ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

ABSTRACT

BACKGROUND

The provision of sufficient basal insulin to normalize fasting plasma glucose levels may reduce cardiovascular events, but such a possibility has not been formally tested.

METHODS

We randomly assigned 12,537 people (mean age, 63.5 years) with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes to receive insulin glargine (with a target fasting blood glucose level of ≤95 mg per deciliter [5.3 mmol per liter]) or standard care and to receive n–3 fatty acids or placebo with the use of a 2-by-2 factorial design. The results of the comparison between insulin glargine and standard care are reported here. The coprimary outcomes were nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes and these events plus revascularization or hospitalization for heart failure. Microvascular outcomes, incident diabetes, hypoglycemia, weight, and cancers were also compared between groups.

RESULTS

The median follow-up was 6.2 years (interquartile range, 5.8 to 6.7). Rates of incident cardiovascular outcomes were similar in the insulin-glargine and standard-care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first coprimary outcome (hazard ratio, 1.02; 95% confidence interval [CI], 0.94 to 1.11; P=0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second coprimary outcome (hazard ratio, 1.04; 95% CI, 0.97 to 1.11; P=0.27). New diabetes was diagnosed approximately 3 months after therapy was stopped among 30% versus 35% of 1456 participants without baseline diabetes (odds ratio, 0.80; 95% CI, 0.64 to 1.00; P=0.05). Rates of severe hypoglycemia were 1.00 versus 0.31 per 100 person-years. Median weight increased by 1.6 kg in the insulin-glargine group and fell by 0.5 kg in the standard-care group. There was no significant difference in cancers (hazard ratio, 1.00; 95% CI, 0.88 to 1.13; P=0.97).

CONCLUSIONS

When used to target normal fasting plasma glucose levels for more than 6 years, insulin glargine had a neutral effect on cardiovascular outcomes and cancers. Although it reduced new-onset diabetes, insulin glargine also increased hypoglycemia and modestly increased weight. (Funded by Sanofi; ORIGIN ClinicalTrials.gov number, NCT00069784.)

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An elevated fasting plasma glucose level is an independent risk factor for adverse cardiovascular outcomes.[1-7] Basal insulin secretion is required to maintain fasting plasma glucose levels below 100 mg per deciliter (5.6 mmol per liter), and an elevated fasting plasma glucose level indicates that there is insufficient endogenous insulin secretion to overcome underlying insulin resistance.[8,9] The correction of this deficiency may reduce cardiovascular outcomes.

Such a possibility has not been formally tested; however, large outcomes trials of more versus less intense glucose lowering in which insulin was used in both study groups have not shown a clear cardiovascular benefit.[7] In addition, one trial showed increased mortality.[10] These findings, the risk of hypoglycemia,[11] and suggestions that insulin might promote cardiovascular disease or cancers[12-14] have raised concerns regarding the safety of insulin for type 2 diabetes. Conversely, extended follow-up of the trial with the biggest between-group difference in insulin use until now (the United Kingdom Prospective Diabetes Study [UKPDS]) revealed a 15% reduction in myocardial infarction and a 13% reduction in death among people with new-onset type 2 diabetes.[15]

The UKPDS findings and the potential cardioprotective effects of insulin[16-18] suggest that early provision of sufficient basal insulin to normalize fasting plasma glucose levels may safely reduce incident cardiovascular outcomes. Evidence that exogenous insulin may slow the decline in pancreatic function with time[19-21] suggests that such an intervention may also reduce incident diabetes in people at risk for the disease. These hypotheses were tested in the present study, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial,[22] which involved people 50 years of age or older with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes in addition to other cardiovascular risk factors.

METHODS

STUDY DESIGN AND OVERSIGHT

The trial tested the effect of titrated basal insulin glargine versus standard care and of n–3 fatty-acid supplements versus placebo on cardiovascular outcomes with the use of a 2-by-2 factorial design.[22] The results of the comparison between n–3 fatty acids and placebo are now reported separately in the *Journal*.[23] The study was approved by the ethics committee at each study site, and all participants provided written informed consent.

