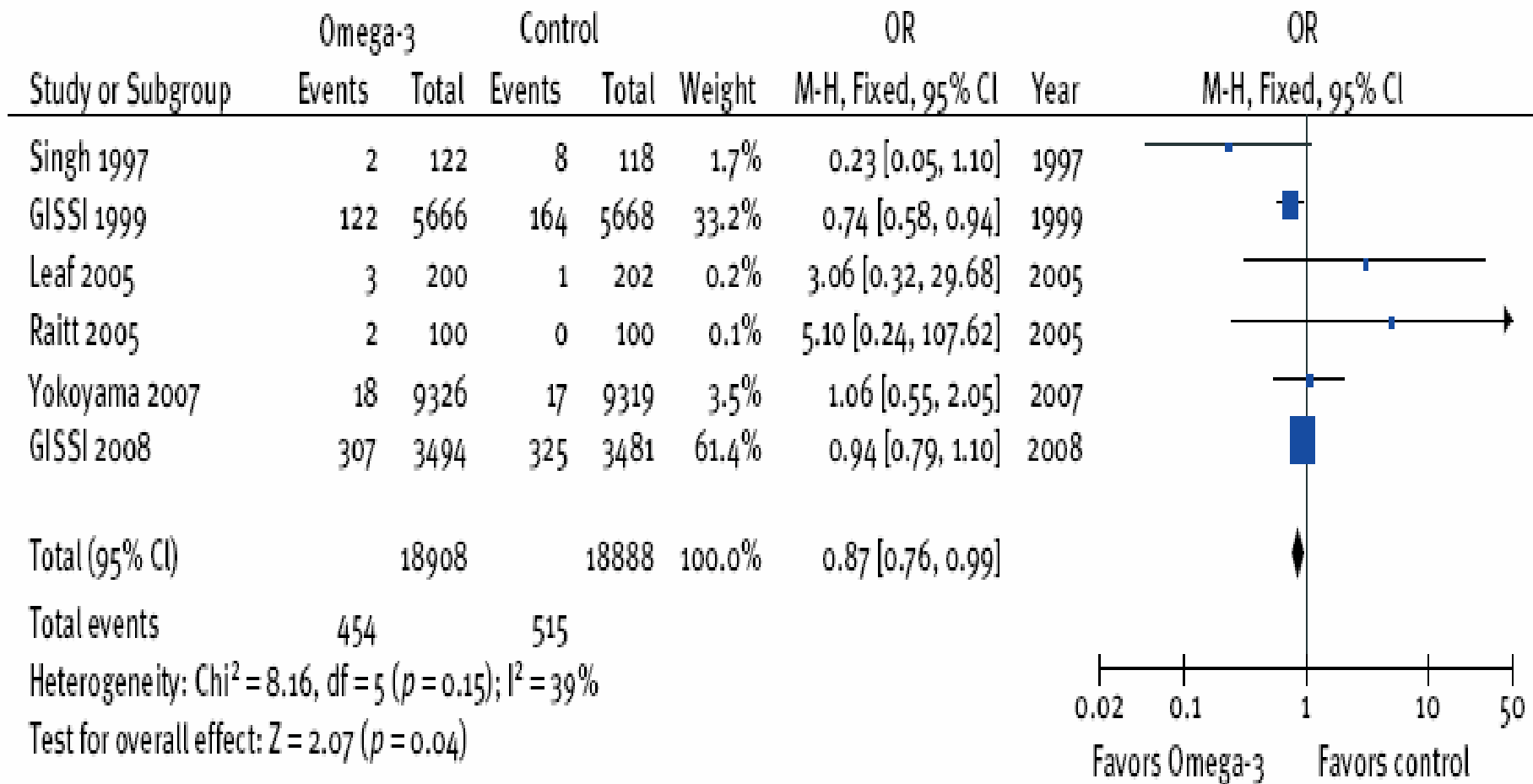
Systematic Review of Trials ≥ 1 Year

Trial	Total Events	OR (95%CI)
Sacks 1995	1	0.29 (0.01-7.44)
Leng 1998	6	1.00 (0.19-5.16)
Von Schacky 1999	3	0.49 (0.04-5.49)
JELIS 2007	551	1.08 (0.91-1.28)
MODERATE RISK	561	1.07 (0.91-1.27)
Singh 1997	0	N/A
GISSI – P 1999	1017	0.85 (0.75-0.97)
Nilson 2001	22	1.00 (0.42-2.38)
Raitt 2005	25	0.38 (0.11-1.24)
Leaf 2005	14	1.10 (0.49-2.47)
Brouwer 2006	22	0.56 (0.23-1.35)
GISSI – HF 2008	1969	0.92 (0.82-1.02)
HIGH RISK	3069	0.89 (0.82-0.96)
ALL TRIALS	3630	0.92 (0.85-0.99)



Ω-3 FA & Sudden Death

Systematic Review Trials ≥ 1 Year



Ω-3 FA & Nonfatal CVD

Systematic Review Trials ≥ 1 Year

Study or subgroup	Omega-3		Control		Weight	OR		OR
	Events	Total	Events	Total		M-H, Fixed, 95% CI	year	
MODERATE RISK								
Sacks 1995	7	31	10	28	0.5%	0.53 [0.17, 1.65]	1995	
Leng 1998	6	60	9	60	0.5%	0.63 [0.21, 1.89]	1998	
von Schacky 1999	2	112	6	111	0.4%	0.32 [0.06, 1.61]	1999	
