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A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study

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Abstract

Aims Insulin is generally withheld until people with Type 2 diabetes are unresponsive to other therapies. However, its potential advantages suggest that it could be added earlier to achieve glycaemic goals; this possibility was tested in a clinical trial.

Methods Consenting adults aged 18–80 years with Type 2 diabetes for at least 6 months, HbA_{1c} of 7.5–11%, and on 0, 1 or 2 oral agents, were randomized to one of two therapeutic approaches for 24 weeks: evening insulin glargine plus self-titration by 1 unit/day if the fasting plasma glucose (FPG) was > 5.5 mmol/l; or conventional therapy with physician adjustment of oral glucose-lowering agents if capillary FPG levels were > 5.5 mmol/l. The primary outcome was the first achievement of two consecutive HbA_{1c} levels ≤ 6.5%.

Results Two hundred and six participants were allocated to glargine and 199 to oral agents. Compared with control subjects, participants receiving glargine: (i) were 1.68 times more likely to achieve two consecutive HbA_{1c} levels ≤ 6.5% (95% CI 1.00–2.83; $P = 0.049$); (ii) reduced their HbA_{1c} by 1.55 vs. 1.25% ($P = 0.005$), achieving adjusted means of 7.0 vs. 7.2% ($P = 0.0007$); (iii) had lower FPG ($P = 0.0001$), non-high-density lipoprotein (HDL) cholesterol ($P = 0.02$) and triglycerides ($P = 0.02$); (iv) had greater increases in treatment satisfaction ($P = 0.045$); and (v) had a 1.9-kg greater increase in weight ($P < 0.0001$). No differences in hypoglycaemia were noted.

Conclusions Adding insulin glargine is more likely to achieve a lower HbA_{1c} level than conventional therapy with oral agents.

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Keywords diabetes, insulin glargine, oral glucose-lowering drugs, randomized controlled trial

Abbreviations BMI, body mass index; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FPG, fasting plasma glucose; HDL, high-density lipoprotein; INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment; LDL, low-density lipoprotein

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Introduction

People with diabetes are either absolutely deficient in insulin or are unable to make sufficient insulin to overcome underlying insulin resistance and normalize glucose metabolism. Nevertheless, until recently, insulin was withheld from people with Type 2 diabetes until they were unresponsive to a combination of lifestyle approaches and one or more oral glucose-lowering agents including metformin, insulin secretagogues, α glucosidase inhibitors or thiazolidinediones. This was justified on the basis of perceived provider and patient difficulties in initiating insulin therapy (i.e. psychological insulin resistance [1]) and concerns that insulin therapy might increase the risk of cardiovascular disease. However, the UK Prospective Diabetes Study (UKPDS) reported that people with newly diagnosed Type 2 diabetes who were allocated to initial therapy with insulin had a trend towards a reduced (and not an increased) risk of myocardial infarction, and other studies have reported that insulin has several potentially beneficial cardiovascular properties [2–10]. These data, combined with: (i) new insulin preparations with more predictable action profiles than older insulin preparations; (ii) recognition of the importance of self-titration of insulin based on capillary glucose levels; (iii) new insulin delivery devices; and (iv) increasingly stringent diabetes guidelines promoting near-normal HbA_{1c} levels have sparked interest in the role of earlier insulin therapy for the management of patients with Type 2 diabetes.

Insulin glargine (Lantus®) is a safe, soluble long-acting insulin preparation which can be administered once daily and which results in a predictable insulin profile (lasting up to 24 h) and glucose-lowering effect. Clinical trials have shown that using insulin glargine to target physiological levels of glucose control in people with Type 2 diabetes leads to lower rates of hypoglycaemia than NPH insulin [11,12]. This suggests that it may allow people with high glucose levels who are on either no or moderate doses of oral glucose-lowering agents to safely achieve recommended HbA_{1c} levels faster and more frequently than the conventional approach of maximizing oral glucose-lowering agent therapy. Moreover, its once-daily profile may facilitate its use in primary-care settings. The INSIGHT trial (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) was designed to explicitly test this hypothesis.

