GRACE

Glucose Reduction and Atherosclerosis Continuing Evaluation

A Substudy of the ORIGIN Trial

Study Rationale

- Atherosclerosis is the major cause of death and disability in people with dyslycemia
- Large epidemiological studies show consistent independent associations between glycemia and CV risk
- Metabolic abnormalities associated with dysglycemia promote atherogenesis
- Exogenous insulin can provide effective glycemic control but its effects on atherosclerosis remain unknown
- Some studies suggest possible proatherogenic effects of exogenous insuline and effects on clinical macrovascular events remain unproven

Study Rationale

- Essential long chain N-3 PUFA may have beneficial effects on atherosclerosis in experimental settings
- Higher intake of fish or of N-3 FA supplements are associated with lower rates of CHD and death
- Some, but not all, previous randomized trials reported reduced CV events in patients receiving N-3 FA supplements
- Effects of these supplements on human atherosclerosis were evaluated in few small studies and remain inconclusive

Research Questions

- In *high risk* people with dysglycemia does treatment with:
  - Basal insulin glargine targeting fasting normoglycemia (≤ 5.3 mM or 95 mg%), reduce the progression of atherosclerosis?
  - Omega-3 Fatty Acid Supplements reduce the progression of atherosclerosis?

Study Organization

- Investigator- initiated substudy of the ORIGIN trial
- Conducted at 32 ORIGIN centers in 7 countries, selected based on interest and availability of adequate US equipment and expert sonographers
- Funding and regulatory support were provided by Sanofi and capsules containing n–3 FA and placebo by Pronova BioPharma, Norway
- Project coordination, data management and statistical analyses - independently provided by the Population Health Research Institute in Hamilton, Canada, which was also the site for the Core CUS and the Central Biochemistry Laboratories

Key Inclusion Criteria

- **Age ≥ 50 yrs** ***AND***
- **Dysglycemia** ***AND***
  - *EITHER* IFG or IGT or new type 2 DM by OGTT
    [i.e. FPG ≥ 6.1 (110); or 2 Hr PG ≥ 7.8 (140)]
  - *OR* early type 2
    - on no more than 1 Oral Antiglycemic Drug
    - HbA1c < 9.0%
- **High CV Risk** ***AND***
- **Adequate baseline CIMT**
  - **≥ 4 measurable segments**

Key Exclusion Criteria

- Type 1 DM
- Insulin requiring, or on ≥ 2 OADs, or “high” HbA1c
- Unable to give insulin or check home glucose levels (at least 4 X)
- Serum Cr > 176μM/L (2); ALT or AST > 2.5 X ULN
- On TZD and unwilling to stop the TZD
- On Omega-3 FA Supplements and unwilling to stop
- Heart Failure
- Recent CABG
- Cancer

ORIGIN-GRACE Factorial Design

N=1091; 32 sites; 7 countries; 2 Comparisons

	Insulin Glargine	Standard Care
N-3FA*	Glargine + N-3 FA	N-3 FA
Placebo	Glargine + Placebo	Placebo

N-3 FA*: double-blind; 1 cap/day*

Insulin Glargine: non-blinded design vs. standard care

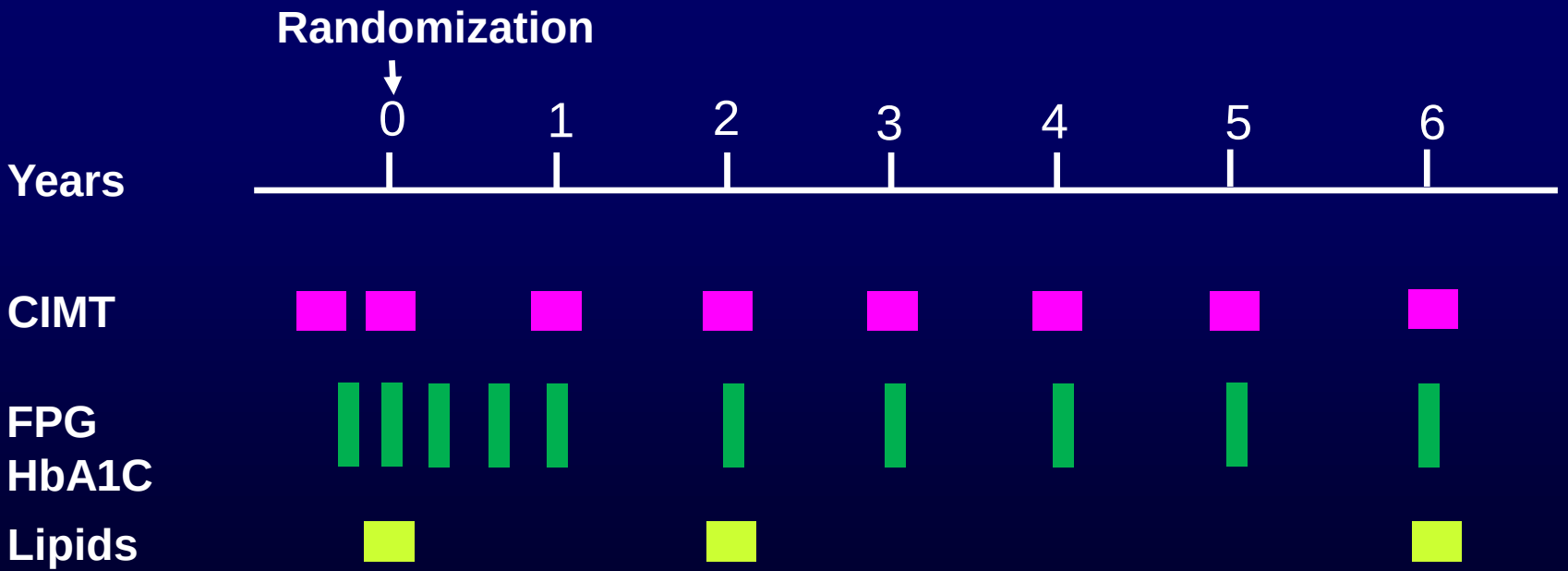
Median Clinical (IQR) F/U: 6.2 yrs (5.8 – 6.5 yrs)
Median (IQR) F/U from BS to last CIMT scan: 4.9 yrs (3.0-5.0)

