Cardiovascular and Other Outcomes Postintervention With Insulin Glargine and Omega-3 Fatty Acids (ORIGINALE)

*ORIGIN Trial Investigators**

DOI: 10.2337/dc15-1676

OBJECTIVE

The Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial reported neutral effects of insulin glargine on cardiovascular outcomes and cancers and reduced incident diabetes in high cardiovascular–risk adults with dysglycemia after 6.2 years of active treatment. Omega-3 fatty acids had neutral effects on cardiovascular outcomes. The ORIGIN and Legacy Effects (ORIGINALE) study measured posttrial effects of these interventions during an additional 2.7 years.

RESEARCH DESIGN AND METHODS

Surviving ORIGIN participants attended up to two additional visits. The hazard of clinical outcomes during the entire follow-up period from randomization was calculated.

RESULTS

Of 12,537 participants randomized, posttrial data were analyzed for 4,718 originally allocated to insulin glargine (2,351) versus standard care (2,367), and 4,771 originally allocated to omega-3 fatty acid supplements (2,368) versus placebo (2,403). Posttrial, small differences in median HbA_{1c} persisted (glargine 6.6% [49 mmol/mol], standard care 6.7% [50 mmol/mol], *P* = 0.025). From randomization to the end of posttrial follow-up, no differences were found between the glargine and standard care groups in myocardial infarction, stroke, or cardiovascular death (1,185 vs. 1,165 events; hazard ratio 1.01 [95% CI 0.94–1.10]; *P* = 0.72); myocardial infarction, stroke, cardiovascular death, revascularization, or hospitalization for heart failure (1,958 vs. 1,910 events; 1.03 [0.97–1.10]; *P* = 0.38); or any cancer (524 vs. 529 events; 0.99 [0.88–1.12]; *P* = 0.91) or between omega-3 and placebo groups in cardiovascular death (688 vs. 700; 0.98 [0.88–1.09]; *P* = 0.68) or other outcomes.

CONCLUSIONS

During >6 years of treatment followed by >2.5 years of observation, insulin glargine had neutral effects on health outcomes and salutary effects on metabolic control, whereas omega-3 fatty acid supplementation had no effect.

Type 2 diabetes is a strong, independent risk factor for myocardial infarction, stroke, premature death, a variety of cancers, and other serious health outcomes. Possible explanations for this are prolonged exposure to elevated glucose levels, insulin resistance, endogenous hyperinsulinemia, and obesity. Observational studies also suggested that exogenous insulin use may provoke these outcomes. However, the

Corresponding author: Zubin Punthakee, zubin.punthakee@mcmaster.ca.

Received 30 July 2015 and accepted 9 November 2015.

Clinical trial reg. no. NCT00069784, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-1676/-/DC1.

**The ORIGIN Trial Investigators are listed in the Supplementary Data.*

large, prospective Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial showed that the addition of exogenous basal insulin (as insulin glargine) sufficient to normalize fasting glucose levels had a neutral effect on cardiovascular events, cancers, and other serious outcomes compared with standard care without insulin in patients with dysglycemia at high risk for cardiovascular disease and reduced the incidence of diabetes in participants without diabetes at randomization (1).

Omega-3 fatty acid supplements are widely taken for their putative cardioprotective effects (2). However, the finding that random allocation to 1 g omega-3 fatty acid supplements daily versus placebo had a neutral effect on cardiovascular death and other serious health outcomes in the ORIGIN trial did not support such supplementation (3).

Several type 2 diabetes trials have reported that the health effects of interventions often persist for several years after the active intervention period (4–7). Analyses of such legacy effects can provide further information about the long-term health effects of a time-limited intervention. The aim of the ORIGIN and Legacy Effects (ORIGINALE) study was to determine the effects of a median 6.2 years exposure to insulin glargine versus standard care or omega-3 fatty acids versus placebo on cardiovascular and other outcomes during an additional median follow-up of 2.7 years.

RESEARCH DESIGN AND METHODS

The design and main results of ORIGIN have been published previously (1,3,8). Briefly, 12,537 people aged ≥50 years with impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes were included if they had additional risk factors for cardiovascular disease. Through a 2 × 2 factorial design, participants were randomized to the addition of one daily injection of insulin glargine targeting a fasting plasma glucose of ≤5.3 mmol/L (95 mg/dL) versus standard care and to n-3 polyunsaturated fatty acid supplement 1 g daily (omega-3) versus placebo.

The trial finished in December 2011, and subsequent use of all medications and supplements was at the discretion of the patients' usual health-care providers, except insulin glargine was discontinued for all patients without diabetes at the end of the trial. Funding was available to continue follow-up until May 2014. All research sites were invited to continue noninterventional posttrial follow-up of participants, and those that agreed obtained local ethics approval. ORIGIN participants (or family members in the case of death since the last study visit) were contacted between July 2012 and May 2014 to ascertain their clinical status. Participants providing informed consent were invited to attend up to two visits during that period, the first at the time of initial contact and the second between February and May 2014. Participants whose first visit was completed after November 2013 did not need a second visit. At study visits, clinical outcomes, episodes of severe hypoglycemia requiring third-party assistance or of any symptomatic hypoglycemia (1), medication use, blood pressure, anthropometry, HbA_{1c}, and serum creatinine were assessed. If the participant could not attend in person, as much data as possible were gathered for that visit by telephone or from the medical record.