Patients and methods

Participants

This trial was conducted in 19 expert sites led by endocrinologists, and in 34 sites led by family physicians. Each family physician site was linked with the nurse and doctor at a specific expert site so that advice could be quickly sought regarding titration of the insulin glargine or other aspects of diabetes management. Volunteers aged 18–80 years with Type 2 diabetes of at least 6 months' duration were recruited through advertisements, or from general or specialty practices throughout Canada. Participants had to be on 0, 1 or 2 oral glucose-lowering agents, where at least one of them was being taken at or below half-maximal dose. Other inclusion criteria included no substantial change in oral glucose-lowering agent dose for at least 3 months before randomization, an HbA_{1c} between 7.5 and 11% and a body mass index (BMI) of 21–41 kg/m^2. Key exclusion criteria included need for or use of insulin or thiazolidinediones as judged by the physician, intolerance to metformin, previous ketoacidosis, night-shift workers, pregnancy or not using contraception, significant co-morbid illnesses, history of alcohol abuse, or a serum creatinine ≥ 133 μmol/l in males and 124 μmol/l in females. People taking thiazolidinediones at baseline were excluded only because combination therapy with insulin was not an approved indication by Canadian regulatory authorities at the time of the study. The study was reviewed and approved by local ethics committees and all participants provided written informed consent.

Allocated therapy and follow-up

Participants were randomly allocated to one of two therapeutic policies: (i) the addition of insulin glargine to their current therapy and provision of a simple protocol for self-titration of the insulin dose; or (ii) conventional glycaemic management based on avoidance of insulin and intensification of oral glucose-lowering therapy by physicians at each visit. Randomization was carried out using sealed envelopes containing 1 : 1 treatment allocations according to strata defined by the baseline use of 0, 1 or 2 oral glucose-lowering agents and study site. As the cost of all oral agents is not universally reimbursed within Canada, any prescribed oral glucose-lowering agent was supplied free of charge to all participants throughout the study to remove any financial barriers to their use. Participants were seen and assessed at baseline, 8, 12 and 24 weeks, with a phone or in-person contact scheduled for 2, 4 and 18 weeks. Participants who elected to stop their allocated therapy or who were advised to do so were explicitly followed off therapy until the final study visit for the ascertainment of outcomes.

Glargine participants were instructed on the use of the OptiPen Pro 1® injection device, freely provided with insulin cartridges, and asked to inject insulin at the same time each evening (between 21.00 and 23.00 h) and to check capillary glucose levels regularly. They were instructed to start with an initial dose of 10 units, and advised to increase this by 1 unit each day until achieving a fasting plasma glucose (FPG) ≤ 5.5 mmol/l. New oral glucose-lowering agents were not permitted in this group; oral glucose-lowering agents taken at baseline were continued after randomization (initially at the same dose) and supplied as needed. Doses were reduced at the discretion of the investigator in response to biochemical or clinical hypoglycaemia.

Control participants were managed with freely supplied oral glucose-lowering agents. Investigators were advised to titrate and/or add oral agents at each visit targeting capillary FPG levels ≤ 5.5 mmol/l and an HbA_{1c} ≤ 7% until maximal doses of two oral agents were used and then to add a third drug as required. Participants did not self-titrate oral glucose-lowering agents. If insulin was required, insulin glargine was not available

for use. Metformin, sulphonylureas, repaglinide, nateglinide or thiazolidinediones were available for addition to current therapy.

The Canadian Diabetes Association clinical practice guidelines [13] (including the target HbA_{1c} of ≤ 7%) were reviewed and reinforced with investigators and research coordinators before and during the study. A dietitian reviewed and discussed an appropriate diet with all participants at the randomization visit. Throughout the study, all participants were encouraged to monitor capillary glucose levels at least three times daily with more frequent measurements at the discretion of the investigator.

Outcomes

The primary outcome was initially defined as the achievement of two consecutive HbA_{1c} levels ≤ 6.5%. While the study was in progress and before any data were summarized or analysed, the Steering Committee refined the primary outcome to the first achievement of two consecutive HbA_{1c} levels ≤ 6.5% and designated the former primary outcome as a secondary outcome. Other secondary outcomes included the first achievement of two consecutive HbA_{1c} levels ≤ 7%; the achieved HbA_{1c} level; lipid profiles; quality of life measured by the Audit of Diabetes Dependent Quality of Life (ADDQoL) [14]; and diabetes treatment satisfaction measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [15]. Hypoglycaemic events were classified as: (i) symptomatic with a capillary glucose level < 3.9 mmol/l; (ii) symptomatic with no confirmed glucose; or (iii) severe (i.e. requiring assistance and at least one of either promptly responding to therapy with oral carbohydrate, intravenous glucose or parenteral glucagon, or a documented capillary glucose ≤ 2 mmol/l).