A detailed description of the design, eligibility criteria, management of disease, and follow-up of both treatment groups has been published previously[22] and is summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. Briefly, participants assigned to insulin glargine added an evening injection to their glycemic-control regimen and increased the dose at least once weekly, targeting a self-measured fasting plasma glucose level of 95 mg per deciliter (5.3 mmol per liter) or less. Participants who had not received a diagnosis of diabetes by the penultimate study visit reduced the dose of insulin by 10 units per day and stopped any metformin by the last visit. Participants assigned to standard care were treated on the basis of the investigator's best judgment and local guidelines. Participants who had not received a diagnosis of diabetes and who were not using glucose-lowering drugs by the last visit were scheduled for a 75-g oral glucose-tolerance test 3 to 4 weeks later. This test was repeated after 10 to 12 weeks (while participants continued to not use diabetes medications) if the first test did not establish a diagnosis of diabetes.

OUTCOMES

There were two coprimary composite cardiovascular outcomes. The first was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second was a composite of any of these events, a revascularization procedure (cardiac, carotid, or peripheral), or hospitalization for heart failure. Other adjudicated outcomes (defined in the Supplementary Appendix) were a composite microvascular outcome, incident cases of diabetes in participants without baseline diabetes, all-cause mortality, and new or recurrent cancers. Hypoglycemic episodes since the previous visit were recorded at each visit, and weight was measured annually.

TRIAL CONDUCT AND FUNDING

The mean follow-up period was originally planned to be approximately 4 years. This was extended by 10 months before recruitment had been completed. Subsequently, in light of clinical trials reported in 2008 and 2009[10,24,25] that suggested that longer follow-up might be required to detect any effect of a glucometabolic intervention and with-

out any knowledge of treatment effects, the steering committee extended the trial for 2 years.

Funding, regulatory support, site monitoring, drug distribution, and insulin glargine (Lantus) were provided by Sanofi, and the n–3 fatty-acid supplements and placebo were provided by Pronova BioPharma Norge. The steering committee (a list of members is provided in the Supplementary Appendix), which comprised the joint principal investigators, one representative from each pharmaceutical company, and the national trial leaders from each country, developed the protocol, conducted the trial, prepared the manuscript, and decided to submit it for publication. Study data were collected and independently analyzed by the ORIGIN Project Office (led by the joint principal investigators, who vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol), which is based at the Population Health Research Institute in Hamilton, Ontario, Canada. The full protocol is available at NEJM.org.

STATISTICAL ANALYSIS

Data were analyzed with the use of SAS software (version 9.1 for Solaris) according to an intention-to-treat approach described in the protocol and a predefined statistical analysis plan. Power calculations and a description of the role of the data and safety monitoring committee are provided in the Supplementary Appendix. Time-to-event curves were constructed with the use of product-limit estimation and were compared with the use of stratified log-rank tests. Hazard ratios were calculated with the use of Cox regression models stratified according to the factorial allocation, baseline diabetes status, and a history of a cardiovascular event before randomization. For secondary and other outcomes with fewer than five participants with events within any stratum, Cox regression models with adjustment for these three factors as covariates were used. The proportional-hazards assumption was assessed by testing for the interaction of time with treatment group. Incident diabetes from the time of randomization was compared with the use of a Cochran–Mantel–Haenszel test stratified according to factorial allocation and a prior cardiovascular event, and an odds ratio was calculated. The durability of this effect was explored by repeating the analysis after the second post-study oral glucose-tolerance test.

The overall type I error rate of 5% for the two coprimary outcomes was partitioned such that the first coprimary outcome was tested at a P value of 0.044 and the second coprimary outcome was tested at a P value of 0.01; the nonadditivity of these error rates reflects the correlation between these coprimary outcomes. The nominal level of significance for all other analyses was $P<0.05$.

RESULTS

STUDY POPULATION

A total of 12,537 participants (mean age, 63.5 years; 35% female) were enrolled from 573 cardiology, diabetes, or other clinical sites in 40 countries. Data from an additional 75 persons at 3 sites were excluded while the trial was ongoing at the request of national regulatory agencies, after their audits of data from these sites. The median follow-up was 6.2 years (interquartile range, 5.8 to 6.7); at study end, the primary-outcome status was known for 12,443 participants (99%) (Fig. S1 in the Supplementary Appendix). Baseline characteristics are shown in Table 1.