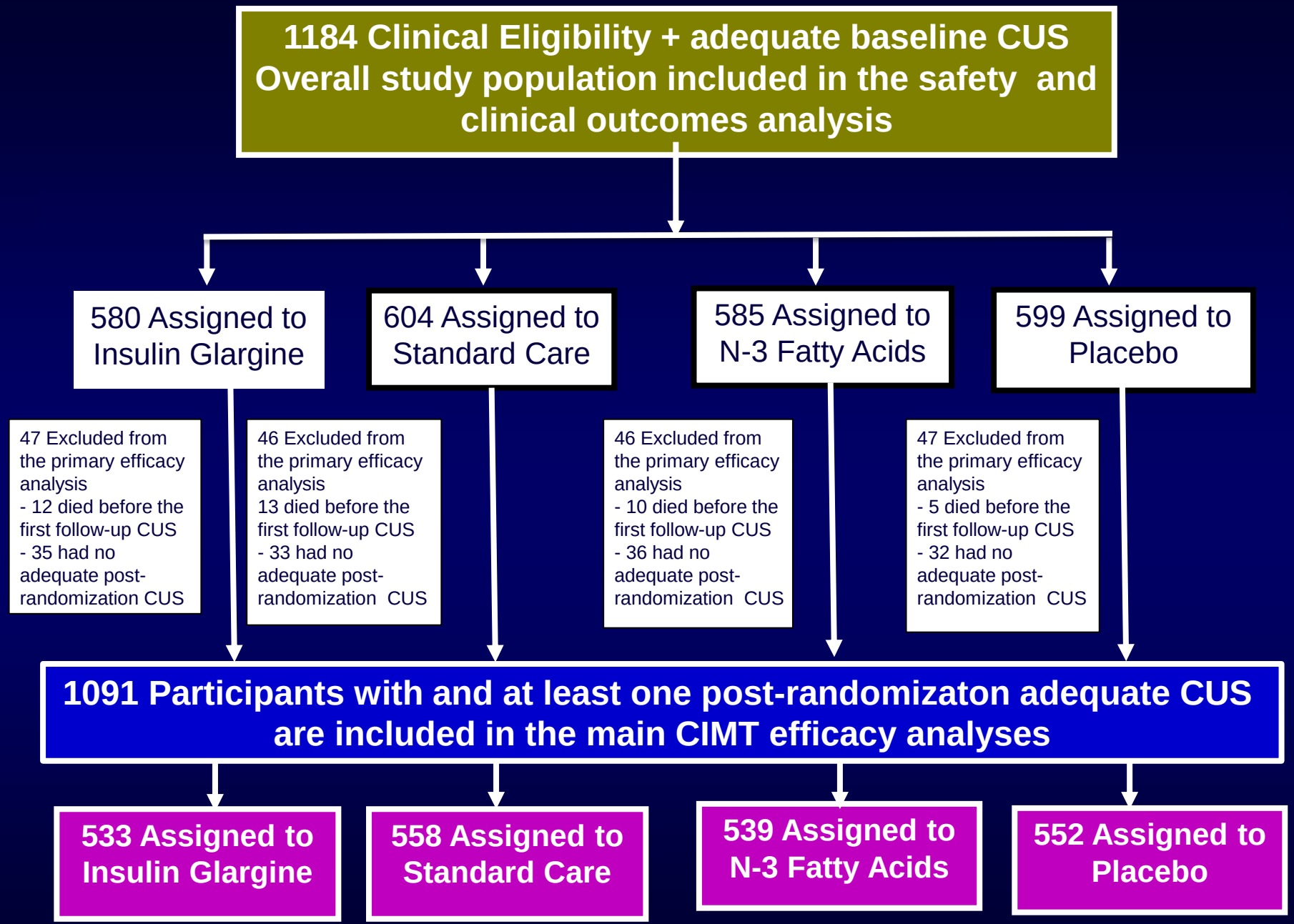
Omacor contains EPA 465 mg & DHA 375 mg

ORIGIN-GRACE- Study Design

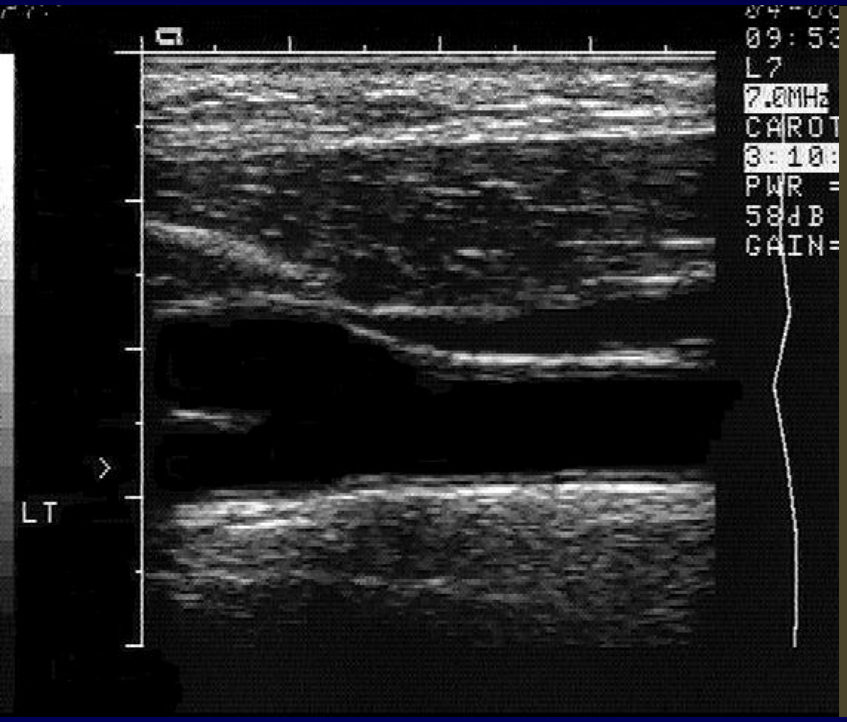
2 x2 Factorial Multicenter International Trial

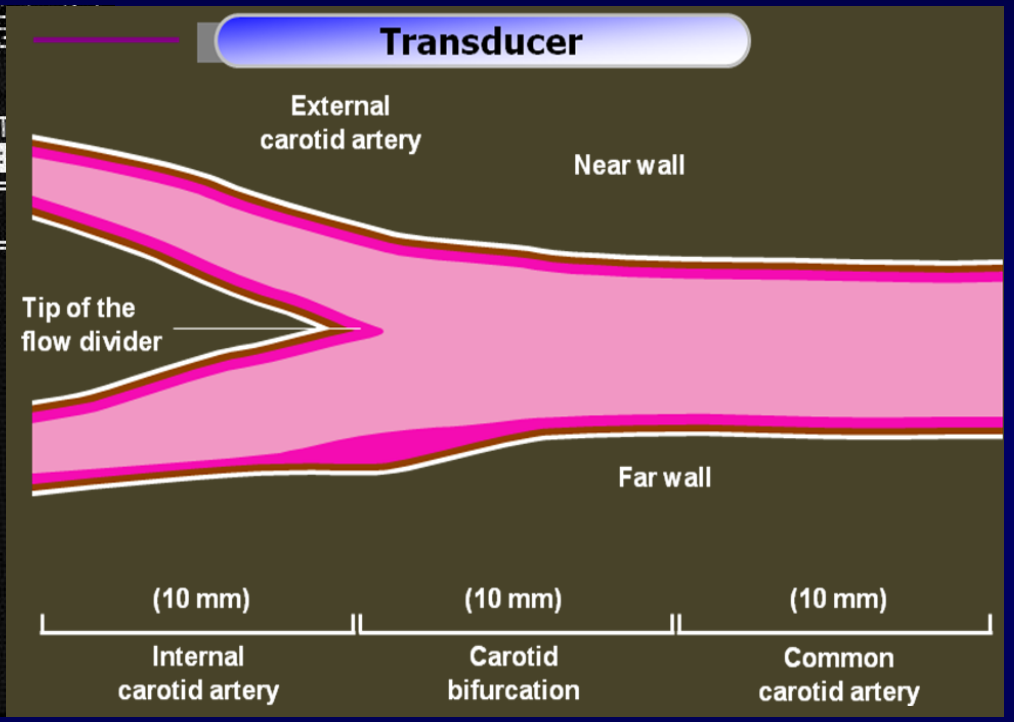
		Insulin Glargine	Standard Care
10 day run-in	N-3FA*	Glargine + N-3 FA	N-3 FA
	Placebo	Glargine + Placebo	Placebo




1184 Clinical Eligibility + adequate baseline CUS
Overall study population included in the safety and clinical outcomes analysis
580 Assigned to Insulin Glargine
604 Assigned to Standard Care
585 Assigned to N-3 Fatty Acids
599 Assigned to Placebo
47 Excluded from the primary efficacy analysis
- 12 died before the first follow-up CUS
- 35 had no adequate post-randomization CUS
46 Excluded from the primary efficacy analysis
13 died before the first follow-up CUS
- 33 had no adequate post-randomization CUS
46 Excluded from the primary efficacy analysis
- 10 died before the first follow-up CUS
- 36 had no adequate post-randomization CUS
47 Excluded from the primary efficacy analysis
- 5 died before the first follow-up CUS
- 32 had no adequate post-randomization CUS
1091 Participants with and at least one post-randomizaton adequate CUS are included in the main CIMT efficacy analyses
533 Assigned to Insulin Glargine
558 Assigned to Standard Care
539 Assigned to N-3 Fatty Acids
552 Assigned to Placebo

Quantitative Carotid Ultrasonography





Reproducibility:

Baseline (250 pairs): ICC=0.98 for Mean maximum CIM T (12 segments)
ICC=0.93-0.98 for additional CIMT measurements

Study End: (26 pairs): ICC=0.95 for Mean maximum CIM T (12 segments)
ICC=0.87-0.98 for additional CIMT measurements

Main Efficacy Outcomes

- **Primary Outcome**
  - The annualized change in Maximum CIMT form 12 sites
- **Secondary Outcomes**
  - The annualized change in Maximum CIMT for the Common Carotid (4 segments)
  - The annualized change in Maximum CIMT for the Common Carotid and Bifurcation (8 segments)
- **Additional Outcome**
  - The annualized change in Maximum Far Wall CIMT (6 segments)

Statistical Analyses

- **Primary Efficacy Analyses**
  - Repeated linear mixed-effects models including all segment maximum measurements for each patient as the dependent variables, with random intercepts and slopes as a function of time and fixed effects for geographic region, age, gender, treatment assignment for the other arm of the factorial design, carotid segment, treatment, time, and interaction between time and treatment.
- **Risk Factor Levels**
  - ANCOVA; repeated measures analyses
- **Clinical Events**
  - Cox Proportional Hazard Models

Adherence and Side Effects (N=1184)

	Insulin Glargine	N-3 FA	Placebo
Year 1	94 %	97%	97%
Year 2	93%	97%	96%
Year 2	91%	95%	95%
Year 4	90%	95%	95%
Year 5	89%	94%	94%
Study End	86%	915	93%

- 91 patients (15.7%) permanently discontinued insulin glargine; most common reasons for discontinuation : patient preference (76 patients) and hypoglycemia (9 patients).

- 66 (11.3% patients in the n-3 FA group and 64 (10.7%) in the placebo group permanently discontinued study drug; most common reasons: patient preference (45 and 43 patients), abdominal discomfort (4 and 2 patients) and lower GI problems (2 and 4 patients).