The HbA_{1c}, FPG and a lipid profile were measured centrally at baseline, 8, 12 and 24 weeks.

The sponsor (Aventis Canada): (i) collaborated in the final design of the study; (ii) funded and monitored the clinical sites; (iii) collected the data; (iv) analysed the data under the direction of the authors; and (v) reviewed (but did not write) the paper.

Statistics

All data was stored and analysed using SPSS version 8.2 (SAS Institute, Cary, NC, USA) on a HP-INUX platform.

A planned sample size of 400 would have 80% power to detect an absolute difference of 15% assuming 40% of glargine participants would achieve the end point (two-tailed $\alpha = 0.05$).

Unless indicated, all randomized participants were included in analyses regardless of adherence to the assigned therapy. The change in continuous variables was assessed using analysis of variance (ANOVA) for raw data, and analysis of covariance (ANCOVA) in which baseline measurement, stratum (baseline use of 0, 1, or 2 oral agents) and site (sites with less than six participants were pooled as composite sites with at least six participants) were entered as covariates. The proportions achieving end points were compared using Fisher's exact tests for unadjusted data and Cochrane–Mantel–Haenszel tests for adjusted data. Kaplan–Meier curves were constructed and compared using Wilcoxon tests. Cox proportional hazards models were used to estimate the hazard and 95% confidence interval of categorical outcomes; proportionality was assessed by inspection of the data. For the 29/405 (7.2%) participants in whom a final end of study HbA_{1c} value was not available, the last recorded value was carried forward.

Results

A total of 209 out of 614 screenees were excluded as a result of the reasons shown in Fig. 1. Baseline characteristics, practice setting and allocation of the 405 randomized participants are shown in Table 1.

Ninety-nine per cent of participants took at least one dose of medication, and at least one follow-up HbA_{1c} measurement was available in 95.6% of glargine participants and 97% of control subjects. For glargine group participants, the insulin dose increased between visits in 88.3, 68.4 and 54.9% of participants at weeks 0 and 8, 8 and 12, and 12 and 24, respectively. The mean (SD) insulin glargine dose reached by the last visit was 38.1 (28.5) units or 0.41 (0.28) units/kg body weight. For control subjects, the dose had either been increased or an oral glucose-lowering agent was added in 93.0, 65.3 and 57.3% during the same time intervals ($P > 0.5$ for the degree of anti-hyperglycaemic medication titration in the two groups within each interval). Table 2 lists the oral agents used in each group by study end.

Participants allocated to insulin glargine reached the primary end point of two consecutive HbA_{1c} levels ≤ 6.5% before control participants (Fig. 2; Wilcoxon $P = 0.041$), and were 1.68 times more likely to achieve this end point (95% CI 1.00, 2.83; $P = 0.049$). These findings became stronger after adjustment for baseline HbA_{1c}, number of oral agents used at baseline, and site (HR 1.71; 95% CI 1.02, 2.88; $P = 0.043$). Moreover, at the final (24 week) visit a higher proportion of glargine participants (17.5%; $n = 36$) than control participants (10.1%; $n = 20$) had achieved the primary end point of ≥ 2 consecutive HbA_{1c} levels ≤ 6.5% (Fisher's $P = 0.032$). As noted in Fig. 2 and Table 3, similar findings were observed for the secondary end point of two consecutive HbA_{1c} levels ≤ 7.0% [unadjusted HR and 95% CI = 1.66 (1.21, 2.29), $P = 0.002$; adjusted HR 1.75 (1.27, 2.41), $P < 0.001$].