Yokoyama 2007	240	9326	297	9319	18.6%	0.80 [0.68, 0.95]	2007	
Subtotal (95% CI)		9529		9518	20.0%	0.78 [0.66, 0.92]		
Total events	255		322					
Heterogeneity: $\text{Chi}^2 = 1.88$, $\text{df} = 3$ ($p = 0.60$); $I^2 = 0\%$								
Test for overall effect: $Z = 2.89$ ($p = 0.004$)								

Ω-3 FA & Nonfatal CVD (Continued)

Systematic Review Trials ≥ 1 Year

HIGH RISK

Singh 1997	16	122	30	118	1.7%	0.44 [0.23, 0.86]	1997
GISSI 1999	287	5666	291	5668	17.8%	0.99 [0.83, 1.17]	1999
Nilson 2001	39	150	31	150	1.5%	1.35 [0.79, 2.31]	2001
Raitt 2005	45	100	35	100	1.2%	1.52 [0.86, 2.68]	2005
GISSI 2008	1635	3494	1687	3481	57.8%	0.94 [0.85, 1.03]	2008
Subtotal (95% CI)		9532		9517	80.0%	0.95 [0.88, 1.03]	

Total events

2022

2074

Heterogeneity: $\text{Chi}^2 = 9.53$, $\text{df} = 4$ ($p = 0.05$); $I^2 = 58\%$

Test for overall effect: $Z = 1.19$ ($p = 0.23$)

Total (95% CI)

19061

19035

100.0%

0.92 [0.85, 0.99]

