Can family physicians help patients initiate basal insulin therapy successfully?

Randomized trial of patient-titrated insulin glargine compared with standard oral therapy: Lessons for family practice from the Canadian INSIGHT trial

Stewart Harris MD MPH FCFP FACPM **Jean-François Yale** MD CSPQ **Ellen Dempsey** MSc **Hertzel Gerstein** MD MSc FRCPC

ABSTRACT

OBJECTIVE To determine whether FPs could help patients implement bedtime basal insulin therapy as successfully as diabetes experts could.

DESIGN National, multicentre, randomized, open-label trial designed to assess use of bedtime basal insulin therapy compared with use of standard oral-agent therapy for patients with type 2 diabetes being treated by diabetes experts or FPs.

SETTING Nineteen endocrinologist or expert sites and 34 family practices.

PARTICIPANTS A total of 405 adult patients with hemoglobin A_{1c} (HbA_{1c}) values of 7.5% to 11.0% who were taking 0 to 2 oral agents.

INTERVENTION Participants were randomized to receive either basal insulin therapy using glargine self-titrated according to a patient algorithm or conventional therapy with physician-adjusted doses of oral agents for a period of 24 weeks.

MAIN OUTCOME MEASURES The primary outcome was time to achieve 2 consecutive HbA_{1c} values ≤6.5%. Secondary outcomes were the proportion of subjects who achieved these HbA_{1c} values, a fasting plasma glucose level ≤5.5 mmol/L, and 2 consecutive HbA_{1c} values ≤7.0%; incidence, rate, and severity of hypoglycemia; daily variations in blood-glucose levels; and participants' lipid profiles. Post-hoc analysis sought to determine whether patients' outcomes differed in terms of the above measures depending on whether they had been treated by diabetes experts or FPs.

RESULTS A total of 206 patients were randomized to the glargine group, and 199 to the oral agents group. In total, 145 patients were followed by experts and 260 by FPs. Mean reductions in HbA_{1c} and fasting plasma glucose levels and rates of hypoglycemia were comparable in the 2 groups. Patients of both types of physicians achieved significantly greater reductions in fasting plasma glucose with glargine than with oral agents (FPs: -4.14 vs -2.45 mmol/L, P=.0001; experts: -3.47 vs -2.19 mmol/L, P=.0013). Patients of FPs achieved significantly greater reductions in HbA_{1c} levels with glargine than with oral agents (FPs: -1.64 vs -1.26%, P=.0058; experts: -1.41 vs -1.24%, P=.3331). Final mean insulin doses were higher among FPs' patients than among experts' patients (41.74 vs 31.66 units, P=.015). Family physicians were more aggressive in their use of insulin, while experts used more oral agents. There were no significant differences in efficacy of treatment.

CONCLUSION In most settings, FPs could easily implement the patient-driven bedtime basal insulin protocol used in this study.

EDITOR'S KEY POINTS

- While many patients with type 2 diabetes could benefit from insulin, insulin prescription in primary care is very low. While many factors contribute to the low prescription rate, unfamiliarity with initiating insulin is a key factor.
- In this study, comparisons were made between targets achieved by patients being treated with a simple bedtime basal insulin protocol by diabetes experts or FPs.
- Patients treated by FPs were able to manage their diabetes with self-titrated doses of insulin glargine as effectively as patients being treated by endocrinologists or diabetes experts. Outcomes were similar in both groups.

This article has been peer reviewed.
Can Fam Physician 2008;54:550-8

Le médecin de famille peut-il aider son patient à amorcer avec succès une insulinothérapie de base?

Essai randomisé comparant les hypoglycémiants oraux standards à l'insuline glargine titrée par le patient: leçons de l'essai canadien Insight à l'intention du médecin de famille

Stewart Harris MD MPH FCFP FACPM **Jean-François Yale** MD CSPQ **Ellen Dempsey** MSc **Hertzel Gerstein** MD MSc FRCPC

RÉSUMÉ

OBJECTIF Déterminer si le MF peut aider son patient à amorcer une insulinothérapie de base au coucher avec autant de succès qu'un expert en diabète.

TYPE D'ÉTUDE Essai multicentrique national contrôlé sans insu comparant l'utilisation d'une insulinothérapie basale au coucher à l'usage d'hypoglycémiants oraux standards chez les diabétiques de type 2 traités par des experts du diabète ou par des MF.