Outcomes

Apart from the composite microvascular outcome and incident diabetes, the ORIGINALE outcomes were identical to those of the ORIGIN trial. The two coprimary composite outcomes for the glargine versus standard care comparison were death from cardiovascular causes or myocardial infarction or stroke and any of these three outcomes or hospitalization for heart failure or carotid, coronary, or peripheral revascularization. The primary outcome for the omega-3 versus placebo comparison was death from cardiovascular causes. Because urine specimens were not collected during the ORIGINALE study, the microvascular composite outcome measured during the ORIGIN trial (death due to renal failure, dialysis, doubling of serum creatinine, treated diabetic retinopathy, or progression of albuminuria) (1) could not be measured. Instead, a clinical microvascular outcome that excluded albuminuria progression but retained all of the other elements of the composite outcome was used. Incident diabetes among participants without diabetes at randomization included a new diabetes diagnosis during the ORIGIN trial based on either oral glucose tolerance tests or other criteria (1). A broader definition included possible but unconfirmed diabetes (i.e., diabetes diagnosed or treated by a nonstudy physician during the trial without documented confirmation) (1). Oral glucose tolerance tests were not performed during posttrial follow-up. Instead, a diagnosis of diabetes during this phase was based on either HbA_{1c} ≥6.5% (48 mmol/mol) or the new use of any glucose-lowering drugs. All events were verified by ensuring that they were consistent with the same event definition criteria used during the ORIGIN trial (1,3).

Statistical Analysis

SAS software was used for analyses according to a prespecified plan finalized before the review of any data by original treatment group. The nominal level of significance was $P < 0.05$, with no adjustments made for multiple testing. All data were analyzed from the time of randomization until the first occurrence of the relevant event, whether it occurred during the active treatment phase or the posttrial follow-up phase. Data for each participant were censored at the time of the relevant event, death, or last contact. Kaplan-Meier curves were plotted and comparisons made using stratified log-rank tests. Hazard ratios (HRs) were calculated based on Cox regression stratified by allocation in the other factorial arm, baseline diabetes status, and baseline history of cardiovascular events. As in the original ORIGIN analyses, for outcomes with fewer than five events in a stratum, Cox regressions treating these three factors as covariates were used (1). For incident diabetes and hypoglycemia, odds ratios (ORs) were calculated, and comparisons were made using Cochran-Mantel-Haenszel tests stratified by allocation to omega-3 or placebo and baseline history of cardiovascular events. Participants were analyzed according to the groups to which they were randomized.

Some sites were unable to include all their surviving participants in ORIGINALE. Participants who agreed to ORIGINALE follow-up may have differed from those who did not, and that may have depended on whether they had been allocated to active or control therapy. This possibility was mitigated by a decision made before data were analyzed to

restrict the posttrial data included in the primary analyses of each of the two factorial arms to only those participants from sites that were able to follow at least 80% of the surviving participants in both treatment groups. Two sensitivity analyses were also conducted. The first included posttrial data from all participants, and the second included all investigator-reported events during the posttrial follow-up phase, regardless of whether they met all the prespecified diagnostic criteria.

RESULTS

Insulin Glargine Versus Standard Care

Supplementary Fig. 1 shows the disposition of the 12,537 participants allocated to insulin glargine or standard care. Of 10,535 participants alive and eligible for posttrial follow-up, 5,869 had posttrial data, and 4,718 were included in the primary analysis. Of these, 293 (6%) were reported dead at the time of the first posttrial contact, 665 (14%) were alive but provided no further information, and 3,760 (80%) consented to further evaluation. A total of 11,911 person-years of posttrial follow-up were added over a median of 2.7 years. Thus, the primary analysis of ORIGINALE included a median of 6.7 years and 85,928 person-years of follow-up from randomization.

Characteristics of the 4,718 participants included in the posttrial follow-up were compared with the remaining 5,817 eligible participants not included in the posttrial follow-up (Supplementary Table 1). Posttrial follow-up participants were older and less likely to be female and had more baseline cardiovascular disease overall and myocardial infarctions but fewer strokes, less severe dysglycemia and use of glucose-lowering medications, and a more favorable lipid profile with more statin use. Comparison of the participants randomized to insulin glargine or standard care who continued in the posttrial follow-up showed no important differences in baseline characteristics (Table 1).