Baseline Characteristics (N=1184)

Mean Age (yrs)	63 ± 7.9
Females	429 (36.2%)
C. Smoking	122 (10.3%)
Hypertension	981 (80.3%)
Hyperlipidemia	707 (59.7%)
Previous CVD	583 (49.2%)
Diabetes	1071 (90.5%)
IFG/IGT	113 (9.5%)

N. America	166 (14.0%)
S. America	824 (69.6%)
Europe	14 (1.1%)
Australia	7 (0.6%)

Baseline Characteristics (N=1184)

BMI	29.8 ± 5.7
BP	146/84 ± 22/12
Cholesterol*	4.90 ± 1.1
LDL –C*	2.95 ± 1.0
HDL-C*	1.15 ± 0.3
TG*	1.9 ± 1.2
Waist/Hip	M 0.98; F 0.91
eGFR	77.9 ± 20.8
FPG*	7.3 ± 2.1
A1C	6.8 ± 1.0

ASA	749 (63.3%)
Statins	485 (41.0%)
ACE-I or ARB	805 (68.0%)
Beta-Blocker	593 (50.1%)
CaChBlocker	271 (22.9%)
Thiazide	155 (13.1%)
Metformin	302 (25.5%)
Sulfonylurea	477 (40.3%)

* in mmol/L

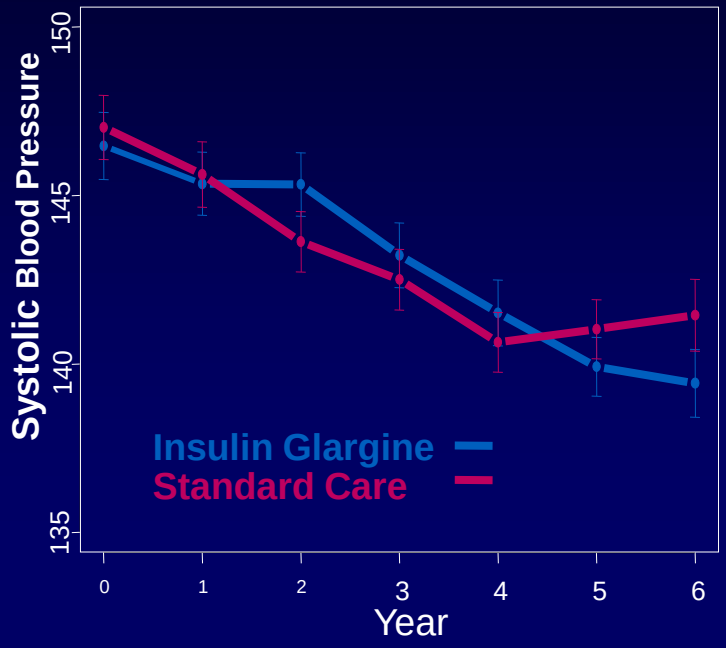
Baseline Characteristics (N=1184)

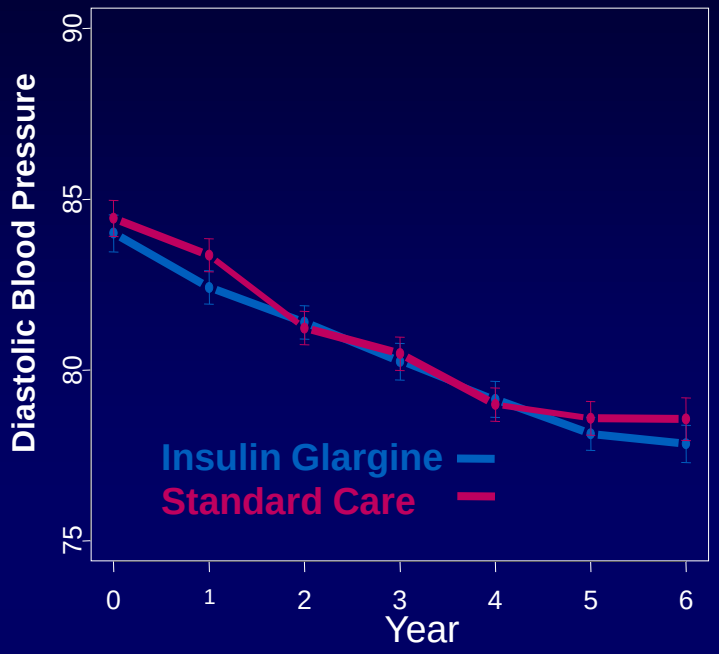
- At study end 51% were taking statins, 75% ACE-I or ARBs, 70% aspirin, 55% BBL, 28% CCBs and 18% thiazides (similar treatment and control groups).

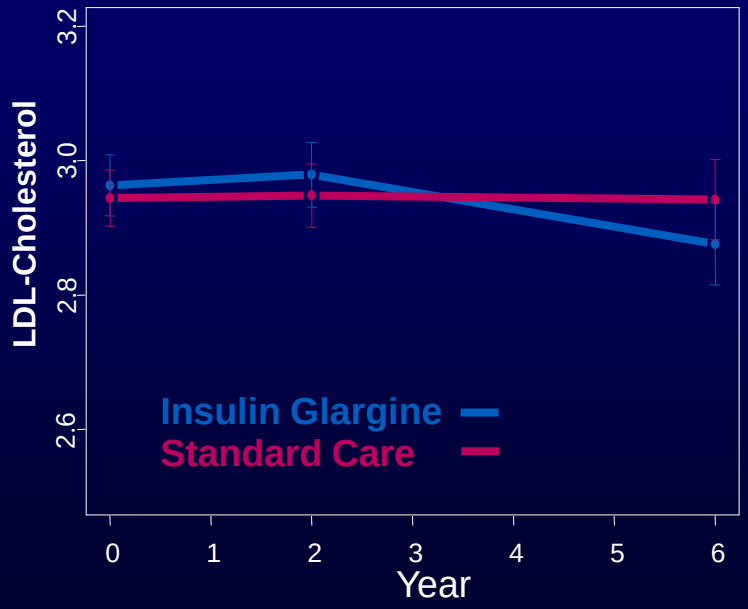
- At study end metformin and sulfonylurea use were 56% and 25% in the insulin glargine and 61% and 53% in the standard care groups.

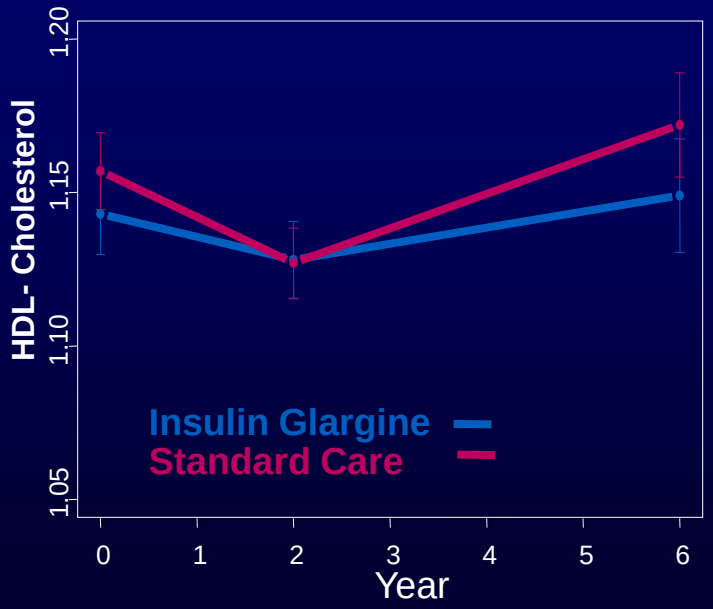
- Study-end use of OADs remained well balanced between the N-3 FA and placebo groups.

