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)

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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 glycated 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 12612 (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.)

Diabetes and lesser degrees of dysglycemia affect two thirds of people presenting to a coronary care unit and are independent risk factors for cardiovascular (CV) events and death. However, it is not known whether glucose lowering with insulin or other therapies can reduce CV disease.

Can insulin-mediated normoglycemia reduce cardiovascular disease?

Elevated fasting plasma glucose (FPG), 2-hour post-load glucose, and/or HbA1c levels all increase the risk for incident CV events in a progressive fashion. When both fasting and post-load glucose levels are known, the latter is a better predictor of CV risk; however, studies in which the FPG is the only measure of glycemic status show a robust relationship with CV events. Thus, a meta-analysis of 17 cohort studies reported that every 1 mmol/L (18 mg/dL) increase in fasting glucose predicted a significant 23% increase in the age- and sex-adjusted risk of total ischemic heart disease, a 21% increase in the risk of stroke, and a 19% increase in the risk of CV death, regardless of diabetes status. At least 3 mechanisms may account for this relationship. First, excess glucose levels may directly harm vascular endothelium and other tissues. Second, reduced levels of insulin relative to tissue insulin sensitivity promotes mobilization of free fatty acids from adipose tissue which reduces high-density lipoproteins; increases low-density lipoproteins, intracellular fat, and insulin resistance at liver and muscle; promotes the occurrence of arrhythmias in response to ischemia; and activates cellular inflammatory processes. Indeed, a recent epidemiologic analysis found that high free fatty
acid levels were an independent risk factor for CV death. Third, both dysglycemia and CV disease may be secondary to a common antecedent risk factor.

Insulin treatment reduces inflammatory markers and improves mechanisms of vasodilation and atherogenic plasma lipid patterns. Insulin infusions to lower glucose can reduce mortality in postoperative patients in an intensive care unit and may reduce mortality after a myocardial infarction (MI). Long-term clinical trials of intensive versus conventional glucose control in type 2 diabetes in which insulin was one of the tools used to achieve glucose control were not powered to detect a CV benefit; however, they generally reported a trend toward reduced CV events. Finally, intensive insulin therapy targeting normoglycemia reduced the long-term risk of CV events by about 50% in people with type 1 diabetes.

These data suggest that insulin-mediated normoglycemia can reduce CV risk. However, no trials directly testing this possibility in people with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or early type 2 diabetes have been completed. If either the rise in glucose and/or the coincident lack of insulin effect is directly related to the increase in CV events noted above, provision of sufficient insulin to normalize the glycemic status may effectively reduce this risk.

Can ω-3 polyunsaturated FAs reduce cardiovascular death?

Essential long chain ω-3 polyunsaturated FAs (PUFA) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are not efficiently synthesized by humans and are best derived from dietary sources such as fish oils. They inhibit platelet aggregation, are anti-inflammatory, reduce blood pressure and endothelial activation, and are antiarrhythmic. Higher intakes of fish or ω-3 PUFA predict a lower incidence of coronary heart disease and death. and trials have generally reported reduced coronary mortality. However, in a recent trial in 3114 men with angina, high-dose fish oil (3 g/d) consumption increased mortality. This, and a new meta-analysis demonstrating uncertain benefits, has highlighted the need for a double-blind trial. This is especially relevant in light of recommendations to increase consumption of ω-3 PUFA.

The ORIGIN trial

The ORIGIN trial is an international multicenter randomized controlled trial of 2 different interventions in dysglycemic individuals with IFG, IGT, newly detected diabetes, or established diabetes. It is determining whether providing sufficient basal insulin (as insulin glargine) to safely achieve fasting normoglycemia reduces the incidence of fatal and nonfatal CV events more than standard glycemic approaches in people with a modest degree of glucose elevation and high CV risk. At the same time, it will determine whether ω-3 acid ethyl esters 90 reduces CV death compared to a placebo.