Event rates during the trial period, the posttrial follow-up period, and overall are shown in Supplementary Table 2. The incidence of both coprimary outcomes was no different for the insulin glargine group versus the standard care group. For the composite of myocardial infarction, stroke, or death from cardiovascular causes, 1,185 of 6,264 insulin glargine participants (18.9%) and 1,165 of 6,273 standard care participants (18.6%) experienced an event (HR 1.01 [95% CI 0.94–1.10]; $P = 0.72$), and for the expanded composite outcome that also included revascularization or hospitalization for heart failure, 1,958 of 6,264 insulin glargine participants (31.3%) and 1,910 of 6,273 standard care participants (30.4%) experienced an event (1.03 [0.97–1.10]; $P = 0.38$) (Fig. 1 and Supplementary Fig. 2). There were also no differences in the rates of clinical microvascular outcomes (221 of 6,264 [3.5%] vs. 249 of 6,273 [4.0%]; 0.89 [0.74–1.07]; $P = 0.20$), total mortality (1,136 of 6,264 [18.1%] vs. 1,158 of 6,273 [18.5%]; 0.98 [0.90–1.06]; $P = 0.63$), or any of the other cardiovascular outcomes (all $P > 0.17$) or any cancer (524 of 6,264 [8.4%] vs. 529 of 6,273 [8.4%]; 0.99 [0.88–1.12]; $P = 0.91$) (Fig. 1 and Supplementary Fig. 2). These findings were unchanged in sensitivity analyses that included all participants and that included events that did not meet all the prespecified diagnostic criteria (data not shown). No differences in the effect of insulin glargine on the coprimary outcomes among various subgroups (Supplementary Figs. 3 and 4) were found.

Among participants without diabetes at baseline, diabetes was diagnosed at some point during the whole study period in 278 of 737 (37.7%) randomized to insulin glargine and 300 of 719 (41.7%) randomized to standard care (OR 0.85 [95% CI 0.69–1.04]; $P = 0.12$). When participants with possible but unconfirmed diabetes were added, the numbers were 304 (41.2%) in the insulin glargine group and 343 (47.7%) in the standard care group (0.77 [0.63–0.95]; $P = 0.014$) (Fig. 2).

The use of medications over the course of the trial and posttrial follow-up is shown in Table 2. At the end of posttrial follow-up, 957 of 1,873 participants (51%) allocated to the insulin glargine group versus 286 of 1,887 (15%) allocated to the standard care group were taking a basal insulin ($P < 0.001$), and 386 of 1,873 (21%) allocated to the insulin glargine group versus 449 of 1,887 (24%) allocated to the standard care group were not taking any glucose-lowering agents ($P = 0.019$). At this time, median HbA_{1c} (interquartile range) levels in participants allocated to the insulin glargine group were lower than in those allocated to the standard care group (6.55% [6.00–7.40%] [48.1 (42.1–57.4) mmol/mol] vs. 6.70% [6.00–7.50%] [49.7 (42.1–58.5) mmol/mol]; $P = 0.025$). There was no effect on blood pressure or renal function, and the small, but significant difference in weight at the end of ORIGIN (greater with glargine) did not persist in posttrial follow-up (Supplementary Table 3). The proportion of participants experiencing at least one hypoglycemic event at some point during the whole study period was higher in the glargine group than in the standard care group for both severe (366 of 6,264 [5.8%] vs. 119 of 6,273 [1.9%]; $P < 0.001$) and nonsevere (3,611 of 6,264 [57.6%] vs. 1,633 of 6,273 [26.0%]; $P < 0.001$) hypoglycemia (Supplementary Table 2).

Omega-3 Fatty Acid Supplement Versus Placebo

Supplementary Fig. 5 shows the disposition of the 12,536 participants allocated to the omega-3 fatty acid supplement or placebo. Of the 5,869 participants who provided posttrial data, 4,771 were included in the primary analysis. These participants differed from the 4,718 analyzed for the glargine comparison because sites that followed comparable numbers of participants in both arms of one intervention did not necessarily follow comparable numbers in both arms of the other intervention. Of the 4,771 participants, 287 (6%) were reported dead at the time of posttrial contact, 696 (15%) were alive but provided no further information, and 3,788 (79%) consented to further evaluation. A total of 12,064 person-years of posttrial follow-up were added over a median of 2.7 years. The primary analysis for omega-3 versus placebo included 85,901 person-years over a median of 6.9 years.

Supplementary Table 1 shows that compared with those who did not participate in posttrial follow-up, the posttrial follow-up participants were minimally older, more were male and had a history of myocardial infarction, but fewer had a history of stroke or hypertension. They had lesser degrees of dysglycemia and more-favorable lipid profiles and were using fewer glucose-lowering medications but more statins and antiplatelet agents. However, no important differences were found

