# GRACE

## Glucose Reduction and Atherosclerosis Continuing Evaluation

## Atherosclerosis Substudy of the ORIGIN Trial

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**for the ORIGIN**
**and ORIGIN-GRACE Investigators**

# Disclosures

Eva Lonn

- Research grants: Astra-Zeneca, CIHR, GSK, Heart and Stroke Foundation of Canada, Merck, Novartis, Servier, Sanofi
- Consulting/ Lectures: Astra Zeneca, Merck, Novartis

Health Through Knowledge
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# Research Objectives

- To evaluate the effects of 2 interventions on carotid atherosclerosis measured by carotid intima media thickness (CIMT) in people with ***dysglycemia*** and at ***high CV risk*** :

  a) Basal insulin glargine targeting fasting normoglycemia (≤ 5.3 mM or 95 mg%),

  b) Omega-3 Fatty Acid Supplements

# Key Inclusion Criteria

- **Age ≥ 50 yrs** ***AND***
- **Dysglycemia** ***AND***
  - *EITHER* IFG or IGT or new type 2 DM by OGTT
    [i.e. FPG ≥ 6.1mmol/L (110 mg/dl); or 2 Hr PG ≥ 7.8 mmol/L (140 mg/dl)]
  - *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**

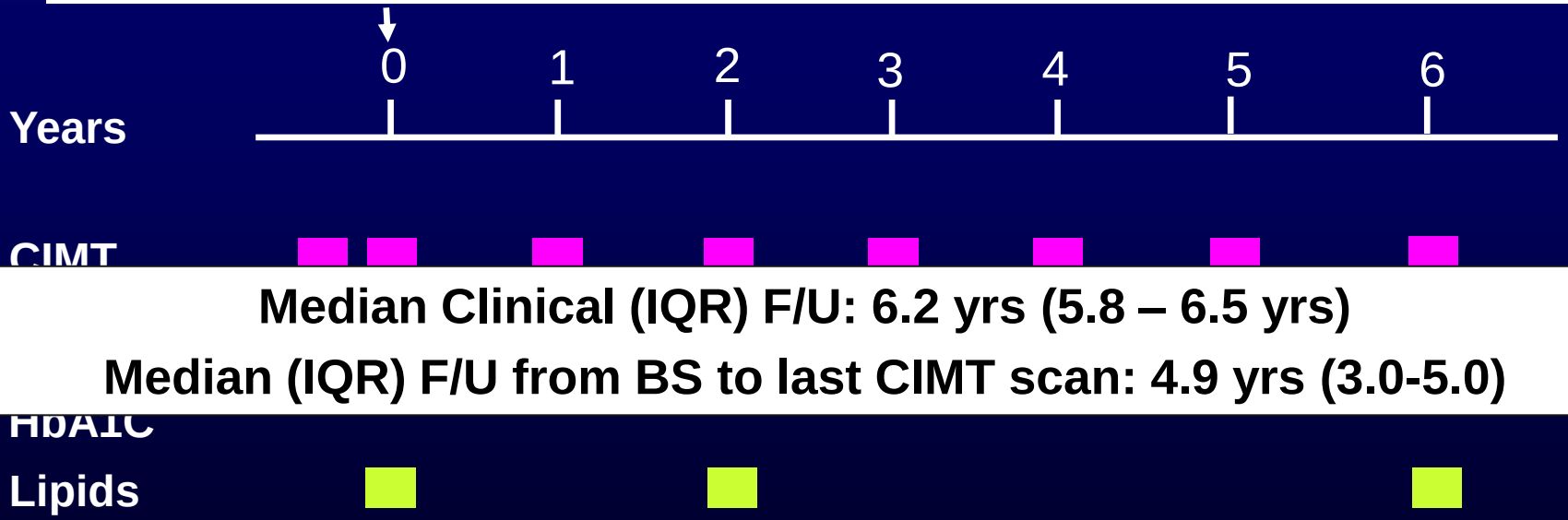
# ORIGIN-GRACE- Study Design

*2 x2 Factorial Multicenter International Trial*

**Insulin Glargine:** non-blinded design vs. standard glycemic care

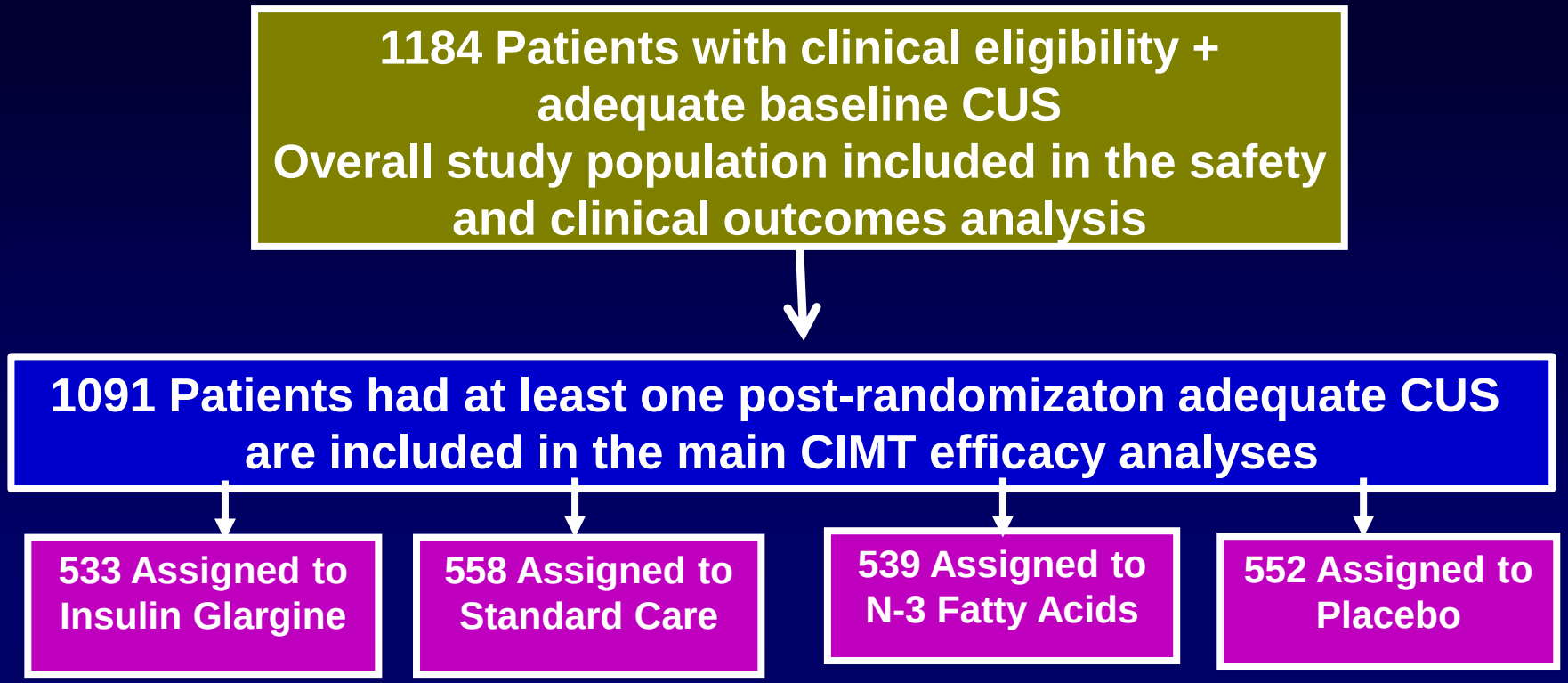
**N-3 FA:** double-blind, placebo controlled

1 g capsule contains EPA 465 mg & DHA 375 or matching placebo




Median Clinical (IQR) F/U: 6.2 yrs (5.8 – 6.5 yrs)