Subjects, materials, and methods

Eligibility

Men and women aged ≥50 years were recruited if they were at high risk for a CV event and had either (a) IFG, IGT, or newly detected diabetes (ie, an FPG ≥7.8 mmol/L [140 mg/dL] or a 2-hour plasma glucose ≥7.8 mmol/L [140 mg/dL] after a 75-g oral glucose load); or (b) established type 2 diabetes on stable therapy with 0 or 1 oral agent for ≥3 months. To be eligible, the locally measured glycated hemoglobin level of participants with established diabetes was low enough to allow investigators to add or adjust oral agents (and to minimize the likelihood that insulin would be needed) to manage diabetes during the trial in participants allocated to the control group. Thus the level had to be (a) ≤150% of the upper limit of normal for the local assay (ie, 9.0% if the upper limit of normal was 6%) for participants on no oral glucose-lowering agents; (b) ≤142% of the upper limit of normal (ie, 8.5%) for participants taking less than half-maximal doses of 1 oral agent; or (c) ≤133% of this limit for the local assay (ie, 8.0%) for participants on higher doses of 1 oral agent. Participants were deemed to be at high CV risk if there was confirmed evidence of at least one of (a) a prior MI, or stroke, or revascularization; (b) angina with documented ischemia; (c) a first morning urinary albumin/creatinine ratio >30 μg/mg; (d) evidence of left ventricular hypertrophy; (e) ≥50% stenosis of a coronary, carotid, or lower extremity artery documented angiographically; or (f) an ankle/brachial index <0.9. They also had to demonstrate their ability to self-inject insulin and check glucose. Key exclusion criteria included the use, indication for, or intolerance to insulin or PUFA; unwillingness to stop thiazolidinediones (TZDs) if allocated to glargine (as they were not approved for use with insulin in most participating countries); a glycated hemoglobin ≥5.8% of the upper limit of normal; coronary artery bypass grafting within 4 years of screening with no intervening CV event; or heart failure.

Screening and run-in

After providing informed consent, participants provided a brief history and a urine and fasting blood sample. Individuals without a history of diabetes then had a 75-g oral glucose tolerance test with local assay of the fasting and 2-hour plasma glucose to determine eligibility. Individuals identified during a hospitalization with a random glucose level ≥8 mmol/L (144 mg/dL) were deemed eligible for run-in, and glucose testing was delayed until the end of the run-in phase.
Eligible participants were taught how to administer insulin and do self-blood glucose monitoring. They were then provided with insulin pens (Optipen Pro1, Sanofi Aventis, Frankfurt, Germany) and carbohydrates containing 0.9% physiologic saline and asked to administer a volume equivalent to 4 U of insulin (ie, 0.04 mL) every evening and check capillary glucose levels every morning. A randomization visit was scheduled within 10 days.

Randomization and study intervention

Adherent participants able to administer insulin placebo and check glucose levels on at least 4 days had a brief exam; provided demographic, clinical, diet, and physical activity data; and had an electrocardiogram. Lifestyle recommendations were reviewed and they were randomized by an automated telephone randomization system (using randomly varying block sizes) according to a 2 × 2 factorial design to (a) either insulin glargine (Lantus, Sanofi Aventis) or standard approaches to glycemic control; and (b) either ω-3-acid esters 90 (Omacor 1 g [Pronova, BioPharma AS, Lysaker, Norway], containing EPA 465 mg and DHA acid 375 mg) or placebo.

Participants allocated to insulin glargine added it to whatever other glucose-lowering medication they may have been taking unless it was a TZD; in that instance, the TZD was stopped. They were instructed to inject insulin glargine in the evening and to record fasting capillary glucose levels daily until achieving target values, and then at least twice per week; more frequent measurements were at the discretion of the investigator. Participants started glargine at 2, 4, or 6 U (based on the FPG level), and were given an algorithm that promoted weekly up titration of the insulin dose (by ≥1 U/wk) targeting self-measured FPG levels between 4 mmol/L (72 mg/dL) and 5.3 mmol/L (95 mg/dL). Investigators are free to reduce oral agents if participants experience hypoglycemic episodes during insulin titration. They may also add metformin if they judge that FPG levels ≤5.3 mmol/L (95 mg/dL) cannot be achieved without symptomatic hypoglycemia. Rapid-acting insulin is the only other antihyperglycemic therapy that can be added if acceptable glycemic control cannot be achieved with maximum doses of 2 oral agents. All study physicians were instructed on the management of diabetes and provided with supporting materials; no explicit algorithm was provided due to different practice patterns in different countries.

Follow-up

All randomized participants are followed until the scheduled study end, regardless of adherence to or discontinuation of study medication for any reason. Clinical outcomes, adherence, and adverse events are ascertained and then followed every 4 months thereafter. Locally measured glycosylated hemoglobin levels are recorded at every visit starting at 2 months in people with diabetes and at 2, 4, 8 months, and annually for others. Blood is stored centrally in subsets of participants at 2 years and study end.