Glargin Arm: Effects on Risk Factor Levels

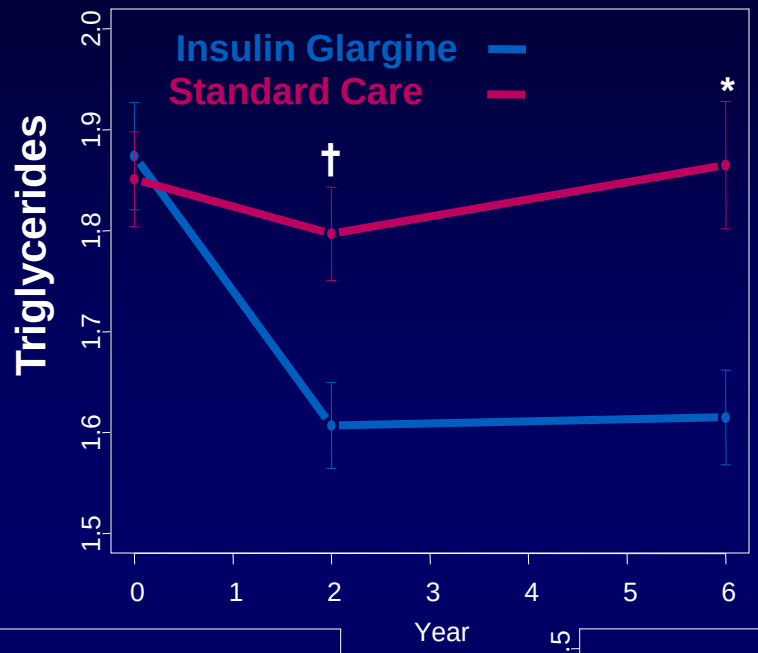




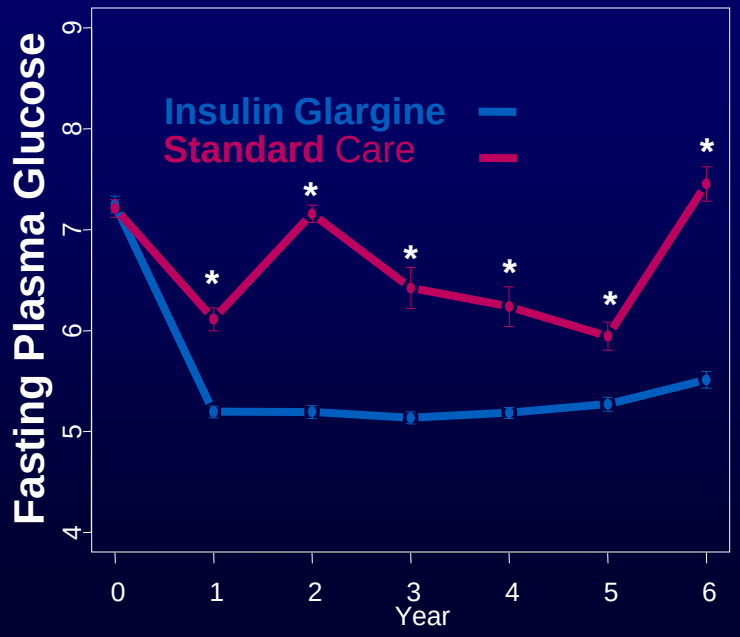


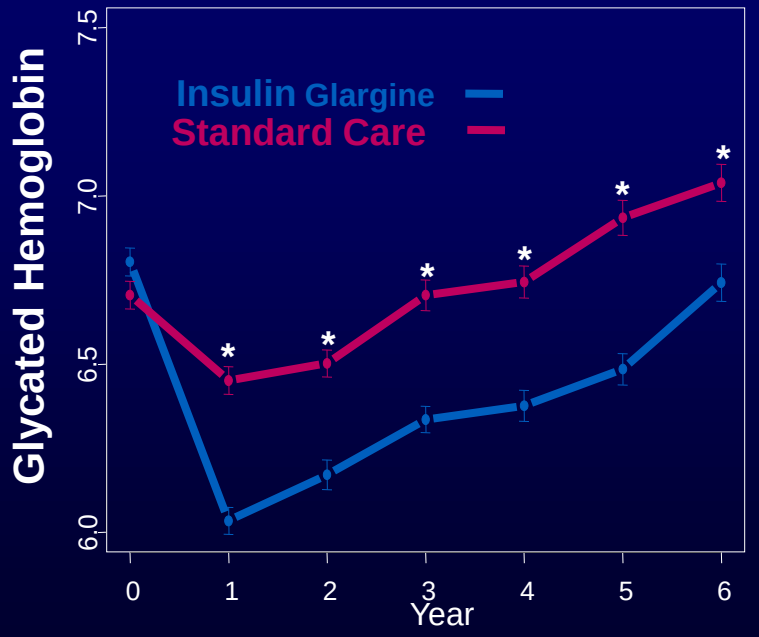


Glargin Arm: Effects on Risk Factor Levels

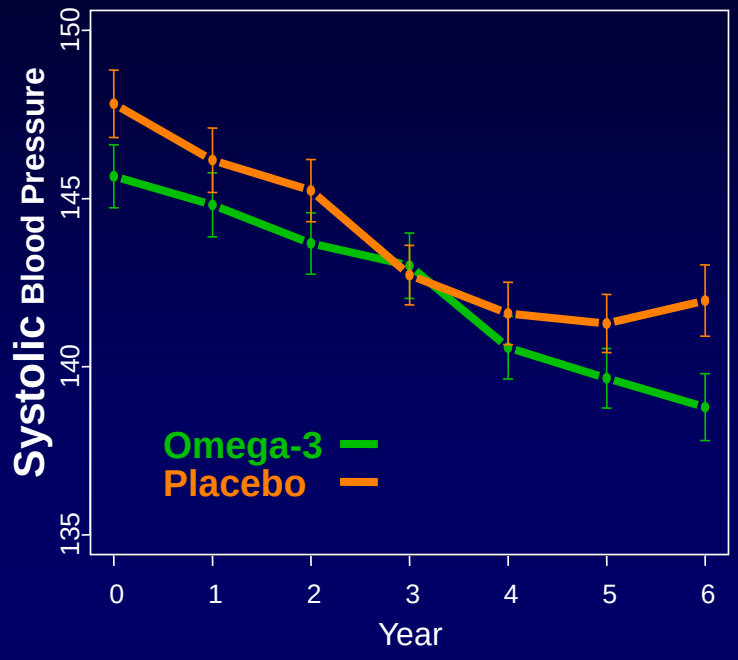


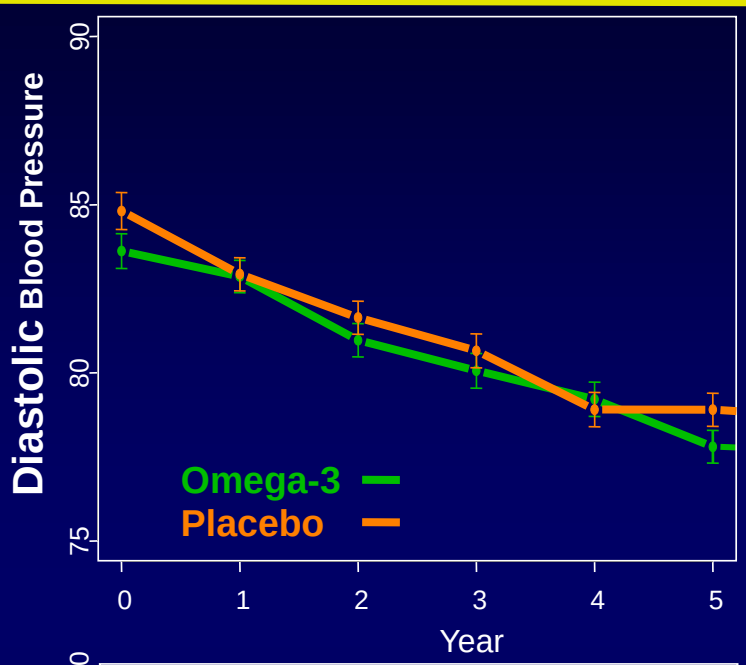
† =0.003; *<0.001

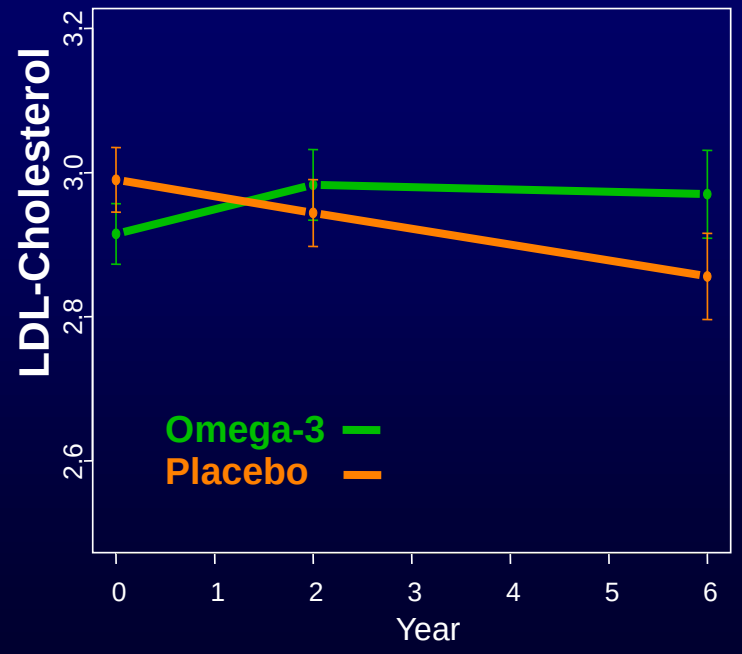


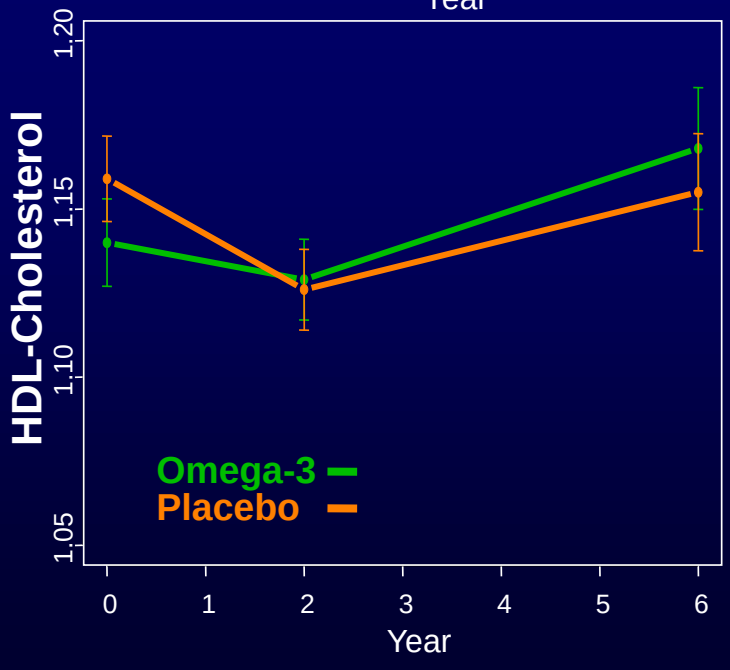


N-3 Fatty Acids Arm: Effects on Risk Factor Levels

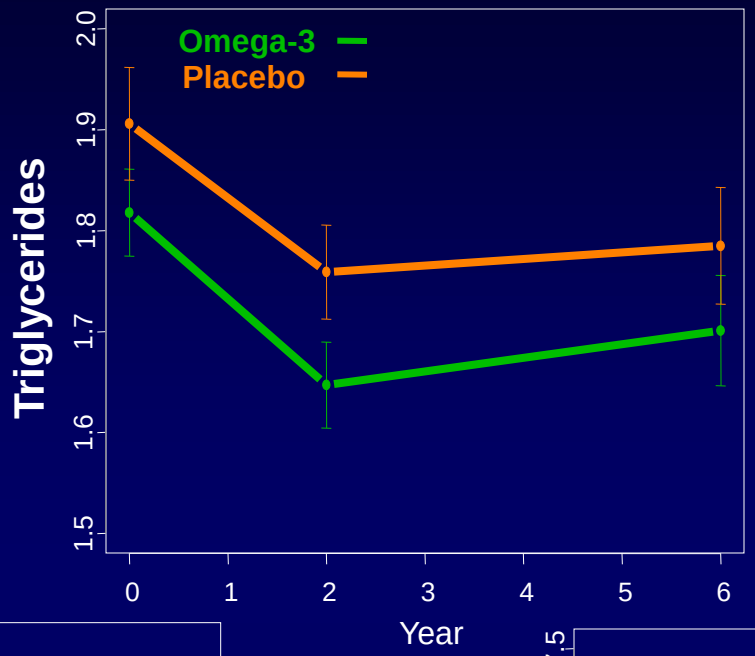


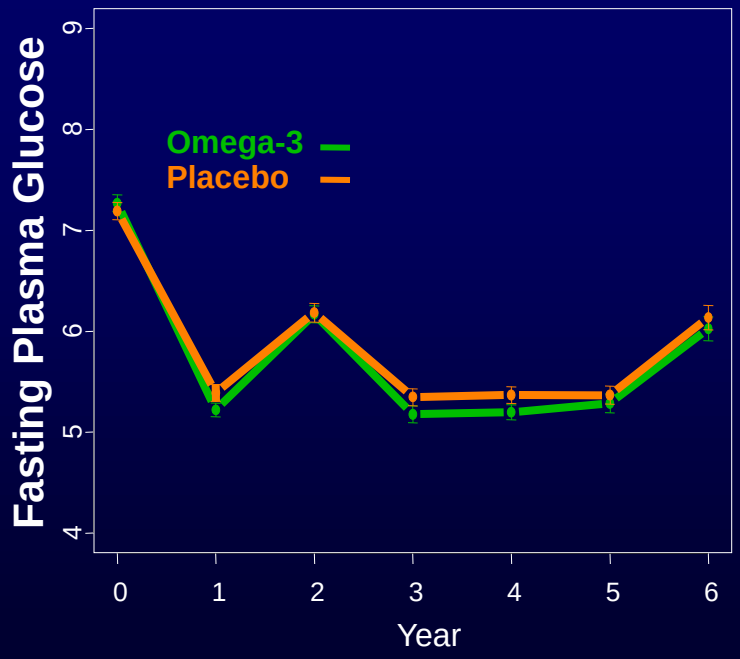


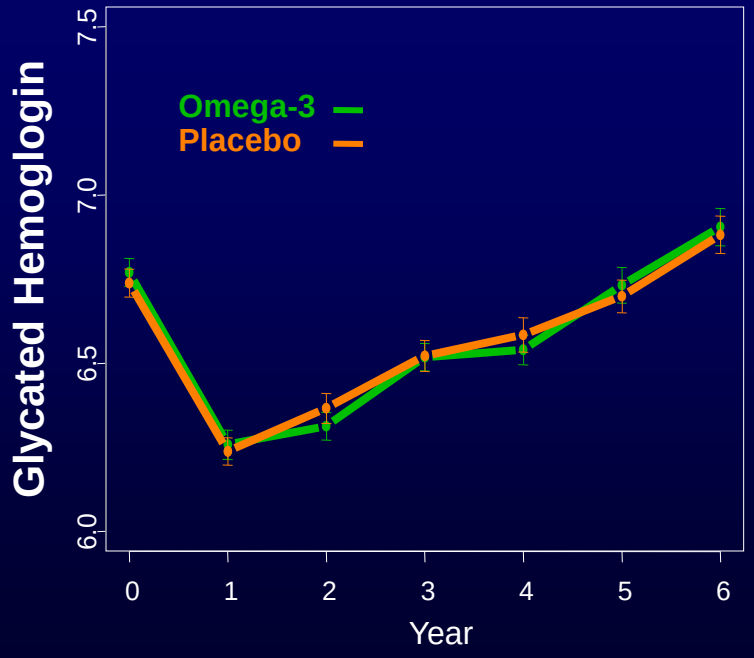




Effects of N-3 Fatty Acids on Risk Factor Levels