Table 1—Characteristics at randomization of participants in posttrial follow-up

	Glargine (n = 2,351)	Standard care (n = 2,367)	P value	Omega-3 (n = 2,368)	Placebo (n = 2,403)	P value
Demographic and clinical characteristics						
Age (years)	63.1 (7.6)	63.3 (7.5)	0.27	63.0 (7.4)	63.3 (7.6)	0.18
Female sex	747 (32)	825 (35)	0.025	786 (34)	820 (34)	0.49
Prior cardiovascular event	1,389 (59)	1,372 (58)	0.44	1,387 (59)	1,405 (59)	0.93
Prior myocardial infarction	866 (37)	853 (36)	0.57	860 (36)	881 (37)	0.81
Prior stroke	223 (9.5)	213 (9.0)	0.56	227 (9.6)	231 (9.6)	0.98
Hypertension	1,799 (77)	1,792 (76)	0.51	1,781 (75)	1,843 (77)	0.24
Current smoker	267 (11)	271 (11)	0.92	267 (11)	288 (12)	0.45
Any albuminuria	368 (16)	355 (15)	0.53	361 (15)	353 (15)	0.59
Ankle-brachial index ≤0.9	127 (5.6)	153 (6.7)	0.12	152 (6.6)	153 (6.6)	0.99
Glycemic characteristics						
Diabetes with use of oral diabetes drugs	1,247 (53)	1,224 (52)	0.35	1,269 (54)	1,299 (54)	0.73
Diabetes with no use of diabetes drugs	565 (24)	591 (25)	0.46	553 (23)	544 (22)	0.56
New diabetes	181 (7.7)	194 (8.2)	0.53	185 (7.8)	199 (8.3)	0.55
IGT or IFG	357 (15)	358 (15)	0.95	361 (15)	360 (15)	0.80
Duration of diabetes (years)	5.22 (5.95)	4.99 (5.60)	0.22	5.05 (5.58)	5.25 (6.01)	0.27
Fasting glucose (mmol/L)	7.00 (6.10–8.17)	6.90 (6.10–8.16)	0.22	6.90 (6.10–8.10)	6.94 (6.10–8.20)	0.62
HbA_{1c} (%)	6.38 (5.80–7.06)	6.28 (5.73–7.01)	0.10	6.30 (5.78–7.06)	6.34 (5.80–7.08)	0.55
HbA_{1c} (mmol/mol)	46.2 (39.9–53.7)	45.1 (39.1–53.1)	0.10	45.4 (39.7–53.7)	45.8 (39.9–53.9)	0.55
Glycemic drugs						
Metformin	594 (25)	585 (25)	0.66	576 (24)	627 (26)	0.16
Sulfonylurea	615 (26)	606 (26)	0.66	642 (27)	651 (27)	0.99
Other	41 (1.7)	48 (2.0)	0.47	56 (2.4)	35 (1.5)	0.022
Nonglycemic cardiovascular risk factors						
Systolic blood pressure (mmHg)	145 (20)	145 (21)	0.74	145 (21)	145.78 (21)	0.17
Diastolic blood pressure (mmHg)	84 (11)	84 (11)	0.96	84 (11)	84 (12)	0.28
Weight (kg)	84.1 (16.4)	85.0 (17.3)	0.068	83.8 (17.1)	83.6 (16.6)	0.71
BMI (kg/m^2)	29.7 (5.0)	30.2 (5.3)	0.002	29.7 (5.2)	29.9 (5.2)	0.44
Waist-to-hip ratio						
Men	0.99 (0.10)	0.99 (0.09)	0.89	0.99 (0.08)	0.99 (0.10)	0.25
Women	0.91 (0.09)	0.91 (0.09)	0.39	0.90 (0.09)	0.91 (0.09)	0.21
Total cholesterol (mmol/L)	4.85 (1.18)	4.81 (1.17)	0.18	4.80 (1.16)	4.84 (1.20)	0.23
LDL cholesterol (mmol/L)	2.83 (1.02)	2.79 (1.00)	0.19	2.79 (0.99)	2.83 (1.02)	0.20
HDL cholesterol (mmol/L)	1.21 (0.32)	1.21 (0.31)	0.59	1.21 (0.33)	1.21 (0.31)	0.50
Triglycerides (mmol/L)	1.60 (1.17–2.29)	1.60 (1.13–2.20)	0.47	1.60 (1.11–2.20)	1.60 (1.12–2.22)	0.47
Creatinine (μmol/L)	88 (21)	88 (21)	0.86	88 (21)	87 (20)	0.63
Urine ACR (mg/mmol)	0.56 (0.28–1.88)	0.54 (0.27–1.57)	0.13	0.56 (0.27–1.79)	0.56 (0.28–1.73)	0.55
Other drugs						
Statin	1,362 (58)	1,378 (58)	0.84	1,348 (57)	1,412 (59)	0.21
Thiazide diuretic	413 (18)	423 (18)	0.79	411 (17)	415 (17)	0.93
ACE inhibitor or ARB	1,555 (66)	1,594 (67)	0.38	1,577 (67)	1,591 (66)	0.76
β-blocker	1,290 (55)	1,338 (57)	0.25	1,301 (55)	1,333 (55)	0.72
Other antihypertensive drug	1,686 (72)	1,701 (72)	0.91	1,684 (71)	1,741 (72)	0.32
Antiplatelet drug	1,662 (71)	1,675 (71)	0.96	1,688 (71)	1,692 (70)	0.49

Data are n (%), mean (SD), or median (interquartile range) for skewed variables unless otherwise indicated. ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

between posttrial follow-up participants randomized to the omega-3 and placebo groups (Table 1).

Event rates are shown in Supplementary Table 4. Over the course of the whole study, no difference was found in the incidence of the primary outcome of cardiovascular death between the omega-3 and placebo groups (688 of 6,281 [11.0%] vs. 700 of 6,255 [11.2%]; HR 0.98 [95% CI 0.88–1.09]; P = 0.68) or all-cause death, arrhythmic death, or the composite of myocardial infarction, stroke, or cardiovascular death or any of the other cardiovascular outcomes assessed (all $P > 0.2$) (Fig. 3 and Supplementary Fig. 6). Inclusion of all investigator-reported events in the posttrial follow-up for all participants from all sites in the posttrial follow-up did not change the results (data not shown). No differences in the effect of omega-3 on cardiovascular death were seen in key subgroups (Supplementary Fig. 7).