Outcomes

For the glargine arm, the 2 coprimary outcomes are composites of major CV events. These are (a) incident CV death (ie, any death for which no noncardiovascular cause has been identified), nonfatal MI diagnosed on the basis of the clinical presentation, elevated cardiac markers and/or new electrocardiographic changes, or nonfatal stroke diagnosed on the basis of clinical presentation and imaging; and (b) these events plus a revascularization procedure or hospitalization for heart failure. Secondary outcomes include (a) each component of the primary outcomes; (b) all-cause mortality; (c) microvascular events (either kidney or eye disease); or (d) new type 2 diabetes in participants without diabetes at baseline (see below). For the ω-3-acid ester 90 arm, the primary outcome is CV death. Secondary outcomes include (a) arrhythmic death (ie, sudden unexpected death, death due to documented arrhythmia, or resuscitated cardiac arrest); (b) all-cause death; or (c) incident CV death, nonfatal MI, or nonfatal stroke; and tertiary outcomes include any secondary outcome for the glargine arm. Other outcomes for both arms include angina; amputations for ischemia; hospitalizations; cognitive function; and reversion of IFG or IGT to normoglycemia. All outcomes are ascertained at every visit and adjudication is based on the information provided and supporting documentation. It is done by an adjudication committee whose members are unaware of participant allocation and who assess all of the available data and documentation with reference to preestablished criteria developed and finalized by this committee.

Episodes of symptomatic hypoglycemia are recorded at each visit and classified as either confirmed by a recorded capillary glucose <3 mmol/L (54 mg/dL) or unconfirmed. Severe hypoglycemia is defined as the need for assistance from another individual due to symptoms or signs of hypoglycemia and either prompt recovery...
with glucose or glucagon or a documented capillary glucose ≤ 2.0 (36 mg/dL).

Participants without diabetes are deemed to have developed diabetes if (a) diagnosed by any physician, an antihyperglycemic agent has been provided, and there is at least 1 supportive glucose level; (b) 2 consecutive FPG levels are ≥7 mmol/L (126 mg/dL) during the study; or (c) an oral glucose tolerance test done in individuals who have not developed diabetes by the end of the study indicates that either the FPG level is ≥7 mmol/L or the 2-hour glucose level is ≥11.1 mmol/L (200 mg/dL).

Subsets of consenting individuals in selected sites were enrolled in substudies assessing the effect of the interventions on cognitive function; cardiac rhythm; autonomic function; erectile dysfunction; bone density; ultrasonographically measured carotid atherosclerosis; left ventricular mass and function; β-cell function; and biochemical measurements.

Trial organization

The ORIGIN trial was designed by the ORIGIN Steering Committee through the ORIGIN Project Office based at the Population Health Research Institute in Hamilton, Ontario Canada. This committee is responsible for all aspects of trial management including collecting and cleaning all data, dealing with all protocol-related issues, monitoring and optimizing adherence to both interventions, adjudicating outcomes, auditing the progress of the study, identifying and providing logistical support for the Independent Data Monitoring Committee (IDMC—see below), and determining, executing, and publishing the final study analysis. Funding, regulatory support, site monitoring, drug distribution, and insulin glargine (Lantus) are provided by Sanofi Aventis and ω-3–acid ethyl esters 90 (Omacor) study drug is provided by Pronova Biocare AS. Each sponsor has 1 representative on the Steering Committee.

Table I. Detectable risk reductions in the ORIGIN Trial

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Outcome</th>
<th>Estimated event rate *</th>
<th>α Error</th>
<th>Detectable RRR with N=12612 †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>1st co-primary</td>
<td>15%</td>
<td>.044</td>
<td>13.5%</td>
</tr>
<tr>
<td>glargine</td>
<td>19%</td>
<td>.044</td>
<td>11.7%</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>23%</td>
<td>.044</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>co-primary</td>
<td>30%</td>
<td>.01</td>
<td>10.3%</td>
<td></td>
</tr>
<tr>
<td>ω-3 PUFA</td>
<td>Primary</td>
<td>38%</td>
<td>.01</td>
<td>8.6%</td>
</tr>
<tr>
<td></td>
<td>46%</td>
<td>.01</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9%</td>
<td>.05</td>
<td>17.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11%</td>
<td>.05</td>
<td>15.8%</td>
<td></td>
</tr>
</tbody>
</table>

* Assumeshas mean follow-up period of up to 5 years.
† Assumes 90% power.