INSULIN USE AND ACHIEVED FASTING GLUCOSE LEVELS

After 1 year, 50% of the insulin-glargine group had a fasting plasma glucose level of 94 mg per deciliter (5.2 mmol per liter) or less, and that level was maintained (Table 2). The median insulin dose rose from 0.31 units per kilogram of body weight (interquartile range, 0.19 to 0.46) by year 1 to 0.40 units per kilogram (interquartile range, 0.27 to 0.56) by year 6 (i.e., 28 units per day in a 70-kg person). After 2 years, 5398 participants in the insulin-glargine group (90%) were adherent to insulin glargine; at 5 years, 4719 (85%) were adherent. At the penultimate visit (i.e., before the tapering and discontinuation of insulin in participants without diabetes), insulin had been permanently discontinued by 19% of the insulin-glargine group (Table S1 in the Supplementary Appendix). At this time, 80% were using any insulin, 35% were not using any oral glucose-lowering agents, and 47% were using metformin.

Few participants in the standard-care group used insulin during the trial (Table 2). By the end of the study, 11% were using insulin, 19% were not using oral glucose-lowering agents, 60% were using metformin (Table S2 in the Supplementary Appendix), and the median fasting plasma glucose

level was 123 mg per deciliter (6.8 mmol per liter). In addition to this contrast in insulin use, median fasting plasma glucose and glycated hemoglobin levels were lower in the insulin-glargine group than in the standard-care group at 2 years (difference in fasting plasma glucose, 29 mg per deciliter [1.6 mmol per liter]; difference in glycated hemoglobin, 0.3 percentage points) (Table 2). The use of drugs that alter cardiovascular risk and measurements at study end of blood pressure, heart rate, waist-to-hip ratio, and lipid levels were similar in the two groups (Tables S2 and S3 in the Supplementary Appendix).

COPRIMARY OUTCOMES

The incidence of both coprimary outcomes did not differ significantly between treatment groups (Fig. 1 and 2), with hazard ratios of 1.02 (95% confidence interval [CI], 0.94 to 1.11; P=0.63) and 1.04 (95% CI, 0.97 to 1.11; P=0.27) for the first and second coprimary outcomes, respectively. There was also no significant difference in mortality (hazard ratio, 0.98; 95% CI, 0.90 to 1.08; P=0.70) or microvascular events (hazard ratio, 0.97; 95% CI, 0.90 to 1.05; P=0.43). The effect of the intervention on the two coprimary outcomes was similar across subgroups (Fig. S2A and S2B in the Supplementary Appendix).

OTHER OUTCOMES

Among 1456 participants without diabetes at randomization (737 assigned to insulin glargine and 719 assigned to standard care), those who were assigned to insulin glargine were 28% less

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Insulin Glargine (N=6264)	Standard Care (N=6273)
Demographic and clinical characteristics		
Age — yr	63.6±7.8	63.5±7.9
Female sex — no. (%)	2082 (33.2)	2304 (36.7)
Prior cardiovascular event — no. (%)†	3712 (59.3)	3666 (58.4)
Prior myocardial infarction — no. (%)	2221 (35.5)	2208 (35.2)
Prior stroke — no. (%)	805 (12.9)	851 (13.6)
Hypertension — no. (%)	4974 (79.4)	4989 (79.5)
Current smoker — no. (%)	781 (12.5)	771 (12.3)
Any albuminuria — no. (%)	939 (15.0)	985 (15.7)
Ankle–brachial index ≤0.9 — no. (%)	470 (7.5)	501 (8.0)
Glycemic characteristics		
Prior diabetes		
Use of oral glucose-lowering agent — no. (%)	3748 (59.8)	3692 (58.9)
No use of diabetes drugs — no. (%)	1414 (22.6)	1467 (23.4)
New diabetes — no. (%)	365 (5.8)	395 (6.3)
Impaired glucose tolerance or impaired fasting glucose — no. (%)	735 (11.7)	717 (11.4)
Duration of diabetes — yr	5.5±6.1	5.3±5.9
Fasting plasma glucose — mg/dl		
Median	125	124
Interquartile range	109–148	108–148
Glycated hemoglobin — %		
Median	6.4	6.4
Interquartile range	5.8–7.2	5.8–7.2
Glycemic drugs		
Metformin — no. (%)	1694 (27.0)	1741 (27.8)
Sulfonylurea — no. (%)	1901 (30.3)	1810 (28.9)
Other — no. (%)	173 (2.8)	178 (2.8)

Table 1. (Continued.)