Total events

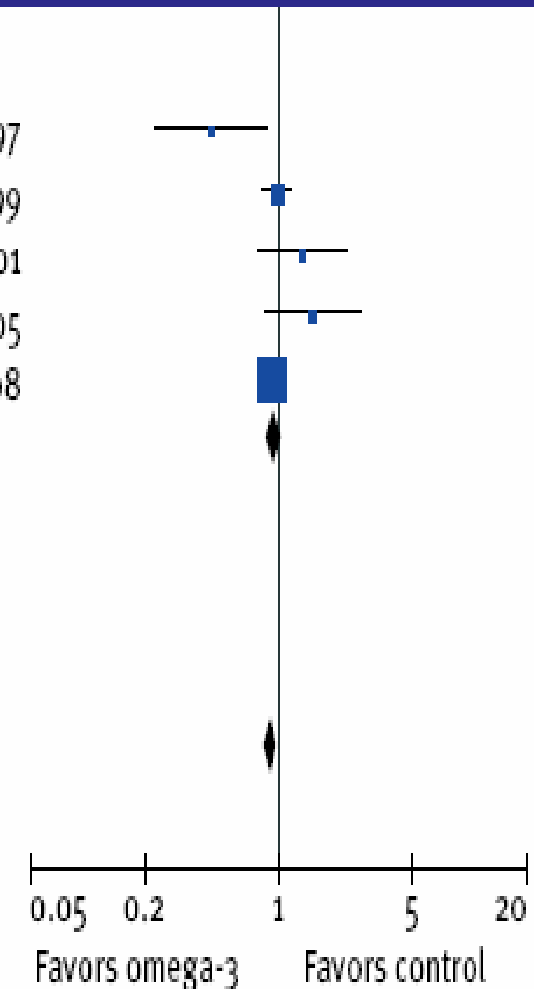
2277

2396

Heterogeneity: $\text{Chi}^2 = 15.73$, $\text{df} = 8$ ($p = 0.05$); $I^2 = 49\%$

Test for overall effect: $Z = 2.32$ ($p = 0.02$)

Test for subgroup differences: Not applicable



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GISSI Trials

Effect in People with/without Diabetes

GISSI – P (Death)

No Diabetes



HR 0.82 (0.67-1.01)

Diabetes



HR 0.72 (0.52-0.99)

Interaction P = 0.5

Favours Ω -3

Favours non- Ω -3

GISSI – HF (Death or CV Hosp)

No Diabetes



HR 0.96 (0.89-1.04)

Diabetes



HR 0.89 (0.80-0.99)