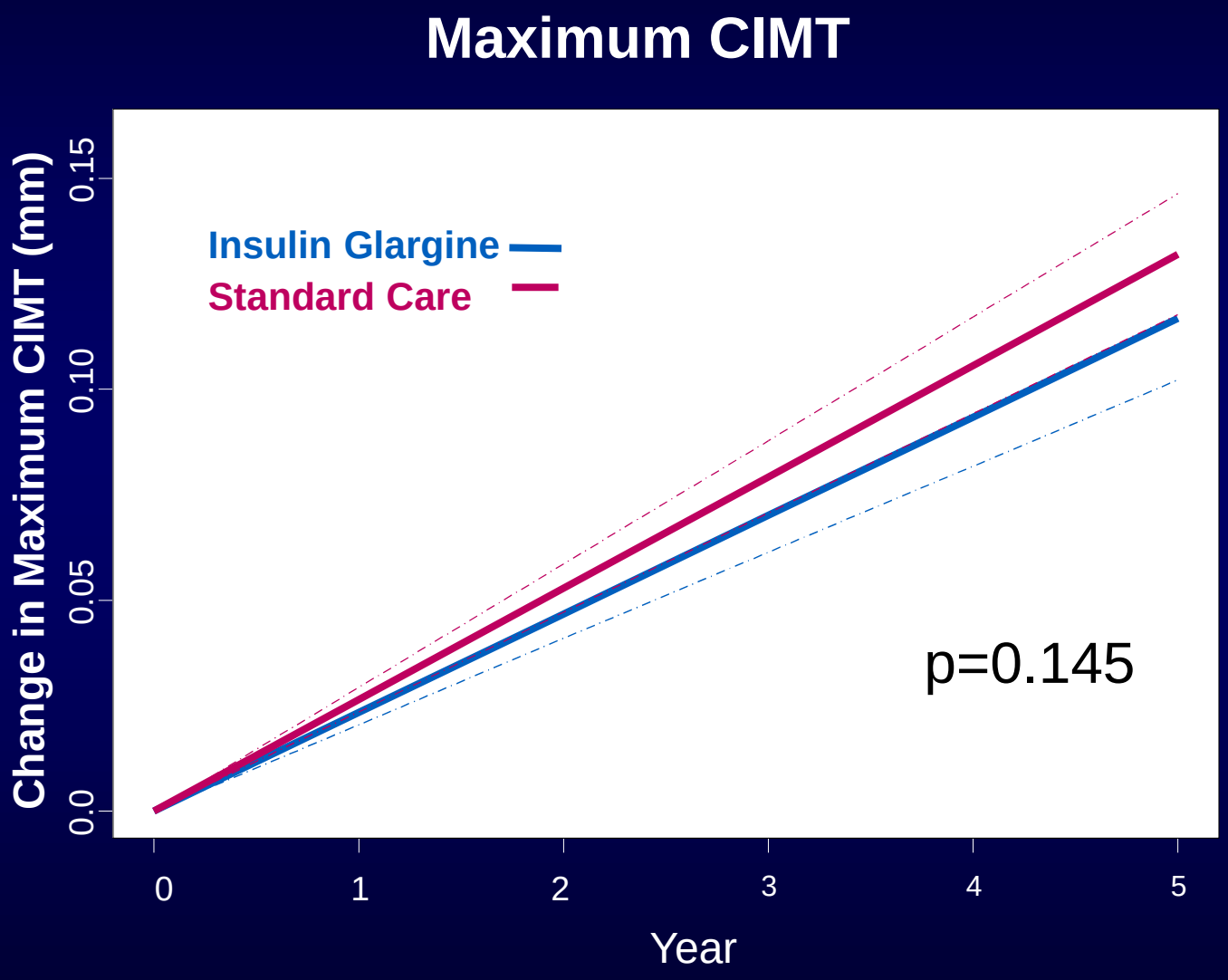
Glargine Arm: Main Efficacy Analysis

	Insulin Glargine Slope (n=533) LSM ± SE (mm/year)	Standard Care Slope (n=558) LSM± SE (mm/year)	Difference (Glargine - Standard Care) LSM ± SE (mm/year)	P
Primary Outcome Maximum CIMT for 12 carotid segments	0.0234 ± 0.0015	0.0264 ± 0.0015	-0.0030 ± 0.0021	0.145
Secondary Outcomes				
- Maximum CC CIMT	0.0126 ± 0.0012	0.0158 ± 0.0012	-0.0033 ± 0.0017	0.049
- Maximum CC and BIF CIMT	0.0209 ± 0.0015	0.0254 ± 0.0015	-0.0045 ± 0.0021	0.032
Additional Outcome				
-Maximum Far Wall CIMT	0.0241 ± 0.0015	0.0285 ± 0.0015	-0.0044 ± 0.0023	0.061