Supplementary Table 5 shows that the use of glucose-lowering medications or other cardiovascular medications was not different between the omega-3 and placebo groups at randomization, the end of the trial, or the end of posttrial follow-up. Omega-3 supplements were used by 89% of the omega-3 group and 1.3% of the placebo group at the end of the trial ($P < 0.001$) by design, but this difference was much smaller at the end of posttrial follow-up (11% vs. 8.8%, respectively, P = 0.04). Anthropometric measures, blood pressure, HbA_{1c}, and renal function were not different

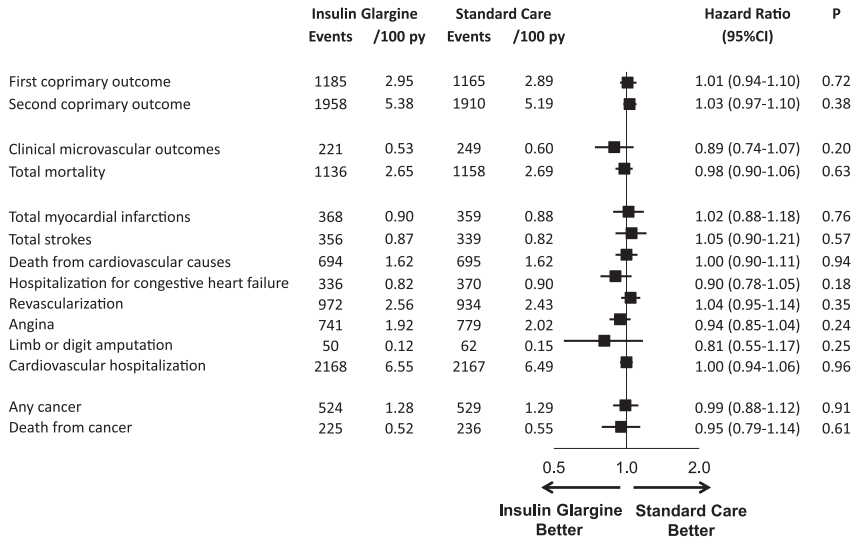

Figure 1—HRs for the coprimary and other outcomes: insulin glargine vs. standard care from randomization to the end of posttrial follow-up. py, patient-years.

between the two groups at any stage of the study (Supplementary Table 6).

CONCLUSIONS

The ORIGINALE study shows that after a median of 6.2 years of treatment and an additional median follow-up of 2.7 years among 45% of the surviving participants from ORIGIN, insulin glargine has a persistently neutral effect on cardiovascular, cancer, and other health outcomes and improves glycemic control. Over the same period, an omega-3 fatty acid supplement had a neutral effect on cardiovascular outcomes. More than 4,700 participants contributed an additional 12,000 person-years of follow-up and >1,000 events to yield these results.

These neutral findings for insulin glargine confirm the main findings of the ORIGIN trial (1) and the findings pertaining to cancers (9). For cancer, the findings also suggest that the previously observed neutral effect of exogenous insulin extends to cancers that may take somewhat longer to develop than in the original trial duration. Moreover, the findings are consistent with the conclusion that the link between basal insulin and serious health outcomes observed in uncontrolled observational studies may not be due to exogenous insulin itself; it may be best explained by the clinical circumstances that led to insulin initiation or other reasons.

Of note, these basal insulin–related neutral findings obtained during follow-up of ~9 years are consistent with those at 10 years in the UK Prospective Diabetes Study, which allocated newly diagnosed patients to glucose lowering with basal insulin or a sulfonylurea versus conventional care starting without insulin (4). Finally, as previously explored (10), the very small difference in HbA_{1c} of 0.15% (1.6 mmol/mol) between the two treatment groups accounts for the absence of reduced microvascular outcomes, which is consistent with the conclusion that insulin itself has no effect on these outcomes.

In ORIGIN, insulin glargine reduced progression to diabetes compared with standard care. During ORIGINALE, incident diabetes was diagnosed by means of the HbA_{1c} level, which is a less sensitive test than the oral glucose tolerance test used in ORIGIN (11). Nevertheless, when incident cases of confirmed diabetes that developed during ORIGINALE (after insulin was discontinued for all participants without diabetes at the end of the trial) were added to those identified during ORIGIN, there was a consistent (albeit nonsignificant) 5% reduction in newly developed diabetes that achieved significance when 69 possible, but unconfirmed cases of diabetes were added. This finding suggests that the effect of providing exogenous insulin (and probably reducing the strain on β-cells and lowering the demand for endogenous insulin secretion) on incident diabetes may persist for up to 2 years after exogenous insulin is discontinued. The finding also is consistent with other evidence that provision of insulin may improve or slow decline in endocrine pancreatic function and promote better long-term glucose homeostasis (12,13).

During the trial and posttrial follow-up, glycemic control was better in the insulin glargine group than in the standard care group, and hypoglycemia rates were higher. This finding may be due to greater posttrial use of basal insulin in the group randomized to glargine. Indeed, 51% of the glargine group that continued to be followed was using basal insulin at the end of the posttrial follow-up despite being permitted to stop at the end of the trial, and fewer were using noninsulin glucose-lowering agents alone. This finding illustrates the effectiveness of basal insulin for glycemic control in type 2 diabetes and shows that continuation of basal insulin therapy is an acceptable therapeutic option for a significant proportion of patients given insulin early in the course of the disease.