Characteristic	Insulin Glargine (N=6264)	Standard Care (N=6273)
Nonglycemic cardiovascular risk factors		
Systolic blood pressure — mm Hg	146±22	146±22
Diastolic blood pressure — mm Hg	84±12	84±12
Weight — kg	83.3±16.8	83.1±17.3
Body-mass index‡	29.8±5.2	29.9±5.3
Waist-to-hip ratio		
Men	0.99±0.09	0.98±0.09
Women	0.90±0.09	0.90±0.09
Total cholesterol — mg/dl	190±46	189±46
LDL cholesterol — mg/dl	113±40	112±40
HDL cholesterol — mg/dl	46±12	46±12
Triglycerides — mg/dl		
Median	140	142
Interquartile range	98–196	97–195
Creatinine — mg/dl	1.0±0.2	1.0±0.2
Urinary albumin-to-creatinine ratio§		
Median	5.2	5.1
Interquartile range	2.5–18.8	2.5–18.6
Other drugs — no. (%)		
Statin	3373 (53.8)	3367 (53.7)
Thiazide diuretic	1147 (18.3)	1224 (19.5)
ACE inhibitor or ARB	4330 (69.1)	4351 (69.4)
Beta-blocker	3273 (52.3)	3325 (53.0)
Other blood-pressure drug	2567 (41.0)	2577 (41.1)
Antiplatelet drug	4296 (68.6)	4370 (69.7)

* Plus–minus values are means ±SD. To convert the values for fasting blood glucose to millimoles per liter, multiply by 0.05551. To convert the values for total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, HDL high-density lipoprotein, and LDL low-density lipoprotein.
† Cardiovascular events include myocardial infarction, stroke, and revascularization.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The ratio is based on measurement of albumin in milligrams and creatinine in grams.

likely to have diabetes develop from the time of randomization until the first oral glucose-tolerance test than were participants assigned to standard care (i.e., 25% vs. 31% with diabetes, on the basis of oral glucose-tolerance tests performed in 64% and 65% of eligible participants, respectively; odds ratio, 0.72; 95% CI, 0.58 to 0.91; P=0.006) (Fig. S3 in the Supplementary Appendix). When persons without diabetes after the first oral glucose-tolerance test underwent a second test a median of 100 days (interquartile range, 95 to 112) after insulin was stopped, additional cases of diabetes were detected in both groups (i.e., 30% and 35% with diabetes, on the basis of oral glucose-tolerance tests performed in 44% and 47% of eligible participants, respectively; odds ratio, 0.80; 95% CI, 0.64 to 1.00; P=0.05). Moreover, when cases of diabetes that could not be confirmed by the predefined adjudication criteria (i.e., uncertain diabetes) were added to those that met the adjudication criteria after both oral glucose-tolerance tests, the incidence of diabetes was reduced by 31% (i.e., 35% vs. 43%; odds ratio, 0.69; 95% CI, 0.56 to 0.86; P=0.001). Reversion rates to no im-

Table 2. Insulin Use and Glycemic Indexes during the Trial.*

Time	Insulin Use†		Fasting Plasma Glucose				Glycated Hemoglobin			
	Insulin Glargine	Standard Care	Insulin Glargine		Standard Care		Insulin Glargine		Standard Care	
			median	IQR	median	IQR	median	IQR	median	IQR
	number/total number (percent)		*mg/dl*				*percent*			
Baseline	6264/6264 (100.0)	0	125	109–148	124	108–148	6.4	5.8–7.2	6.4	5.8–7.2
1 yr	5636/6140 (91.8)	110/6155 (1.8)	93	82–106	NA		5.9	5.5–6.4	6.2	5.7–6.9
2 yr	5398/6019 (89.7)	208/6021 (3.5)	90	79–104	119	103–142	6.0	5.5–6.5	6.3	5.8–6.9
3 yr	5190/5850 (88.7)	305/5871 (5.2)	90	80–103	NA		6.0	5.6–6.6	6.4	5.8–7.0
4 yr	4953/5684 (87.1)	400/5705 (7.0)	91	81–105	NA		6.1	5.7–6.7	6.4	5.9–7.1
5 yr	4719/5522 (85.5)	494/5519 (9.0)	92	81–108	NA		6.2	5.7–6.8	6.5	6.0–7.2
6 yr	3281/3929 (83.5)	392/3925 (10.0)	94	82–110	NA		6.3	5.8–6.9	6.5	6.0–7.2
7 yr	713/853 (83.6)	99/865 (11.4)	94	81–113	NA		6.2	5.8–6.8	6.5	6.0–7.1

* IQR denotes interquartile range, and NA not available. To convert the values for fasting plasma glucose to millimoles per liter, multiply by 0.05551.