Table II. Clinical characteristics of randomized participants in ORIGIN

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>n (%) or mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized/screened, n</td>
<td>12612/15356</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>63.6 (7.84) y</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>4402 (34.90) %</td>
</tr>
<tr>
<td>No. in each geographical region (%)</td>
<td>1314 (10.4) %</td>
</tr>
<tr>
<td>North America</td>
<td>3853 (30.6) %</td>
</tr>
<tr>
<td>South America</td>
<td>3752 (29.8) %</td>
</tr>
<tr>
<td>Western Europe</td>
<td>2383 (18.9) %</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>390 (3.1) %</td>
</tr>
<tr>
<td>China</td>
<td>718 (5.7) %</td>
</tr>
<tr>
<td>Australia</td>
<td>202 (1.6) %</td>
</tr>
<tr>
<td>With &gt;8 y of education, n (%)</td>
<td>8108 (64.3) %</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>1563 (12.4) %</td>
</tr>
<tr>
<td>Current alcohol, n (%)</td>
<td>2870 (22.8) %</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10824 (85.8) %</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>8765 (69.5) %</td>
</tr>
<tr>
<td>Known albuminuria, n (%)</td>
<td>1942 (15.4) %</td>
</tr>
<tr>
<td>With previous CVD, n (%)</td>
<td>8374 (66.4) %</td>
</tr>
<tr>
<td>With previous revascularization, n (%)</td>
<td>4139 (32.8) %</td>
</tr>
<tr>
<td>With neuropathy, n (%)</td>
<td>1215 (9.6) %</td>
</tr>
</tbody>
</table>

CVD Medications

- Statins
- Fibrates
- ACE Inhibitors
- ARBs
- Thiazides
- Other BP drugs
- ASA
- Other antiplatelet

Body mass index

SBP/DBP

83.3 (11.7) mm Hg

ABI

1.15 (0.21)

Waist/hip

Males

1.0 (0.30)

Females

0.91 (0.34)

Lipid values

LDL

2.94 (0.98) mmol/L

[113 (35) mg/dL]

HDL

1.19 (0.32) mmol/L

[46 (12) mg/dL]

Cholesterol

4.85 (1.09) mmol/L

[187 (42) mg/dL]

Triglycerides

1.74 (0.86) mmol/L

[158 (78) mg/dL]

Abnormal ECG

8095 (64.2) %

ABI, Ankle/brachial index; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ASA, acetylsalicylic acid; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

* ≥ 3 drinks per week.
† History of MI or stroke or angina with documented ischemic changes or unstable angina or other coronary disease at or before randomization.

Statistical analyses and power

Efficacy will be analyzed using an intent-to-treat approach, in which all participants in their randomly assigned treatment group will be included, regardless of adherence. It is assumed that any effect of the factorial
The ORIGIN Trial Investigators

Results

Between September 2003 and December 2005, 578 clinical sites in 40 countries screened 15,374 individuals and randomized 12,612 participants. The ratio of screened to randomized participants was 1.3:1. Of those randomized, 81.9% (n = 10,326) had previously diagnosed diabetes, 6.3% (n = 788) had biochemical evidence suggesting possible diabetes, and 11.5% (n = 1454) had either IFG or IGT. The mean FPG was 7.3 mmol/L (132 mg/dL) and the mean glycated hemoglobin was 6.5%. Baseline characteristics are shown in Tables II and III.

Discussion

The ORIGIN trial is determining whether insulin glargine (Lantus)-mediated normoglycemia reduces CV events more than standard approaches to managing glycemia in 12,612 high-risk individuals with IFG, IGT, newly detected, or relatively well-controlled diabetes. It targets normoglycemia with only 1 daily insulin injection daily; promotes self-titration; and measures both benefits and harms. Moreover, it is studying a population of individuals whose modest degree of dysglycemia is typical of most CV patients and not just those with diabetes. Because baseline glycated hemoglobin levels are ≤9%, and because 18% of participants did not have preexisting diabetes, the results will be broadly applicable to the majority of dysglycemic individuals at high risk for CV disease. Indeed, this is currently the only trial assessing the insulin replacement therapy in modestly dysglycemic ambulatory individuals; other trials are using a variety of pharmacologic approaches to glucose lowering and are restricted to individuals with established diabetes.39

The rapid rate of recruitment and high ratio of screened to randomized ORIGIN participants are likely due to the high prevalence of dysglycemia in individuals with CV disease. This also suggests that the commonly held perception that people will refuse insulin therapy until other glucose-lowering therapies are ineffective may be wrong, at least in situations where a case can be made that such therapy may have survival benefits. Thus, if the insulin glargine arm of the study is positive, it is likely that insulin-mediated normoglycemia may become an acceptable form of CV disease prevention.