Individuals allocated to insulin glargine experienced a greater fall in HbA_{1c} level, FPG level, total cholesterol, non-high-density lipoprotein (HDL) cholesterol, and triglycerides than those allocated to the control group during the 24-week trial; they also experienced a greater improvement in diabetes treatment satisfaction. Compared with the control group, the HbA_{1c} fell by an absolute amount of 1.55% in the glargine group vs. 1.25% ($P = 0.005$); the FPG fell by 3.89 mmol/l in the glargine group vs. 2.31 mmol/l ($P = 0.0001$); triglyceride levels fell by 1.08 mmol/l in the glargine group vs. 0.47 mmol/l ($P = 0.02$); cholesterol levels fell by 0.38 mmol/l in the glargine group vs. 0.11 mmol/l ($P = 0.015$); and non-HDL cholesterol levels fell by 0.37 mmol/l in the glargine group vs. 0.13 mmol/l ($P = 0.02$). Diabetes treatment satisfaction also increased by 1.03 in the glargine group and 0.82 in the control group ($P = 0.045$). Similar results were noted after adjustment for baseline levels, site and stratum. Moreover, after adjustment

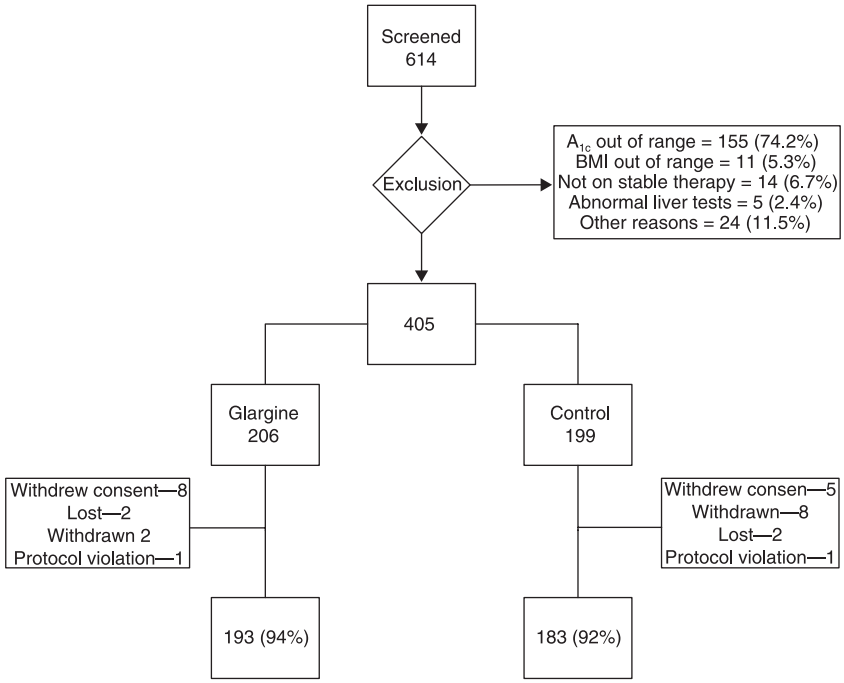

Figure 1 Numbers of screened participants and reasons for not randomizing those who were excluded are listed.

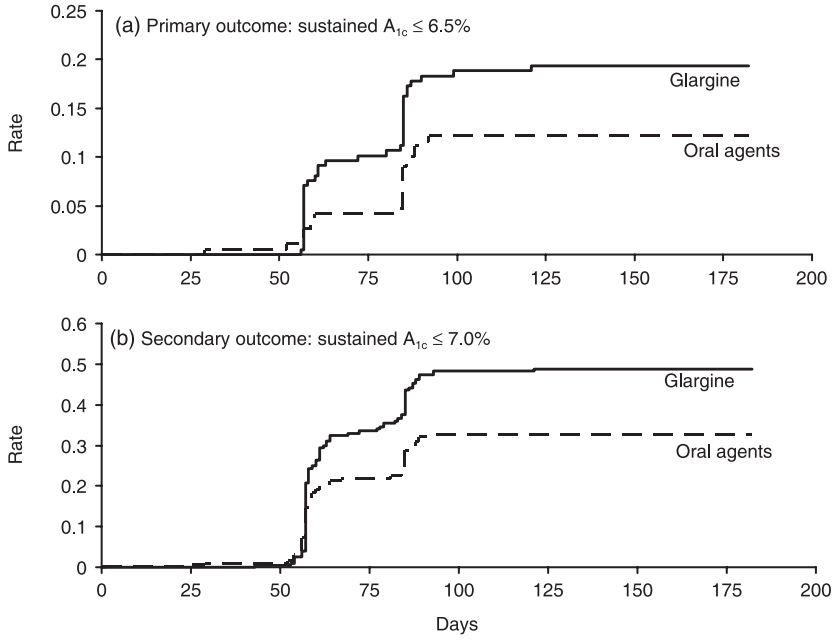

Figure 2 Proportion of participants allocated to glargine (solid) or oral agents (dashed) who achieved two consecutive HbA_{1c} levels ≤ 6.5% (a) or ≤ 7% (b) by days of therapy. OAD.

for these variables, the final mean (SE) HbA_{1c} in the glargine group was 6.96% (0.06) and in the control group was 7.24% (0.06; $P = 0.0007$). The allocated therapy had no effect on blood pressure, HDL or low-density lipoprotein (LDL) cholesterol. From the time of randomization until the end of the study, a lipid-lowering medication was added to 21 (10.2%) glargine participants and 27 (13.6%) control participants ($P = 0.36$).