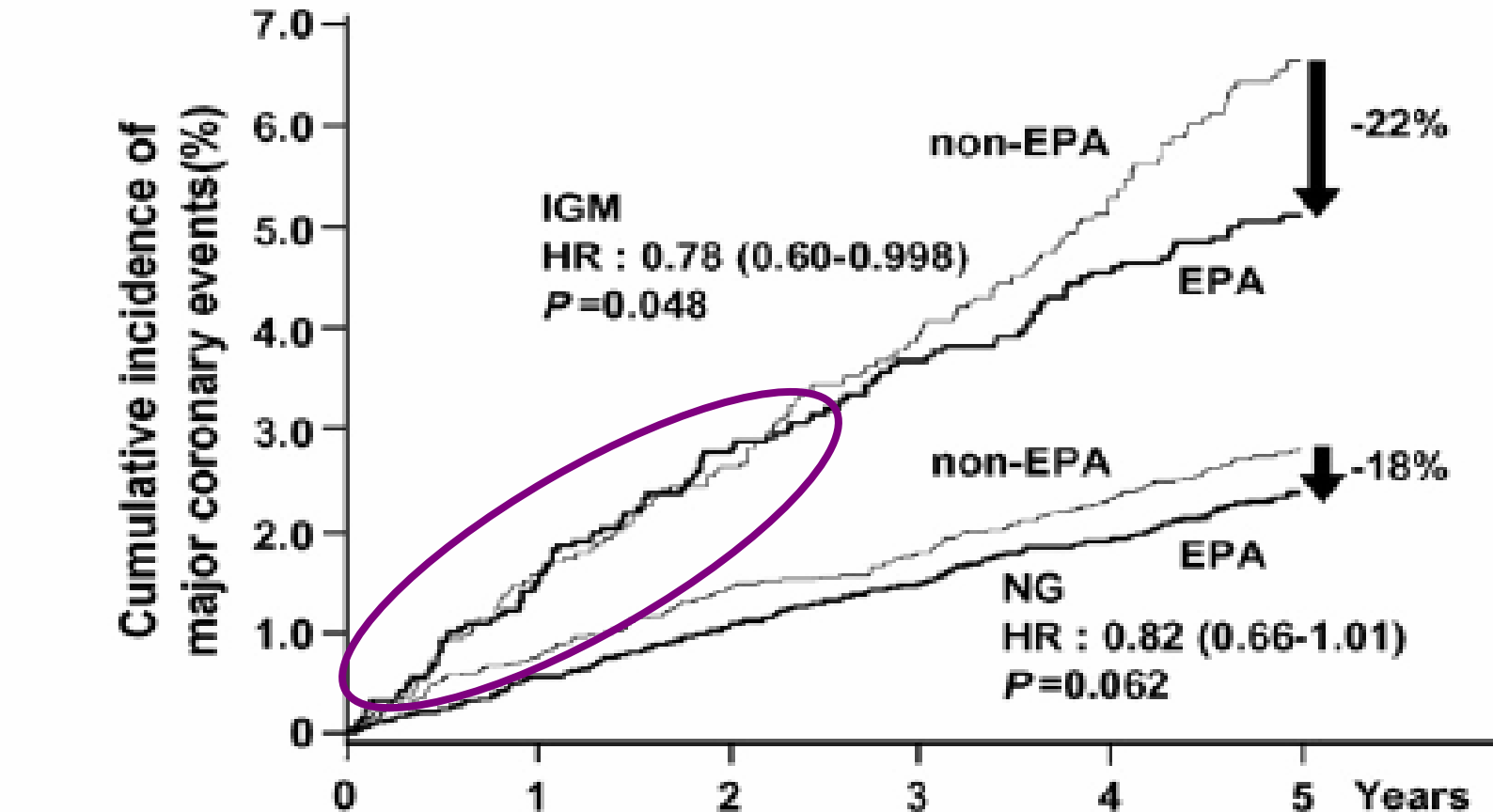
Interaction P = NS

Favours Ω -3

Favours non- Ω -3

JELIS (Japan EPA Lipid Int'n Study)

Effect in People with Dysglycemia (IFG or Diabetes)



Number of patients

IGM	non-EPA	2262	2146	2075	1996	1923	1835
	EPA	2303	2173	2090	2014	1940	1867
NG	non-EPA	7057	6785	6596	6438	6270	6123
	EPA	7023	6756	6568	6378	6215	6057

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ORIGIN Study Questions

In people at **high risk** for CV outcomes who have dysglycemia (i.e. IFG, IGT or early diabetes)....

a) does insulin replacement therapy targeting fasting normoglycemia (using insulin glargine) reduce CV events more than standard approaches to dysglycemia?

b) does adding 1 g/d Ω -3 PUFA (EE90) reduce CV death vs. adding placebo?

Participants (Key Inclusion Criteria)

- Men & women ≥ 50 yrs **AND**
- Glycemic Criteria **AND**
 - IFG or IGT or new type 2 DM by OGTT
[i.e. FPG ≥ 6.1 (110); or 2 Hr PG ≥ 7.8 (140)]
 - **OR** established type 2 DM @ stable dose ≥ 10 wks & ...
 - on no OADs ... + HbA1c $< 9.0\%$ (i.e. 150% ULN)
 - $<$ half-max 1 OAD + HbA1c $< 8.5\%$ (i.e. 142% ULN)
 - \geq half-max 1 OAD + HbA1c $< 8.0\%$ (i.e. 133% ULN)
- High CV Risk
 - Prior MI, stroke, revasc, angina + doc. ischemia
 - **OR** MA, proteinuria, LVH, 50% art. stenosis, ABI < 0.9

ORIGIN Factorial Design

	Glargine	Standard Care
Omacor	Glargine + Omacor	Omacor
Placebo	Glargine + Placebo	Placebo

Omacor: double-blind; 1 cap/day*

Glargine: open

Recruit: Sep '03 – Dec'05 Mean F/U: 6.5 yrs

Final Visit: Oct 2011 N: 12,578

*Omacor contains EPA 465 mg & DHA 375 mg

Outcomes: Omega 3 PUFA

Primary

- CV death

Secondary

- CV death OR MI OR stroke
- All cause death
- Death that is sudden & unexpected OR due to documented arrhythmia OR due to resuscitated cardiac arrest

ORIGIN Other Outcomes/Substudies

- Angina, limb/digit amputation for ischemia
- CV hospitalization
- Any other hospitalization or death
- Cognitive function, Bone Density, Fractures, W/H ratio, Weight, ED, Lipids, CGMS, Holter
- Change in glycemic status (IFG, IGT, DM)