The absence of any emerging long-term effect of omega-3 fatty acid supplements on cardiovascular or other outcomes and that contemporary trials have not detected any benefits (14–18) provide more evidence against their

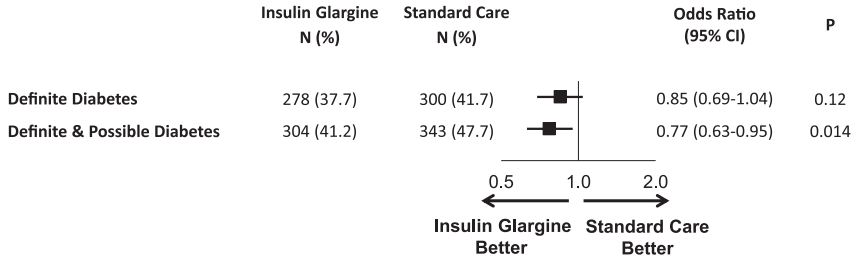

Figure 2—ORs for new diabetes: insulin glargine vs. standard care from randomization to the end of posttrial follow-up. Possible diabetes was diabetes diagnosed or treated by a nonstudy physician during the trial without documented confirmation.

Table 2—Medication use during the trial and posttrial follow-up in the glargine study

	Randomization			End of trial			End of posttrial follow-up		
	Glargine	Control	*P* value	Glargine	Control	*P* value	Glargine	Control	*P* value
No. participants*	6,264	6,273		5,267	5,260		1,873	1,887	
Glucose-lowering drugs									
None	2,527 (40)	2,577 (41)	0.40	375 (7.1)	1,013 (19)	<0.001	386 (21)	449 (24)	0.019
One drug	3,732 (60)	3,689 (59)	0.38	2,017 (38)	2,056 (39)	0.40	691 (37)	718 (38)	0.46
Insulin only**	0	0	—	1,520 (29)	98 (1.9)	<0.001	303 (16)	83 (4.4)	<0.001
Other monotherapy	3,732 (60)	3,689 (59)	0.38	497 (9.4)	1,958 (37)	<0.001	388 (21)	635 (34)	<0.001
Two or more drugs	5 (0.1)	7 (0.1)	0.57	2,875 (55)	2,191 (42)	<0.001	796 (42)	720 (38)	0.007
Combination with insulin**	0 (0)	0 (0)	—	2,725 (52)	473 (9.0)	<0.001	605 (32)	203 (11)	<0.001
Combination without insulin	5 (0.08)	7 (0.11)	0.57	150 (2.9)	1,718 (33)	<0.001	191 (10)	517 (27)	<0.001
Basal insulin	0 (0)	0 (0)	—	4,259 (81)	610 (12)	<0.001	957 (51)	286 (15)	<0.001
Insulin glargine	0	0	—	4,225 (80)	52 (1.0)	<0.001	772 (41)	94 (5.0)	<0.001
Other basal insulin	0	0	—	19 (0.4)	451 (8.6)	<0.001	185 (9.9)	192 (10)	0.75
Bolus insulin	0	0	—	103 (2.0)	265 (5.0)	<0.001	99 (5.3)	94 (5.0)	0.68
Metformin	1,694 (27)	1,741 (28)	0.37	2,451 (47)	3,142 (60)	<0.001	969 (52)	1,089 (58)	<0.001
Sulfonylurea	1,901 (30)	1,810 (29)	0.067	1,295 (25)	2,446 (47)	<0.001	351 (19)	646 (34)	<0.001
DPP-4 inhibitor or GLP-1 analog	0	0	—	4 (0.08)	18 (0.34)	0.003	174 (9.3)	256 (14)	<0.001
Other glucose-lowering drug	173 (2.8)	178 (2.8)	0.76	195 (3.7)	614 (12)	<0.001	55 (2.9)	92 (4.9)	0.002
Other cardiovascular drugs									
ACE inhibitor or ARB	4,330 (69)	4,351 (69)	0.82	3,932 (77)	3,926 (76)	0.71	1,461 (78)	1,438 (76)	0.22
Other antihypertension drug	4,478 (72)	4,518 (72)	0.54	3,918 (76)	3,916 (76)	0.78	1,532 (82)	1,514 (80)	0.26
Statin	3,373 (54)	3,367 (54)	0.82	3,179 (62)	3,096 (60)	0.058	1,353 (72)	1,346 (72)	0.59
Antiplatelet	4,296 (69)	4,370 (70)	0.21	3,644 (71)	3,630 (71)	0.57	1,424 (76)	1,394 (74)	0.15
Omega-3 fatty acid	0	0	—	2,386 (45)	2,404 (46)	0.67	201 (11)	181 (9.6)	0.25

Data are *n* (%). ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4. *Total number of consenting participants providing any medication history at each stage. Denominators for percentages in subsequent rows may be smaller. **Any basal or bolus or combination or premixed insulin.

routine use. Because only 9–11% of patients in both groups continued on omega-3 supplements during ORIGINALE, it appears that the message from evidence of this sort is reaching patients and providers.