Regardless of allocated therapy, the primary outcome was more likely to be achieved in participants who were drug naïve vs. those on oral glucose-lowering agents at baseline ($P = 0.0007$); and in those with a duration of diabetes of less than 5 years vs. 5 years or more ($P = 0.03$). However, no differences in the effect of insulin glargine on the primary outcome were observed according to subgroups defined by gender, follow-up at specialist sites vs. family practice sites, prior drug therapy, body mass index, age or duration of diabetes (P heterogeneity for all subgroups > 0.05).

The groups did not differ with respect to overall hypoglycaemia rates, that were reported in 100 (48.5%) glargine participants and 84 (42.2%) control participants (Fisher's exact, $P = 0.23$). Similarly there were no differences in the subset of

Table 1 Baseline characteristics of study population

	Total	Glargine	Conventional
Randomized (*n*)	405	206	199
Expert recruits	145 (35.8)	75 (36.4)	70 (35.2)
Family doctor recruits	260 (64.2)	131 (63.6)	129 (64.8)
Took any drug	400 (98.8)	203 (98.5)	197 (99.0)
Any follow-up HbA_{1c}	390 (96.3)	197 (95.6)	193 (97.0)
Age (years)	56.5 (9.8)	56.3 (9.4)	56.8 (10.1)
Females (%)	138 (34.1)	68 (33.0)	70 (35.2)
Age DM diagnosed (years)	49.1 (9.9)	49.1 (9.6)	49.0 (10.2)
DM duration (years)	7.9 (6.0)	7.6 (5.4)	8.2 (6.5)
Drug naïve	68 (16.8)	38 (18.4)	30 (15.1)
Metformin alone	84 (20.7)	42 (20.4)	42 (21.1)
Secretagogue alone	81 (20.0)	39 (18.9)	42 (21.1)
Metformin + secretagogue	172 (42.5)	87 (42.2)	85 (42.7)
Cardiovascular disease*	97 (24.7)	44 (21.8)	53 (27.7)
Hypertension*	238 (60.6)	114 (56.4)	124 (64.9)
Body mass index (kg/m^2)	31.3 (4.5)	31.1 (4.4)	31.5 (4.6)
Weight (kg)	89.2 (16.2)	88.7 (15.7)	89.7 (16.7)
Systolic BP (mm)	133 (15.4)	132 (14.7)	134 (16.1)
Diastolic BP (mm)	80 (9.1)	79 (8.2)	81 (10.0)
Waist circumference (cm)	104.9 (11.8)	104.8 (12.2)	105.1 (11.5)
HbA_{1c} (%)	8.6 (1.0)	8.6 (1.0)	8.5 (1.0)
FPG (mmol/l)	10.7 (2.7)	10.6 (2.7)	10.7 (2.7)
Cholesterol (mmol/l)	5.1 (1.31)	5.2 (1.42)	5.0 (1.18)
HDL (mmol/l)	1.18 (0.30)	1.17 (0.32)	1.18 (0.28)
Non-HDL (mmol/l)	3.93 (1.26)	4.01 (1.32)	3.85 (1.19)
LDL (mmol/l)	2.6 (0.92)	2.6 (0.95)	2.6 (0.90)
Triglyceride (mmol/l)	2.96 (3.14)	3.19 (3.85)	2.72 (2.16)
DTSQ score	−0.21 (0.87)	−0.27 (0.87)	−0.15 (0.86)

Continuous variables are expressed as mean (SD) and categorical variables as *n* (%); no baseline differences were detected between allocated groups using both unadjusted and adjusted (for site and stratum) *P*-values derived from ANOVA for continuous variables and Fisher's exact tests for categorical variables.