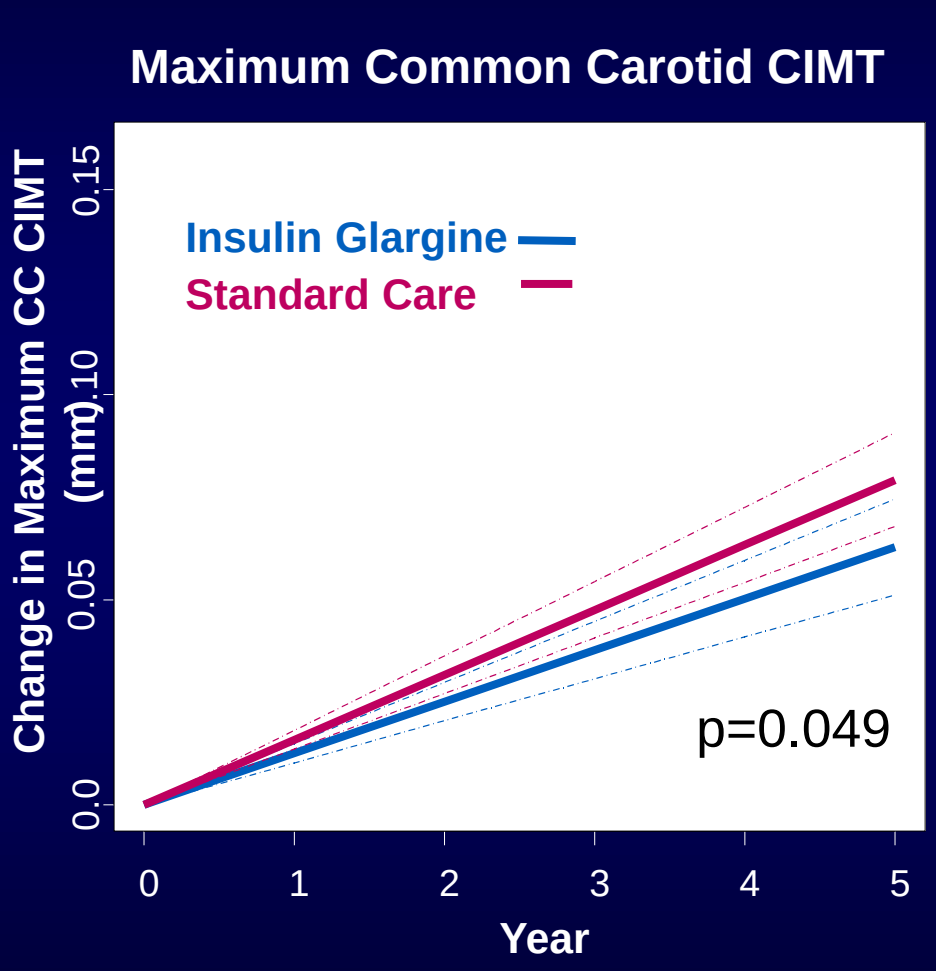
Fatty Acids Arm: Main Efficacy Analysis

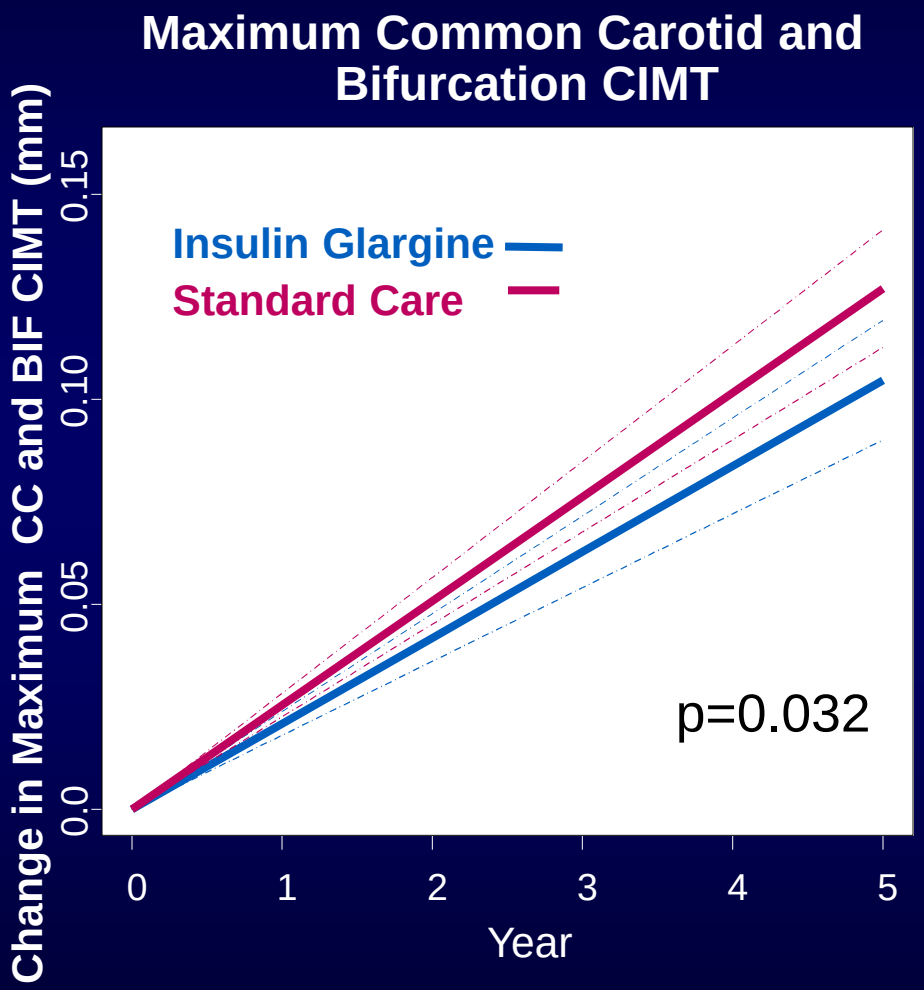
	N-3 Fatty Acids Slope (n=533) LSM ± SE (mm/year)	Placebo Slope (n=558) LSM± SE (mm/year)	Difference (N-3 Fatty Acids-Placebo) LSM ± SE (mm/year)	P
Primary Outcome Maximum CIMT for 12 carotid segments	0.0254 ± 0.0015	0.0244 ± 0.0015	0.0009 ± 0.0021	0.650
Secondary Outcomes				
- Maximum CC CIMT	0.0140 ± 0.0012	0.0144 ± 0.0012	-0.0004 ± 0.0017	0.812
- Maximum CC and BIF CIMT	0.0243 ± 0.0015	0.0221 ± 0.0015	0.0022 ± 0.0021	0.288
Additional Outcome				
-Maximum Far Wall CIMT	0.0280 ± 0.0017	0.0247 ± 0.0016	0.0033 ± 0.0023	0.152

Glargine Arm: Primary Efficacy Outcome (n=1091)

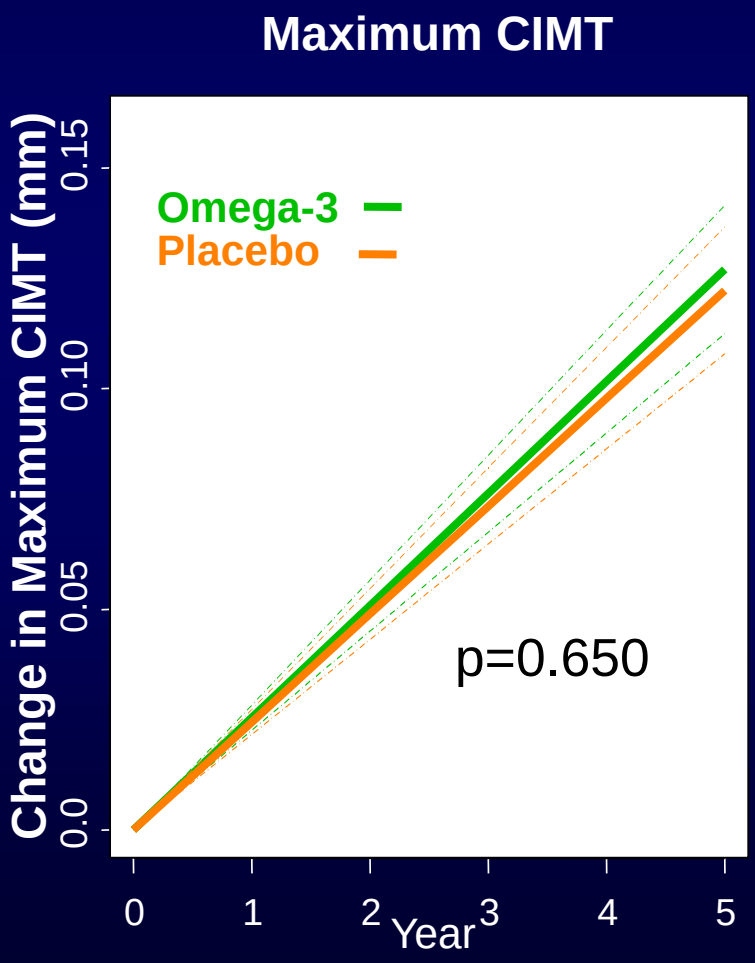


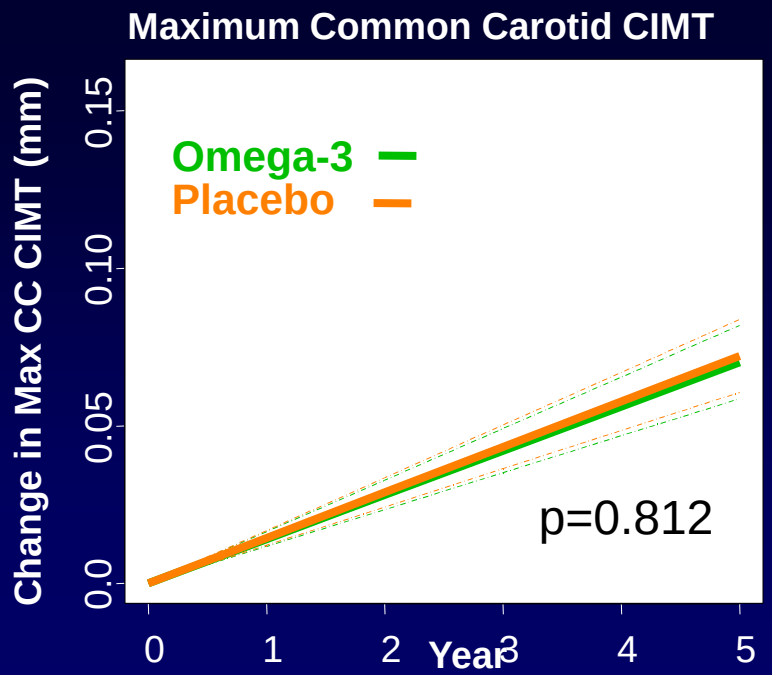
Glargine Arm: Secondary Efficacy Outcomes