† Participants who attended each visit and who were using insulin glargine (in the insulin-glargine group) or any insulin (in the standard-care group) are shown.

paired fasting glucose and no impaired glucose tolerance did not differ significantly between groups.

Other analyses showed no significant difference in each component of the two coprimary outcomes (Fig. 1) or in the incidence of any cancer (hazard ratio, 1.00; 95% CI, 0.88 to 1.13; P=0.97), death from cancer (hazard ratio, 0.94; 95% CI, 0.77 to 1.15; P=0.52), or cancer at specific sites (Table S4 in the Supplementary Appendix). There was also no significant difference in angina, amputations, cardiovascular or noncardiovascular hospitalizations, motor vehicle accidents, or fractures.

The incidence of a first episode of severe hypoglycemia was 1.00 per 100 person-years in the insulin-glargine group and 0.31 per 100 person-years in the standard-care group (P<0.001) (Table 3). One death attributed to hypoglycemia occurred in a participant while taking insulin glargine. The incidence of a first episode of nonsevere symptomatic hypoglycemia that was confirmed by a self-measured glucose level of 54 mg per deciliter (3.0 mmol per liter) or less was 9.83 and 2.68 per 100 person-years in the insulin-glargine and standard-care groups, respectively (P<0.001); the incidence of any (i.e., confirmed or unconfirmed) nonsevere symptomatic hypoglycemia was 16.72 and 5.16 per 100 person-years, respectively (P<0.001). A total of 2689 participants in the insulin-glargine group (43%) and 4693 in the standard-care group (75%) did not have any symptomatic hypoglycemia during the ORIGIN trial (Table 3). Participants in the insulin-glargine group gained a median of 1.6 kg (interquartile range, –2.0 to 5.5), and participants in the standard-care group lost a median of 0.5 kg (interquartile range, –4.3 to 3.2) during a median follow-up of 6.2 years.

DISCUSSION

The present trial showed that the early use of basal insulin to target normal fasting plasma glucose levels neither reduced nor increased cardiovascular outcomes as compared with guideline-suggested glycemic control. Moreover, this intervention reduced incident diabetes in participants with impaired fasting glucose or impaired glucose tolerance, though it was associated with modest weight gain and more episodes of hypoglycemia. There was not an increase in incident cancers; thus, these data do not support epidemiologic analyses that have linked insulin in general or insulin glargine in particular to incident cancers during several years of exposure.[12,13]

Our trial also showed that near-normal fasting plasma glucose and glycated hemoglobin levels can be achieved and maintained for more than 6 years with a daily injection of basal insulin with or without an oral agent when self-monitored fasting glucose levels are used by high-risk patients to adjust the dose of insulin glargine. Indeed, fast-

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52

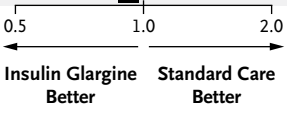


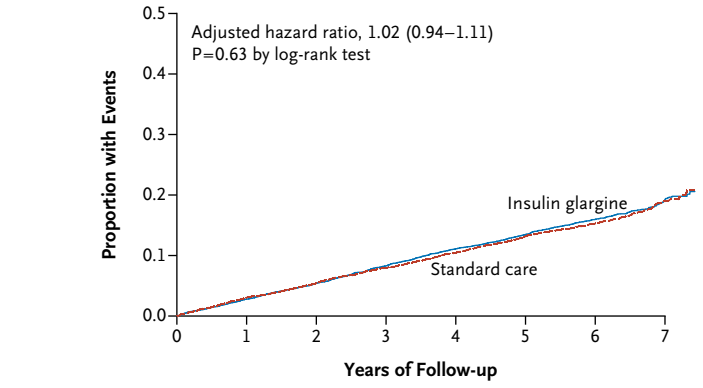
Figure 1. Hazard Ratios for the Coprimary and Other Outcomes.