The ORIGIN trial is also determining whether a pharmaceutical ω-3 PUFA formulation (Omacor) reduces CV death in dysglycemic individuals. If positive, it will strongly support current recommendations that people at risk for CV events should have a high ω-3 PUFA intake and/or increase their intake of fatty fish.

Both arms of the ORIGIN trial are therefore testing novel approaches to CV prevention in a high-risk population, for which there is inconsistent evidence for efficacy.

Table III. Glycemic characteristics of randomized participants in ORIGIN

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>n (%) or mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established diabetes</td>
<td>10,334 (81.9) %</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>5.41 (6.0) y</td>
</tr>
<tr>
<td>Newly detected diabetes</td>
<td>788 (6.3) %</td>
</tr>
<tr>
<td>IFG or IGT</td>
<td>1,454 (11.5) %</td>
</tr>
<tr>
<td>Isolated IFG</td>
<td>331 (2.6) %</td>
</tr>
<tr>
<td>Isolated IGT</td>
<td>678 (5.4) %</td>
</tr>
<tr>
<td>Both IGT and IFG</td>
<td>445 (3.5) %</td>
</tr>
<tr>
<td>Dysglycemia status uncertain</td>
<td>17 (0.13) %</td>
</tr>
<tr>
<td>IFG (ADA definition)†</td>
<td>348 (2.72) %</td>
</tr>
<tr>
<td>Glycated hemoglobin</td>
<td>6.49 (0.97) %</td>
</tr>
<tr>
<td>FPG</td>
<td>7.32 (2.0) mmol/L</td>
</tr>
<tr>
<td>2-h plasma glucose in 2247 people without established diabetes</td>
<td>[132 (36) mg/dl]</td>
</tr>
<tr>
<td>Antihyperglycemic medications at screening</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>3,434 (27.2) %</td>
</tr>
<tr>
<td>Insulin secretagogue</td>
<td>3,871 (30.7) %</td>
</tr>
<tr>
<td>α Glucosidase inhibitor</td>
<td>102 (0.8) %</td>
</tr>
<tr>
<td>TZD</td>
<td>61 (0.5) %</td>
</tr>
</tbody>
</table>

ADA, American Diabetes Association.
† This includes people with IFG according to the American Diabetes Association definition of a fasting plasma glucose value of 5.6 to 6.9 mmol/L (100-110 mg/dL) as well as 17 people who had isolated IFG using the ADA criteria.

Arms is independent. If there is no statistical interaction, analyses of each arm will be stratified for the other arm’s allocation, previous CV event, and diabetes status at randomization, and analyzed at the margins. Time-to-event curves will be constructed for each primary outcome and compared with log-rank tests; hazard ratios and 95% CIs will be estimated using Cox regression.

For both arms of the study, statistical significance will be claimed if the overall P value is ≤ .05. For the 2 co-primary outcomes in the glargine arm, statistical significance will be claimed if the P value for the first co-primary outcome is ≤ .044 and/or for the second co-primary outcome is ≤ .01; the nonadditivity of these type 1 error rates reflects the correlation between these 2 outcomes and assumes that the first co-primary outcome will comprise 50% of the events in the second co-primary outcome.

An IDMC reviews the 2 planned interim analyses. The IDMC may recommend an extension in follow-up duration to maintain study power; alternatively, if the analyses show a clear benefit, the IDMC can recommend early termination. If the results are clear for one intervention, but not for the other, the study will continue to evaluate the other intervention.

The study will continue until 1,771 first co-primary events occur and 3,608 second co-primary events occur. Table 1 lists the detectable relative risk reductions with 90% power and the sample size of 12,612 participants for each arm’s primary outcomes, assuming different control rates of these outcomes and mean study duration between 4.5 and 5 years.
References


Appendix A

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