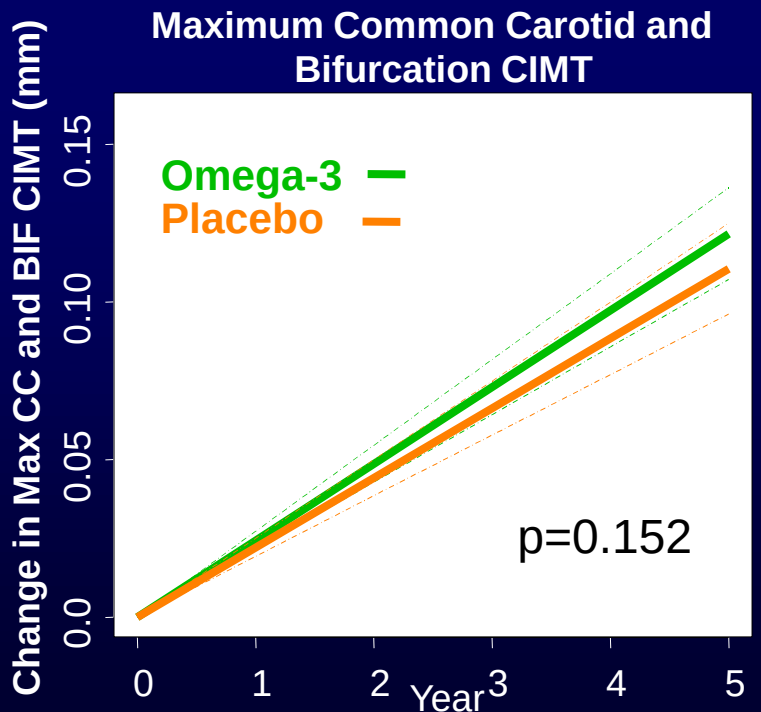




N-3 Fatty Acids Arm: Primary and Secondary Efficacy Outcomes (N=1091)





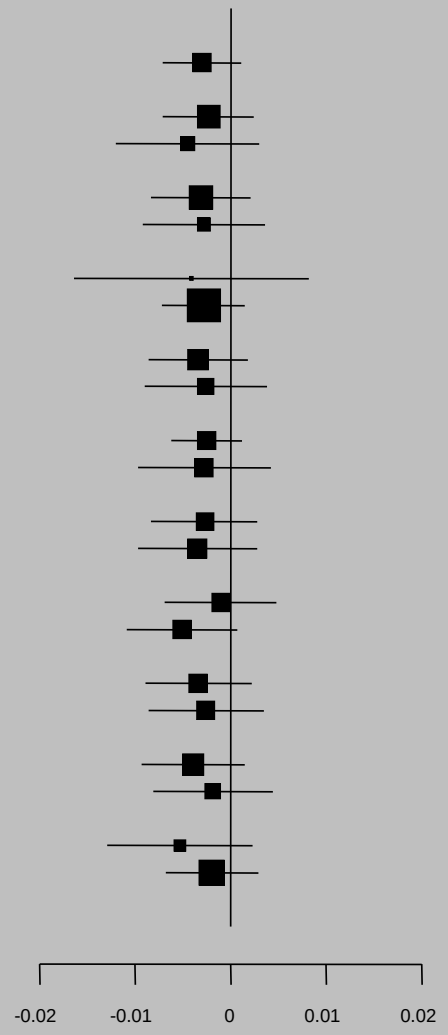


Clinical Events

	Insulin Glargine (n=580)	Standard Care (n=604)	HR (95%CI)
CV death, non-fatal MI or non-fatal stroke	108 (18.6)	102 (16.9)	1.10 (0.84-1.44)
All cause death	99 (17.1)	105(17.4)	0.97 (0.74-1.28)

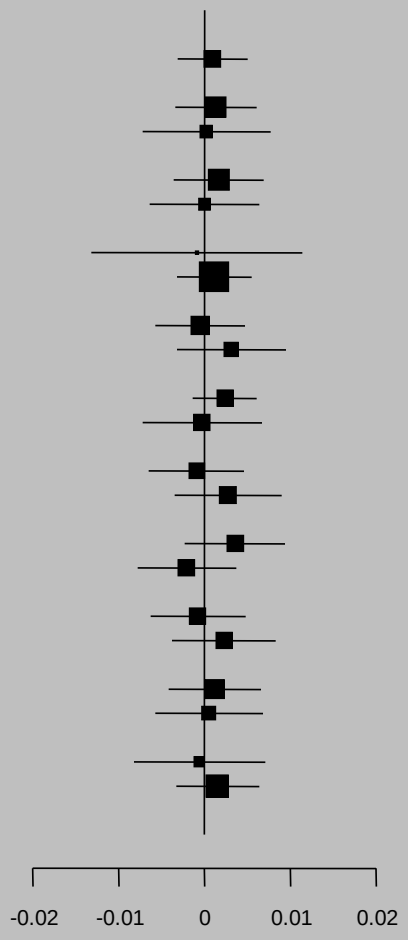
	N-3 Fatty Acids (n=585)	Placebo (n=599)	HR (95%CI)
CV death, non-fatal MI or non-fatal stroke	102 (17.4)	108 ((18.0)	0.95 (0.72-1.24)
All cause death	95 (16.2)	109 (18.2)	0.88 (0.67-1.15)

Subgroup Analysis – Glargine Arm



	Insulin Glargine - Standard LSM (95% CI)	Interaction p-value
Overall	-0.0030 (-0.0071 - 0.0011)	
Age < 65 yrs	-0.0023 (-0.0071 - 0.0024)	
Age≥ 65 yrs	-0.0045 (-0.0120 - 0.0030)	0.255
Male	-0.0031 (-0.0083 - 0.0021)	
Female	-0.0028 (-0.0092 - 0.0036)	0.686
No Diabetes	-0.0041 (-0.0164 - 0.0082)	
Diabetes	-0.0028 (-0.0072 - 0.0015)	0.671
No Prev CV Event	-0.0034 (-0.0086 - 0.0018)	
Prev CV Event	-0.0026 (-0.0090 - 0.0038)	0.973
Max IMT < Median	-0.0025 (-0.0062 - 0.0012)	
Max IMT ≥ Median	-0.0028 (-0.0097 - 0.0042)	0.179
A1c < Median	-0.0027 (-0.0083 - 0.0028)	
A1c ≥ Median	-0.0035 (-0.0097 - 0.0028)	0.162
Triglyc < Median	-0.0010 (-0.0069 - 0.0048)	
Triglyc ≥ Median	-0.0051 (-0.0109 - 0.0007)	0.674
FPG < Median	-0.0034 (-0.0089 - 0.0022)	
FPG ≥ Median	-0.0026 (-0.0086 - 0.0035)	0.221
No Statin	-0.0039 (-0.0093 - 0.0015)	
Statin	-0.0019 (-0.0081 - 0.0044)	0.229
No ACE/ARB	-0.0053 (-0.0129 - 0.0023)	
ACE/ARB	-0.0020 (-0.0068 - 0.0029)	0.891