Estimated Detectable RRR

		Detectable RRR If no effect X 1 st 12 Mo.	
Study	Outcome	90% Power	80% Power
Glargine*	1 st co-primary (MI/Stroke/CV Death)	18%	16%
	2 nd co-primary (1 st + revasc. + CHF)	16%	14%
	New Diabetes in IFG/IGT (N=1454)	40%	34%
Omacor#	Primary (CV Death)	20%	17%

* Assumes 20% nonadherence to glargine & 5% insulin use in standard care

Assumes 10% nonadherence to omacor & 10% omacor use in standard arm

NB: As power is based on number of events, this is being blindly audited by the SC

Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: The ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention)

The ORIGIN Trial Investigators *Hamilton, Ontario, Canada*

Aims Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes arise due to insufficient insulin secretion and are risk factors for cardiovascular (CV) events. Thus, targeting normal fasting glucose levels with insulin may reduce CV events. Previous studies suggest that ω -3 fatty acid supplements may reduce CV death; however, their effect in high-risk dysglycemic individuals is not known.

Methods People aged ≥ 50 years with evidence of CV disease and with IFG, IGT, newly detected or established diabetes (on 0 or 1 oral agent), and a local glycosylated hemoglobin $< 150\%$ of the upper limit of normal for that assay were recruited and allocated to (a) either 1 daily injection of insulin glargine with the dose titrated to achieve a fasting plasma glucose ≤ 5.3 mmol/L (95 mg/dL), or standard glycemic care; and (b) either ω -3-acid ethyl esters 90 (1 g consisting of EPA 465 mg and DHA 375 mg) or identical placebo, according to a 2×2 factorial design. The 2 different primary outcomes for the insulin and ω -3 fatty acid arms are CV events and CV death, respectively.

Results A total of 12 612 (mean age 64, 35% women) people in 40 countries were randomized during a 2-year period ending December 2005. Eighty-two percent had established diabetes, 6% had new diabetes, and 12% had IGT or IFG; the mean fasting plasma glucose was 7.3 mmol/L (131 mg/dL).

Conclusions The ORIGIN trial will determine whether or not either or both of these interventions can reduce CV events. (Am Heart J 2008;155:26-32.e6.)

ORIGIN Key Baseline Data: N=12578

Recruited in 40 Countries; Screen/Rand = 1.3/1

Characteristic	Level	Characteristic	Level
Mean Age	63.6 yrs	Mean BMI	29.8
Females	4402 (35%)	Mean BP	143/83
Smoking	1563 (12%)	Mean LDL	2.94 (113)
Hypertension	10824 (86%)	Mean Cholest	4.86 (187)
Dyslipidemia	8765 (70%)	Mean HDL	1.19 (46)
Previous CVD	8374 (66%)	Mean TG	1.74 (158)
Prior DM (x 5.4 y)	10336 (82%)	Waist/Hip	M -1.0; F-0.91
New DM	788 (6.3%)	FPG	7.3 (131)
IFG/IGT	1454 (11.5%)	A1C	6.5



ORIGIN Key Baseline Data: N=12578

Recruited in 40 Countries; Screen/Rand = 1.3/1

Region	N (%)	Drug Use	N (%)
N. America	1314 (10%)	Statins	6798 (54%)
S. America	3853 (31%)	Fibrates	573 (4.6%)
W. Europe	3752 (30%)	ACE-Is	7126 (57%)
E. Europe	2383 (19%)	ARBs	1767 (14%)
India	390 (3.1%)	Thiazides	2379 (19%)
Asia/Pacific	718 (5.7%)	Other BP Rx	7910 (63%)
Australia	202 (1.6%)	ASA	8261 (66%)
		Other Antiplat	1718 (14%)

Conclusions

- *Dysglycemia is a strong independent risk factor for CV outcomes & death*
- *Large outcomes trials to date in high-risk people have reported small effects*
- *Effect of Ω -3 PUFA EE appear to be at least similar in dysglycemia vs. normoglycemia*
- *For the effects of Ω -3 FA EEs supplements, ORIGIN*
 - *has high power to detect clinically important effects throughout the world*
 - *will provide a robust estimate of long-term effects*
 - *is 1 of 2 large outcome trials in people with dysglycemia (2nd is ASCEND in UK: N=10,000)*