Results of this study should be interpreted in the context of two major limitations. First, the relatively short duration of additional posttrial follow-up limited the ability to identify potential emerging effects of the interventions. Second, 56% of eligible ORIGIN participants continued in the posttrial follow-up. Because of these limitations, posttrial follow-up contributed only about one-tenth of the coprimary events, limiting the power to detect differences. However, although event rates among the nonparticipants in the posttrial follow-up remain unknown (and given their lower cardiovascular risk profile, may have had a different response to glucose lowering with insulin), risk of bias was minimized by the analytic strategies used for the primary analyses.

Taken together, the combined findings from ORIGIN and the smaller number of participants in ORIGINALE may be reassuring to patients and providers regarding the long-term safety and glycemic control efficacy of basal insulin glargine when it is used to lower glucose levels. The findings also provide further evidence against any cardiovascular benefits of omega-3 fatty acid supplements.

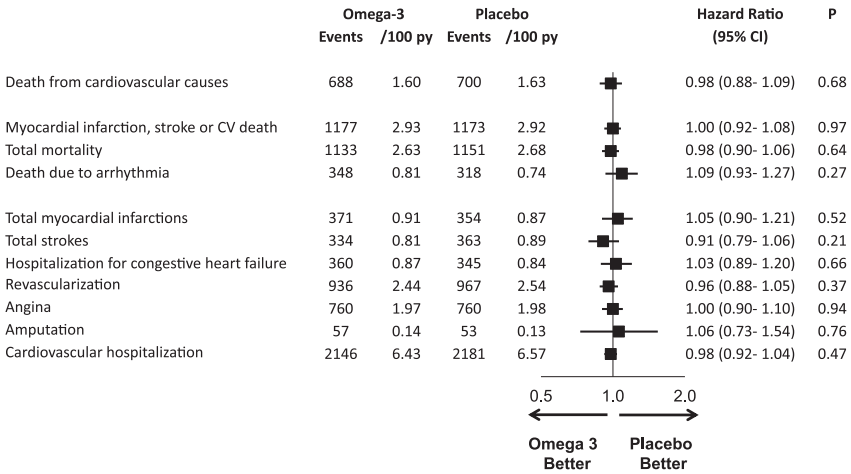

Figure 3—HRs for cardiovascular death and other outcomes: omega-3 vs. placebo from randomization to the end of posttrial follow-up. CV, cardiovascular; py, patient-years.

Funding. P.C. received funding from the Public Health Research Institute for conduct of the study in South Africa and institutional support for ORIGIN.

Duality of Interest. The ORIGIN trial was sponsored and funded by Sanofi. ORIGINALE was funded by a grant from Sanofi. The Population Health Research Institute and McMaster University received funds from Sanofi, maker of insulin glargine, to complete this study. Z.P. has received fees for advice and lectures, and

research funds from Sanofi, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squib, Eli Lilly, Merck Sharp & Dohme, and Novo Nordisk. H.C.G. has received fees for advice and lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann LaRoche, Novo Nordisk, and Sanofi, as well as grants from Sanofi and Eli Lilly. A.P.M. received research funds from Sanofi, Novartis, Bayer, and Cardiorentis. J.P. has received grant and contract money for research purposes from Sanofi. A.R. received funds from Sanofi for this study. M.C.R. has received research grant support through his institution from AstraZeneca, Eli Lilly, Novo Nordisk, and Sanofi and honoraria for consulting or lectures from Biodel, Elcelyx, Sanofi, and Valeritas. These dualities of interest have been reviewed and managed by Oregon Health & Science University. L.E.R. has received fees for advice and lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Hoffmann LaRoche, and Sanofi and grants from Hoffmann LaRoche and Bayer. E.A.B. has received fees for advice and lectures from Merck Sharp & Dohme and Sanofi. K.I.B. has received fees for advice, lectures, and research grants from Sanofi, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, and Novo Nordisk. M.D. has acted as consultant, advisory board member, and speaker for Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi, and Eli Lilly. M.H. has received speaker honoraria from Takeda, GlaxoSmithKline, Hoffmann LaRoche, Bayer, Eli Lilly, and Sanofi and advisory board honoraria from Sanofi, Takeda, Bristol-Myers Squibb, and GlaxoSmithKline. P.H. has received fees for advice and lectures from Amgen, AstraZeneca, Servier, and Novo Nordisk. B.S.L. has received fees for advice and lectures from AstraZeneca, Hoffman LaRoche, and Sanofi and grants from AstraZeneca and Sanofi. E.L. has received honoraria for presentations and advisory boards from Amgen and Sanofi, and research funding from Amgen, AstraZeneca, Bayer, and Sanofi. P.L.-J. has received fees for lectures from Sanofi, Merck Sharp & Dohme, and Boehringer Ingelheim. M.M. has received fees for advisory boards and lectures from Abbott, AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, and Servier and research grants from Novo Nordisk. M.J.M. has received research funding from Sanofi, Roche Diagnostics, and Abbott Diagnostics. C.A.M. has received research grants from Merck Sharp & Dohme, Pfizer, Boston Scientific, and Biosense Webster; speaker fees from Bayer, Biotronik, Boehringer Ingelheim, and St. Jude Medical; and advisory fees from Boston Scientific. J.R. has received, pertinent to this article, honoraria for presentations and scientific advisory boards and research grants from insulin manufacturers Sanofi, Eli Lilly, and Novo Nordisk. G.A.S. has received fees for advice and lectures from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Novartis, Medtonic, and Sanofi and research support from Novo Nordisk. S.S. has received fees for lecturing and advice from Novo Nordisk, Sanofi, AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Janssen, Boehringer Ingelheim, Menarini, Novartis, and Merck Sharp & Dohme and research support from Novo Nordisk, Eli Lilly, and AstraZeneca. M.S. has received fees for advice and lectures from Merck Sharp & Dohme, Pfizer, Bristol-Myers Squibb, AstraZeneca, Leiras Takeda, Bayer, Novo Nordisk, Orion, Chiesi Pharma, and Lundbeck and a travel grant from Sanofi. J.-F.Y. has received fees for advisory boards and lectures from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medtronic, Merck Sharp & Dohme, Novo Nordisk, and Sanofi and research grants from AstraZeneca, Janssen, Medtronic, Merck Sharp & Dohme, and Sanofi. S.Y. has received grants and lecture fees and related travel expenses from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, Sanofi, Novartis, and Cadila. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. Z.P. and H.C.G. contributed to the study design; data collection and interpretation; and drafting, critical revision, and final approval of the manuscript. J.B. contributed to the study design, data collection and interpretation, and critical revision and final approval of the manuscript. H.J. contributed to the study design; data collection, analysis, and interpretation; and critical revision and final approval of the manuscript. F.L. and T.M. contributed to the data collection, analysis, and interpretation and critical revision and final approval of the manuscript. J.T., G.R.D., R.D., A.P.M., J.P., A.R., M.C.R., L.E.R., E.A.B., K.I.B., E.C., P.C., M.D., J.G.F., R.G., M.H., P.H., G.K.-B., M.K., S.F.L., B.S.L., E.L., P.L.-J., J.M.-N., M.M., R.M., M.J.M., I.M., C.A.M., C.Y.P., V.P., J.R., G.A.S., S.S., M.S., J.-F.Y., and S.Y. contributed to the data collection and interpretation and critical revision and final approval of the manuscript. Z.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