Subgroup Analysis – N-3 Fatty Acids Arm



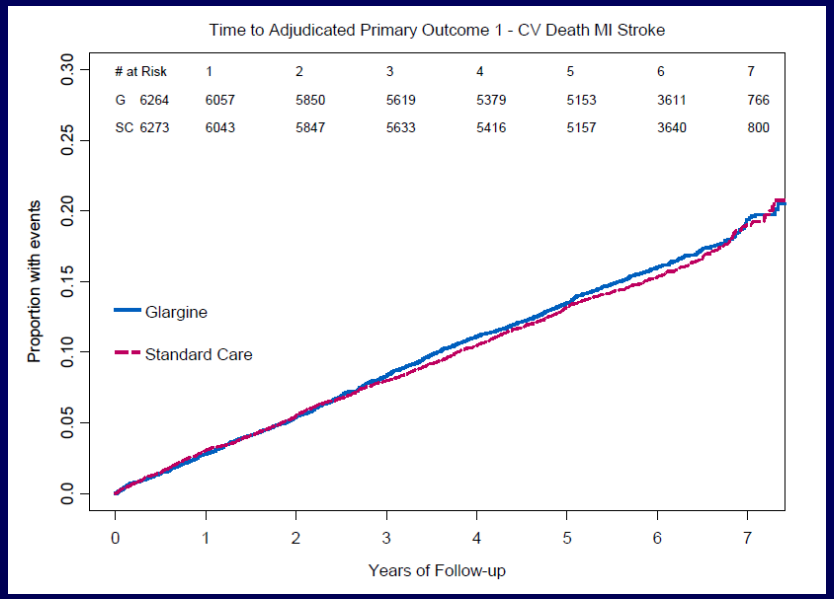
	Omega3 - Placebo LSM (95% CI)	Interaction p-value
Overall	0.0009 (-0.0031 - 0.0050)	
Age<65	0.0013 (-0.0034 - 0.0061)	
Age>=65	0.0002 (-0.0072 - 0.0077)	0.463
Male	0.0017 (-0.0036 - 0.0069)	
Female	0.0000 (-0.0064 - 0.0064)	0.707
No Diabetes	-0.0009 (-0.0132 - 0.0114)	
Diabetes	0.0011 (-0.0032 - 0.0055)	0.361
No Prev CV Event	-0.0005 (-0.0057 - 0.0047)	
Prev CV Event	0.0031 (-0.0032 - 0.0095)	0.150
Max IMT < Median	0.0024 (-0.0014 - 0.0061)	
Max IMT >= Median	-0.0003 (-0.0072 - 0.0067)	0.643
A1c < Median	-0.0009 (-0.0065 - 0.0046)	
A1c >= Median	0.0027 (-0.0035 - 0.0090)	0.395
Triglyc < Median	0.0036 (-0.0023 - 0.0094)	
Triglyc >= Median	-0.0021 (-0.0078 - 0.0037)	0.717
FPG < Median	-0.0008 (-0.0063 - 0.0048)	
FPG >= Median	0.0023 (-0.0038 - 0.0083)	0.737
No Statin	0.0012 (-0.0042 - 0.0066)	
Statin	0.0005 (-0.0057 - 0.0068)	0.648
No ACE/ARB	-0.0006 (-0.0082 - 0.0071)	
ACE/ARB	0.0015 (-0.0033 - 0.0064)	0.826

Glargin Arm: Conclusions

- ORIGIN-GRACE is the largest RCT of insulin and of N-3 FA supplements on atherosclerosis
- Insulin glargine, a basal insulin, titrated to achieve normoglycemia, was well tolerated, significantly lowered FPG, HbA1C and TG levels and had consistent effects on CIMT progression, favoring a benefit
- ORIGIN-GRACE confirms the CV safety of insulin glargine
- Although not conclusive, our study suggests a beneficial effect of insulin glargine on vascular disease progression

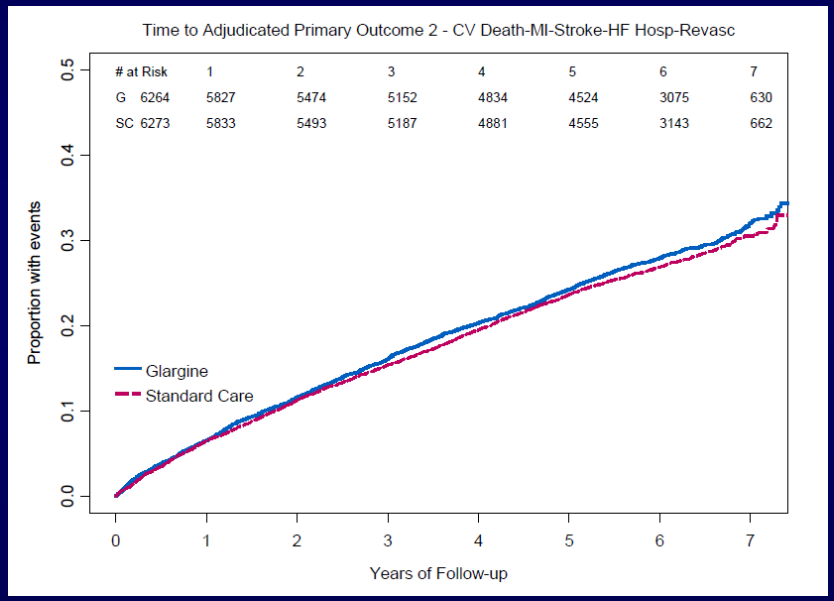
ORIGIN Trial Results

1st Co-primary: MI, Stroke, or CV Death



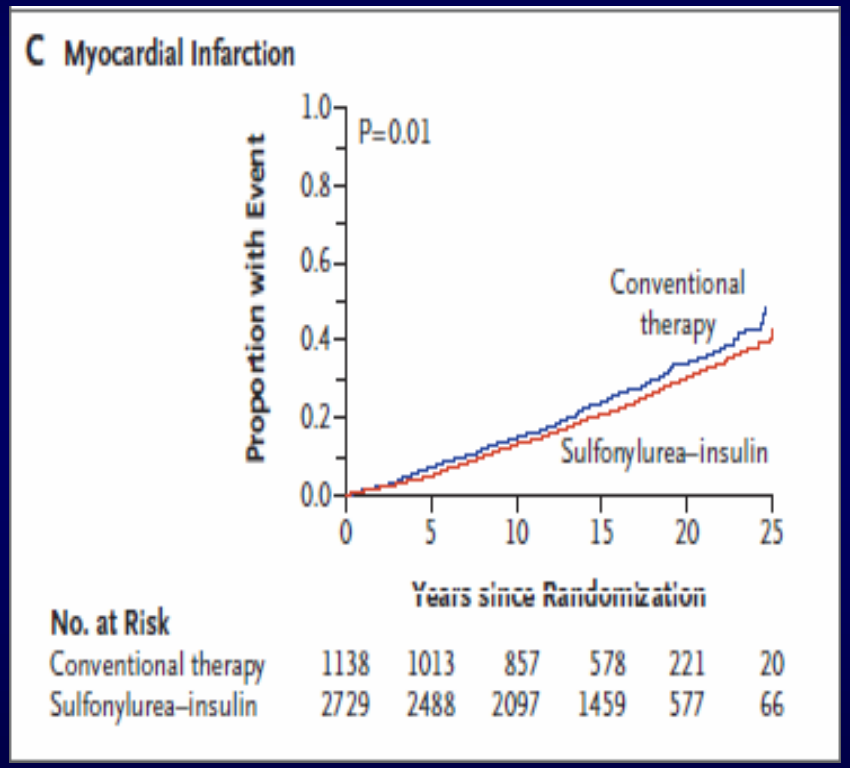
Adjusted HR = 1.02 (0.94–1.11)
P=0.63 by log-rank test

2nd Co-Primary: MI, Stroke, CV Death, Revascularization, Heart Failure

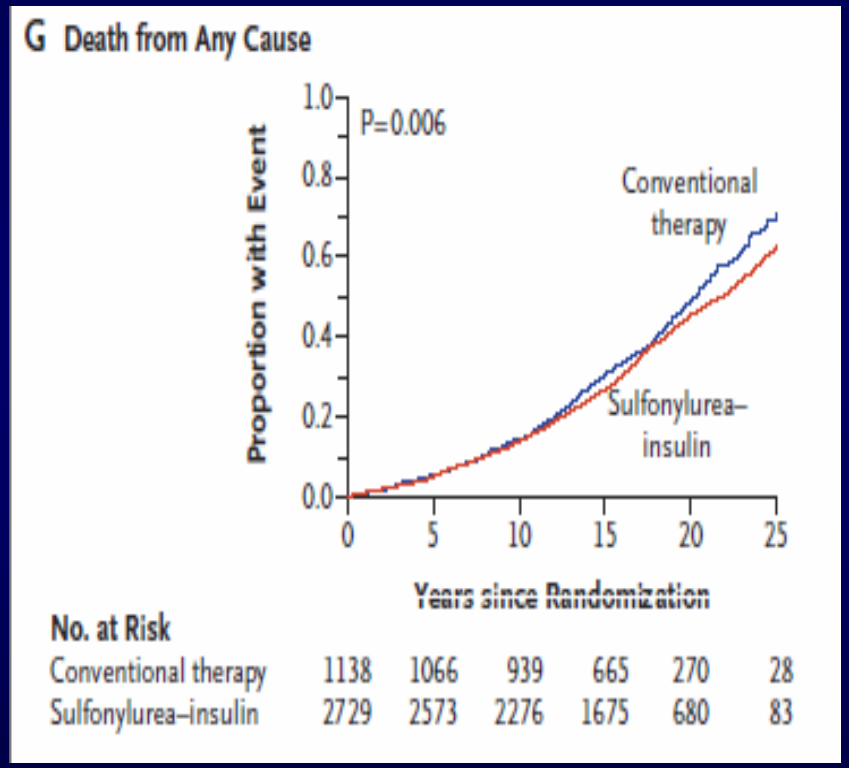


Adjusted HR = 1.04 (0.97–1.11)
P=0.27 by log-rank test

UKPDS: 10 Year Follow-up
Legacy Effect



HR= 0.85 (0.74-0.97)
p=0.01



HR= 0.87 (0.87-0.96)
p=0.007

Glargin Arm: Conclusions

- The ORIGIN-GRACE findings raise the possibility that longer-term treatment might result in CV event reduction.
- This hypothesis is currently under evaluation in the ORIGIN passive extended follow-up, the ORIGIN And Legacy Effects (ORIGINALE) study.

N-3 Fatty Acids Arm: Conclusions

- N-3 Fatty Acid supplements had a neutral effect on risk factor levels, carotid atherosclerosis and on clinical events
- It is unclear if these findings are unique to our study population and the n-3 FA supplements dose used
- Several clinical endpoint trials are still ongoing
- Our study does not address the CV effects of *dietary* fish consumption.
- The main ORIGIN trial and the GRACE-ORIGIN substudy do not support the use of N-3 FA supplement sin high-risk people with dysglycemia