BP, blood pressure; DM, diabetes mellitus; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

*Twelve had missing data regarding a history of either cardiovascular disease or hypertension.

Table 2 Oral agent use at study end by allocated group

	Glargine	Conventional
	n (%)	*n* (%)
n	206	199
Drug naïve	45 (21.8)	1 (0.5)
Metformin alone	52 (25.2)	26 (13.1)
Secretagogue alone	36 (17.5)	9 (4.5)
Metformin + secretagogue	73 (35.4)	109 (54.8)
Metformin + rosiglitazone	0	2 (1.0)
Secretagogue + rosiglitazone	0	5 (2.5)
Metformin + secretagogue + rosiglitazone	0	47 (23.6)

confirmed or unconfirmed hypoglycaemia at each visit (data not shown) or other adverse events. One case (0.5%) of severe hypoglycaemia occurred in each group. Glargine participants' weight, BMI and waist circumference increased by an absolute amount of 1.89 kg, 0.64 kg/m^2 and 2.05 cm, respectively, more than these measures increased in control subjects ($P < 0.001$). The final weight, BMI and waist circumference in the glargine and control groups was 90.6 kg, 31.8 kg/m^2, 106.0 cm, and 89.8 kg, 31.5 kg/m^2, and 104.3 cm, respectively. Several statistical models were constructed to estimate the degree to which the increase in weight was as a result of the improved HbA_{1c} and the baseline weight. After adjusting for the change in HbA_{1c} and the baseline weight in a multiple regression model, the estimated increase in weight because of glargine was 1.69 kg (95% CI 0.91, 2.46). This estimate was not affected by further adjustment for age, sex, and baseline therapy.

Discussion

As people with Type 2 diabetes eventually become refractory to oral glucose-lowering agents and require insulin therapy, adding insulin earlier than it would otherwise have been added should improve glycaemic control. Nevertheless, clinicians typically reserve insulin until other therapies have been exhausted. These data demonstrate that, in drug-naïve patients with Type 2 diabetes or in those taking one or less than maximal doses of two oral glucose-lowering agents, the introduction of insulin glargine plus promotion of a simple self-titration protocol is more likely to safely achieve near-physiological glucose control than a conventional therapeutic policy in which physicians defer adding insulin by increasing or adding oral agents. Specifically, adding a daily injection of insulin glargine and simply titrating the dose by 1 unit per day was 1.7 times more likely to achieve two consecutive HbA_{1c} levels ≤ 6.5% than conventional therapy with oral glucose-lowering agents. Compared with the conventional policy, it also reduced: (i) HbA_{1c} by 0.3% more; (ii) fasting plasma glucose by 1.6 mmol/l more; (iii) total cholesterol by 0.27 mmol/l more; (iv) non-HDL cholesterol by 0.24 mmol/l more; and (v) triglycerides by 0.61 mmol/l more. Its effect was observed in all relevant subgroups; the amount of total cholesterol reduction is consistent with the fall in very low-density lipoprotein (VLDL) cholesterol (i.e. as a consequence of the fall in total triglycerides as a result of insulin-mediated glucose lowering). Rates of symptomatic hypoglycaemia were comparable, however, glargine participants experienced a weight gain of 1.89 kg, and an increase in BMI of 0.64 kg/m^2 relative to control subjects.

The fact that insulin glargine administration leads to a predictable insulin effect for up to 24 h [16] suggests that it can achieve lower fasting and pre-meal glucose levels than older insulin preparations without causing frequent unpredictable hypoglycaemic episodes—properties that would facilitate the safe attainment of good glycaemic control and a near-normal HbA_{1c} level. These results support this hypothesis. They also suggest that postprandial glucose levels may not need to be explicitly targeted to achieve good HbA_{1c} levels when insulin glargine is used to target physiological fasting glucose levels in people who are not on maximal oral therapy.