Writing Group Zubin Punthakee, Hertzel C. Gerstein, Jackie Bosch, Jessica Tyrwhitt, Hyejung Jung, Shun Fu Lee, Tamara Marsden, Robert McKelvie, Matthew J. McQueen, Carlos A. Morillo, and Salim Yusuf, Population Health Research Institute and McMaster University, Hamilton, ON, Canada; Gilles R. Dagenais, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, QC, Canada; Rafael Díaz, Estudios Clínicos Latino América, Rosario, Argentina; Aldo P. Maggioni, Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy; Jeffrey Probstfield, University of Washington, Seattle, WA; Ambady Ramachandran, India Diabetes Research Foundation, Chennai, India; Matthew C. Riddle, Oregon Health & Science University, Portland, OR; Lars E. Rydén, Cardiology Unit, Department of Medicine K2, Karolinska Institute, Stockholm, Sweden; Erik A. Badings, Department of Cardiology Research, Deventer Hospital, Deventer, The Netherlands; Kåre I. Birkeland, Oslo University Hospital and University of Oslo, Oslo, Norway; Ernesto Cardona, Universidad de Guadalajara, Guadalajara, Mexico; Patrick Commerford, University of Cape Town, Cape Town, South Africa; Melanie Davies, University of Leicester, Diabetes Research Centre, Leicester, U.K.; J. George Fodor, University of Ottawa Heart Institute, Ottawa, ON, Canada; Ramon Gomis, L'Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; Markolf Hanefeld, GWT-TUD GmbH, Studycenter 'Prof. Hanefeld,' Dresden, Germany; Per Hildebrandt, Department of Cardiology and Endocrinology, Frederiksberg Hospital, Frederiksberg, Denmark; Gertrud Kacerovsky-Bielesz, Hanusch-Krankenhaus Diabetesambulanz, Mauerbach, Austria; Mátyás Keltai, Hungarian Institute of Cardiology, Semmelweis University, Budapest, Hungary; Fernando Lanas, Universidad de La Frontera, Temuco, Chile; Basil S. Lewis, Lady Davis Carmel Medical Center, Haifa, Israel; Patricio Lopez-Jaramillo, Fundacion Oftalmologica de Santander (FOSCAL) and Universidad de Santander, Bucaramanga, Colombia; Jose Marin-Neto, Faculdade de Medicina de Riberirao Preto USP, Ribeirao Preto, Brazil; Michel Marre, Groupe Hospitalier Bichat–Claude Bernard, Assistance Publique des Hôpitaux de Paris, Paris, France; Ivan Mendoza, Urologico San Roman, Caracas, Venezuela; Chang Yu Pan, Chinese PLA General Hospital, Beijing, China; Valdis Pīrāgs, Centre of Endocrinology, Pauls Stradiņš Clinical University Hospital, Riga, Latvia; Julio Rosenstock, Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX; Giatgen A. Spinas, University Hospital Zurich, Zurich, Switzerland; Seamus Sreenan, 3U Diabetes, Connolly Hospital Blanchardstown, Dublin, Ireland; Mikko Syvänne, Finnish Heart Association, Helsinki, Finland; and Jean-François Yale, McGill University, Montreal, QC, Canada.

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