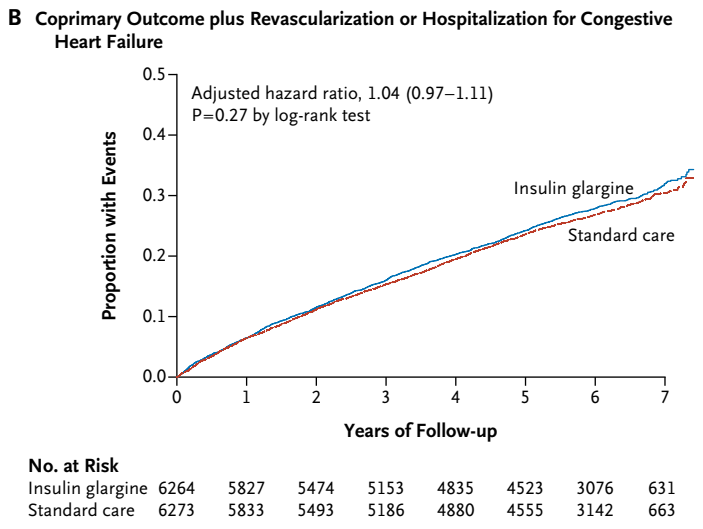
Hazard ratios are adjusted for the factorial allocation, baseline diabetes status, and the presence or absence of a history of a cardiovascular event before randomization, as described in the protocol.

ing plasma glucose levels of less than 95 mg per deciliter were achieved and maintained for at least 5 years in more than 50% of the insulin-glargine group, and values of less than 108 mg per deciliter (6.0 mmol per liter) were maintained in more than 75% of the group. In contrast, participants in the standard-care group who used oral agents had a median fasting plasma glucose level of 123 mg per deciliter and glycated hemoglobin levels consistent with those recommended in clinical-practice guidelines at the end of the study.

Although insulin glargine increased the risk of hypoglycemia, the absolute increase in risk was low, with approximately 0.7 more severe episodes and 11 more suspected or confirmed episodes per 100 person-years. In contrast, the insulin group in the UKPDS had a severe hypoglycemia rate of 1.8% per year as compared with 0.7% per year in controls, representing an absolute difference of 1.1 percentage points per year.[26] This lower rate and the observation that 43% of the insulin-glargine group had no episodes over a median of 6.2 years may have been due to selection of people with mild glucose abnormalities; the use of insulin glargine, which has a long duration of action and predictable effect on fasting plasma glucose levels; the fact that basal and not prandial insulin was used; and the concomitant use of metformin in 47% of participants. Nevertheless, the risk of hypoglycemia was lower by a factor of approximately 3 among participants in the standard-care group, who had a median weight loss of 0.5 kg, as compared with participants in the insulin-glargine group. Both hypoglycemia and weight gain are associated with cardiovascular outcomes in epidemiologic studies, so the lack of differences in cardiovascular outcomes in our study suggests that these adverse effects do not cause outcomes or that any harm was offset by benefit.

The intervention with basal insulin glargine reduced diabetes incidence, and this occurred despite weight gain (which is a known risk factor





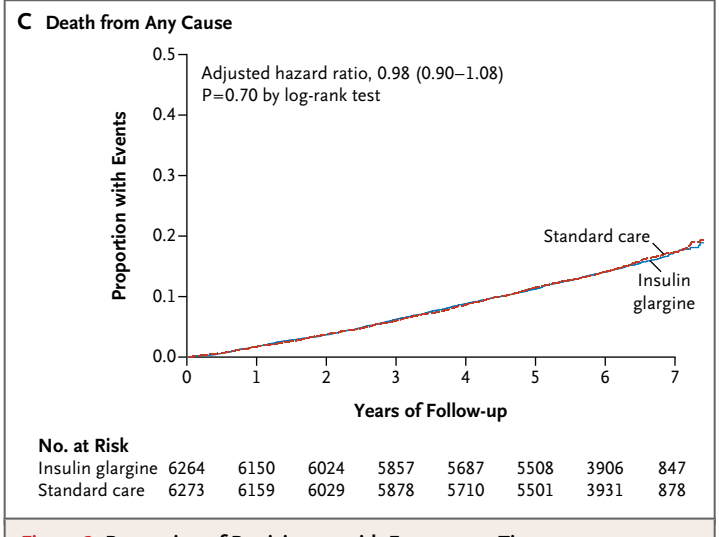


Figure 2. Proportion of Participants with Events over Time.

for diabetes). The reduction in incident diabetes is unlikely to be due to the masking of hyperglycemia by residual injected insulin glargine, because the mean duration of action is approximately 1 day.[27] It is also unlikely to be due to concomitant metformin, because less metformin was used in the insulin-glargine group than in the standard-care group. Whether the decrease in incident diabetes will lead to long-term clinical benefits is unknown. Nevertheless, the finding supports further research into the effect of insulin regimens on endocrine pancreatic function.