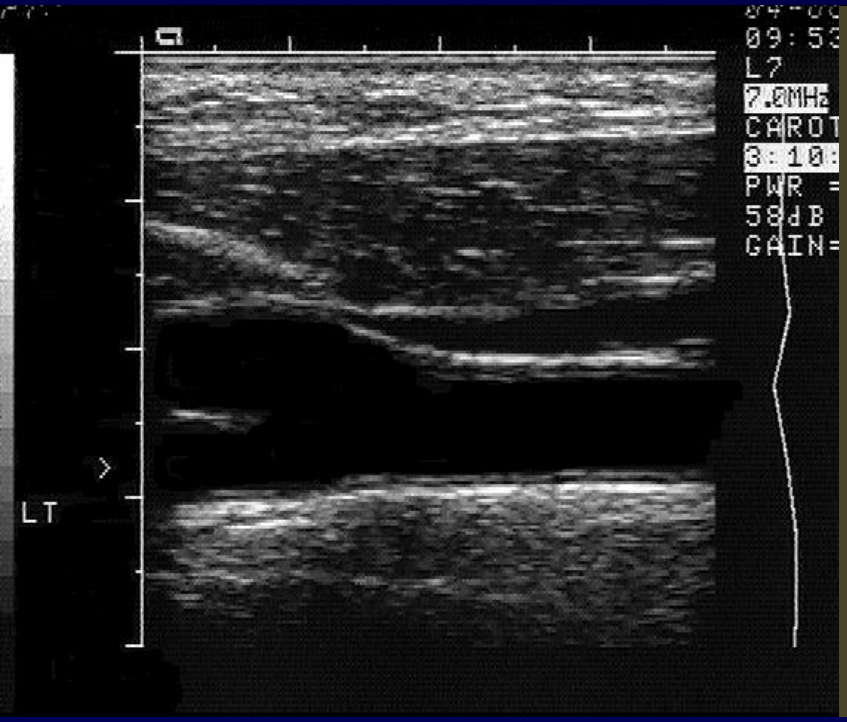
Median (IQR) F/U from BS to last CIMT scan: 4.9 yrs (3.0-5.0)

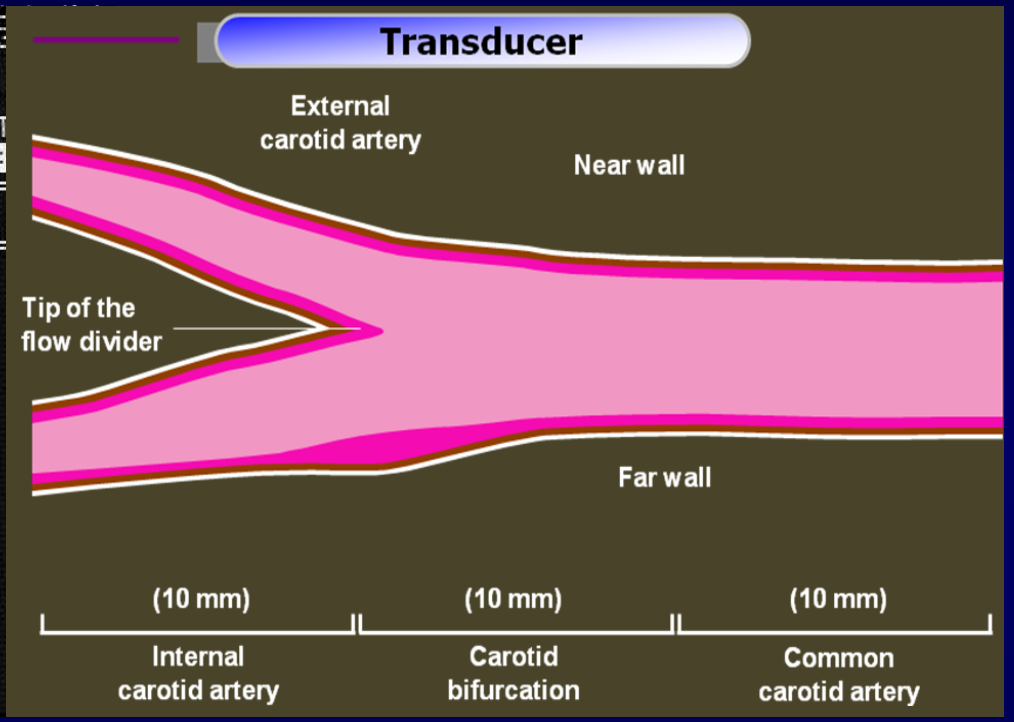



**Study Organization:**

- Investigator- initiated substudy of the ORIGIN trial
- 32 ORIGIN centers in 7 countries
- Funding: Sanofi and in kind contribution Pronova BioPharma, Norway
- Project coordination, data management, statistical analyses and Core CIMT Laboratory: Population Health Research Institute in Hamilton, Canada

# 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

# 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 |

# 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, safe, significantly lowered FPG, HbA1C and TG levels and had consistent effects on CIMT progression, favoring a benefit
- N-3 Fatty Acid supplements had a neutral effect on risk factor levels, carotid atherosclerosis and on clinical events