Table 3 Primary and secondary results

	Glargine *n* (%)†	Control *n* (%)†	Unadjusted*			Adjusted*		
			HR	95% CI	*P*	HR	95% CI	*P*
Two consecutive $HbA_{1c} \leq 6.5\%$	36 (17.5)	20 (10.1)‡	1.68	(1.00, 2.83)	0.049	1.71	(1.02, 2.88)	0.043
Two consecutive $HbA_{1c} \leq 7.0\%$	90 (43.7)	54 (27.1)§	1.66	(1.21, 2.29)	0.002	1.75	(1.27, 2.41)	0.001
First $HbA_{1c} \leq 6.5\%$	58 (28.2)	46 (23.1)¶	1.25	(0.87, 1.80)	0.22	1.31	(0.91, 1.89)	0.14
First $HbA_{1c} \leq 7.0\%$	120 (58.3)	88 (44.2)**	1.45	(1.13, 1.88)	0.004	1.52	(1.17, 1.96)	0.002

*Estimates of the likelihood of achieving and maintaining the indicated outcome based on the Cox regression before and after adjustment for baseline HbA_{1c}, baseline oral agent use and site.
†Fisher's *P*-values comparing the two proportions at the end of the study are as follows: ‡$P = 0.032$; §$P = 0.0006$; ¶$P = 0.3$; **$P = 0.005$.
HR, hazard ratio.

This trial has a variety of limitations and advantages. First, it was an open trial and investigators and patients were not blind to the HbA_{1c} levels. It is therefore clearly possible that more intensive glycaemic control was purposely sought in the glargine group than in the control group despite clear instructions to investigators to target an $HbA_{1c} < 7\%$ in each group using the therapeutic tools at their disposal. The fact that doses of both oral agents and insulin were increased in similar proportions at each visit reduces, but does not eliminate, this possible bias. Second, the study design precluded assessment of the durability of the effect beyond 6 months; it is possible that more titration opportunities in the control group that would have been offered by a longer study may have eliminated the glycaemic benefit of the intervention. Third, the HbA_{1c} level fell by an absolute amount of 0.3% more in the insulin glargine group than in the control group. Although this difference is modest, it was accompanied by favourable differences in other risk factors and quality of life. Fourth, promotion of self-titration of insulin glargine but not oral agents means that there were many more opportunities for glucose-lowering therapy to be adjusted in the glargine group compared with the control group and this may explain the results. However, this trial was explicitly not designed to compare the glucose-lowering efficacy of insulin glargine to the glucose-lowering efficacy of one or more oral glucose-lowering agents when used under ideal conditions. It was designed to compare the effect on HbA_{1c} levels of a therapeutic policy of insulin introduction and self-titration, as might be used in clinical practice, to a policy of oral agent adjustment as is typically used in a clinical setting, in which capillary glucose levels and HbA_{1c} levels are openly available to clinicians. As such, it says nothing about whether or not insulin-mediated glycaemic control leads to lower HbA_{1c} levels than oral agent-mediated glycaemic control under ideal conditions.

Despite the foregoing, the Canadian INSIGHT trial suggests that insulin glargine can be prescribed in both primary and specialty care to people with a wide variety of characteristics. It also supports ongoing studies of the addition of insulin glargine to: (i) rapidly control glucose levels; and (ii) determine if such an approach reduces the risk of cardiovascular and other serious outcomes.

Competing interests

HCG, JFY and SBH have received research funds, consulting and speaker fees from Sanofi-Aventis, the manufacturer of insulin glargine. MI, JAS and ED are employees of Sanofi-Aventis. Sanofi-Aventis sponsored this study.

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Appendix

INSIGHT investigators

Alberta: Gordon Bailey, Connie Ellis, Dennis Ethier, Stuart Ross, Richard Ward; *British Columbia*: Peter House, Daniel Shu, Donald Studney, Rizwan Somani; *Manitoba*: Liam Murphy, Kevin Saunders, Stewart Silagy; *Ontario*: Ronnie Aronson, James Conway, Joseph D'Ignazio, Frederick Fraser, Anne Gaskin, Amir Hanna, Robyn Houlden, Norman Isenstein, Sherif Kodsi, Cyril Lacko, Heather Lochnan, Ruth Morris, Gordon Schachter, Eckhart Schweihofer, Salim Sunderji, Yaw Twum-Barima, Robert Wahby, Min Wong; *Newfoundland*: Carol Joyce, Dennis O'Keefe, Randy Smith; *Nova Scotia*: Ehud Ur, William Booth; *Prince Edward Island*: Douglas Tweel; *Quebec*: André Bélanger, Donald Breton, Jean Duckett, Richard Dumas, Armand Elbaz, Raphaël Evanson, Richard Germain, Chantal Godin, Rafik Habib, Claude Laroche, Jean-Pascal Ouellet, Robert Paré, Maurice Pilon, Guy Tellier.