The current trial had several strengths. A large difference in insulin therapy was achieved and maintained between groups. The trial duration of more than 6 years, the high rates of follow-up and treatment adherence, the large number of cardiovascular outcomes, and the prospective collection and adjudication of these outcomes ensured sufficient power to detect a clinically important short-term or medium-term cardiovascular effect. In addition, the prospective collection of data pertaining to hypoglycemia, weight gain, and cancers ensured that potential harms were detected and quantified.

Limitations of the study include the fact that metformin was ultimately used by 47% of the insulin-glargine group. Evidence that metformin is cardioprotective[14,15,28] raises the possibility that any cardiovascular harm of insulin may have been mitigated by metformin. However, any benefit of metformin would have also applied to the 60% of the standard-care group who used metformin. Second, the ORIGIN trial involved people who are not normally prescribed insulin and in whom insulin glargine was used to achieve fasting plasma glucose levels much lower than those typically achieved with insulin therapy. However, the effect in participants with and those without diabetes was similar. Finally, the ORIGIN trial was designed to test the effect of using titrated basal insulin to control glucose levels versus standard care with guideline-suggested degrees of glycemic control. The ORIGIN trial was specifically not designed to test more intense versus less intense glucose lowering. As a large difference in insulin use was achieved (vs. a small difference in glycemic control), these findings are most relevant to the effect of insulin therapy and not the effect of glucose lowering on cardiovascular or microvascular outcomes, which has been studied in other trials.[7,10,15,24,25]

Finally, no previously unrecognized adverse

Table 3. Incidence of a First Episode of Severe Hypoglycemia.

Variable	Insulin Glargine (N=6264)	Standard Care (N=6273)	P Value
Severe hypoglycemia*			
Participants with ≥1 episode — no. (no./100 person-yr)	359 (1.00)	113 (0.31)	<0.001
Total episodes during follow-up — no.	457	134	
Confirmed nonsevere symptomatic hypoglycemia†			
Participants with ≥1 episode — no. (no./100 person-yr)	2614 (9.83)	904 (2.68)	<0.001
Episodes/yr in participants with ≥1 episode — median (interquartile range)	0.5 (0.2–1.4)	0.3 (0.2–0.8)	<0.001
Participants with no confirmed episodes during follow-up — no. (%)	3650 (58.3)	5369 (85.6)	<0.001
Any nonsevere symptomatic hypoglycemia			
Participants with ≥1 episode — no. (no./100 person-yr)	3575 (16.72)	1580 (5.16)	<0.001
Episodes/yr in participants with ≥1 episode — median (interquartile range)	1.1 (0.4–3.1)	0.5 (0.2–1.3)	<0.001
Participants with no episodes during follow-up — no. (%)	2689 (42.9)	4693 (74.8)	<0.001

* This category included any episode of hypoglycemia for which the patient required assistance and that was confirmed by a self-measured or laboratory plasma glucose level of 2 mmol per liter (36 mg per deciliter) or less or from which the patient recovered promptly after oral carbohydrate, intravenous glucose, or glucagon administration.

† This category included any symptomatic nonsevere hypoglycemic episode that was confirmed by a self-measured glucose level of 3 mmol per liter (54 mg per deciliter) or less.

effects of basal insulin were identified during careful follow-up for a median of 6.2 years; hypoglycemia rates were low and weight gain modest. This suggests that the main clinical use of insulin is as a flexible glucose-lowering drug and that previously reported cardiovascular benefits in type 1[29] and type 2[7,15] diabetes may have been mediated through metabolic effects rather than direct cardiovascular effects.

In summary, therapy with basal insulin glargine for more than 6 years had a neutral effect on cardiovascular outcomes and cancers. Moreover, this therapy maintained near-normal glycemic control and slowed progression of dysglycemia, but it was associated with a modest increase in hypoglycemic episodes and in weight. Whether the glycemic benefit will affect future microvascular or other outcomes remains unknown. In the meantime, the findings of the ORIGIN trial do not support changing standard therapies for early dysglycemia.

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APPENDIX

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