CONTEXTE Dix-neuf cliniques d'endocrinologues ou d'experts en diabète et 34 cliniques de médecine familiale.

PARTICIPANTS Un total de 405 adultes avec des valeurs d'hémoglobine A_{1c} (HbA_{1c}) entre 7,5% et 11,0% et prenant 0-2 hypoglycémiants oraux.

INTERVENTION Les participants ont été choisis au hasard pour recevoir soit une insulinothérapie basale à l'aide de glargine auto-titrée suivant un algorithme propre au patient, soit un traitement conventionnel avec des doses d'hypoglycémiants ajustées par un médecin sur une période de 24 semaines.

PRINCIPAUX PARAMÈTRES MESURÉS L'issue primaire était le temps requis pour atteindre 2 valeurs consécutives d'$HbA_{1c} \leq 6,5\%$. Les issues secondaires étaient: nombre de sujets atteignant ce niveau d' HbA_{1c}, une glycémie à jeun ≤ 5,5 mmol/L et 2 valeurs consécutives d'$HbA_{1c} \leq 7,0\%$; incidence, taux et sévérité des hypoglycémies; variations quotidiennes de la glycémie; et profil lipidique des participants. Une analyse subséquente cherchait à savoir si les issues des paramètres ci-haut mentionnés différaient selon que les patients avaient été traités par des experts du diabète ou par des MF.

RÉSULTATS Un total de 206 patients ont été choisis pour le groupe glargine et 199 pour le groupe hypoglycémiants oraux. Au total, 145 patients ont été suivis par des experts et 260 par des MF. Les réductions moyennes d'HbA_{1c} et de glycémie à jeun et les taux d'hypoglycémie étaient comparables dans les 2 groupes. Les patients suivis par les 2 types de médecins ont atteint une diminution de glycémie à jeun significativement plus grande avec la glargine qu'avec les hypoglycémiants oraux (MF: -4,14 vs –2,45 mmol/L, P=0,0001; experts: -3,47 vs –2,19 mmol/L, P=0,0013). Les patients des MF ont obtenu des diminutions d'HbA_{1c} significativement plus grandes avec la glargine qu'avec ; les hypoglycémiants oraux (MF: -1,64 vs –1,26%, P=0,0058; experts: -1,41 vs –1,24%, P=0,3331). Les doses finales d'insuline étaient plus élevées en moyenne chez les patients des MF que chez ceux des experts (41,74 vs 31,66 unités, P=0,015). Les MF étaient plus agressifs dans l'usage de l'insuline alors que les experts recouraient davantage aux hypoglycémiants oraux. Il n'y avait pas de différence significative dans l'efficacité du traitement.

CONCLUSION Dans la plupart des contextes, le MF pourrait facilement instaurer le protocole basal d'insuline au coucher géré par le patient utilisé dans cette étude.

POINTS DE REPÈRE DU RÉDACTEUR

- De nombreux diabétiques de type 2 pourraient bénéficier de l'insuline; pourtant, très peu d'insuline est prescrite dans les soins primaires. Plusieurs facteurs contribuent à ce faible taux de prescription, mais le manque de familiarité avec l'introduction de l'insuline demeure un facteur clé.
- Dans cette étude, on a comparé les cibles atteintes par des patients traités avec un protocole basal simple d'insuline au coucher soit par des experts du diabète ou par des MF.
- Les patients traités par les MF contrôlaient leur diabète avec des doses auto-titrées d'insuline glargine aussi efficacement que ceux traités par des endocrinologues ou des experts du diabète. Les issues étaient semblables dans les deux groupes.

Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2008;54:550-8

Type 2 diabetes is a progressive disease,[1] and many patients will ultimately require exogenous insulin to achieve and maintain increasingly stringent target levels of glycemic control.[2-4] The vast majority of patients with type 2 diabetes are cared for exclusively by their FPs.[5] These patients visit their FPs an average of 8 times a year,[6] which gives physicians numerous opportunities for intensification of therapy. Most patients in North America, however, are not achieving the glycated hemoglobin target value (HbA_{1c}) of < 7.0%.[6-12]

While many patients would benefit from the addition of insulin, FPs are often unfamiliar with this therapy, are hesitant to use it, or see insulin as a therapeutic option of last resort. In an international survey of health care providers' opinions on initiating insulin therapy, 40% admitted that they preferred to delay initiating insulin until "absolutely essential."[13] Chart audit studies have confirmed that the rate of insulin prescribing in primary care is very low, ranging from 6%[10] to 20%.[8] Combination therapy (oral agents plus insulin) is also underused; rates range from 0%[8,9] to 6%.[6,10] Despite evidence to the contrary,[1,14] some physicians still fear that exogenous insulin will increase the already high risk of macrovascular complications in patients with diabetes. Other barriers to initiating insulin therapy include concerns that using it is complex and time-consuming; that patients will gain weight; that the risk of hypoglycemia will increase; and that elderly patients might make serious errors in dosing.[15,16] Compounding the problem are patients' misconceptions that requiring insulin represents a "failure" on their part or that it is an indication of worsening diabetes, and needle phobias.[17]

Dr Harris *is a Professor in the Department of Family Medicine at the Schulich School of Medicine & Dentistry and holds the Ian McWhinney Chair of Family Medicine Studies and the CDA Chair in Diabetes Management at the University of Western Ontario in London.* **Dr Yale** *is a Professor of Medicine at McGill University in Montreal, Que, and Senior Physician and Director of the Metabolic Day Centre at the Royal Victoria Hospital in the McGill University Health Centre.* **Ms Dempsey** *was a Medical Advisor in the Cardiovascular and Metabolism Division of Sanofi-Aventis Canada in Laval, Que, at the time of this study.* **Dr Gerstein** *is a Professor in the Departments of Medicine and Clinical Epidemiology and Biostatistics and holds the Population Health Institute Chair in Diabetes Research at McMaster University in Hamilton, Ont. He is also Director of the Division of Endocrinology and Metabolism at McMaster University and Head of the Service of Endocrinology and Metabolism and Director of the Diabetes Care and Research Program at Hamilton Health Sciences.*

METHODS

Design

The Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) study was a Canadian national, multicentre, randomized, open-label trial designed to assess the therapeutic strategy of using a simple patient-titration protocol for administration of basal insulin at bedtime, using the insulin analogue glargine (Lantus), compared with standard oral-agent therapy for patients with type 2 diabetes being treated by diabetes experts or FPs. Primary results of the INSIGHT trial are reported elsewhere.[18] This paper reports on a post-hoc analysis of the performance of FPs relative to that of diabetes experts in the INSIGHT trial.

Setting and participants

Physicians were recruited from 19 endocrinologist or expert sites and 34 family practices. Nonacademic community FPs were canvassed about their interest in learning more about insulin and offered a chance to participate in the trial. They were not required to have a given number of patients with diabetes. Physicians were screened to eliminate those known to be experienced in use of insulin (eg, general practitioner diabetologists).

Patients aged 18 to 80 with type 2 diabetes were recruited through newspaper advertisements and from general or specialist practices throughout Canada. To be included, patients had to have been receiving treatment for at least 3 months with 0, 1, or 2 oral agents (sulfonylurea, metformin, or repaglinide). For patients taking 2 oral agents, at least 1 of the agents had to be at or below the half-maximal dose. Other inclusion criteria were an HbA_{1c} value of 7.5% to 11%, a body mass index of 21 to 41, and no substantial change in oral agent dosing for at least the preceding 3 months. Exclusion criteria included taking insulin or a thiazolidinedione (TZD), such as pioglitazone or rosiglitazone; intolerance of metformin; working night shifts; previous ketoacidosis; serious comorbidity that might preclude completing the protocol; history of alcohol abuse; or hepatic or renal insufficiency. People taking TZDs were excluded only because a combination of insulin and TZDs is not an approved treatment in Canada.

The study design was reviewed and approved by academic ethics committees across Canada, including the University of Western Ontario and central ethics committees, and all participants provided written informed consent.

Randomization

At each practice site, consenting patients were randomized to either the treatment arm (addition of nightly basal insulin using the insulin analogue glargine and no change to oral therapy) or the control arm (optimization

of oral therapy according to Canadian diabetes guidelines[19] and physicians' usual practices). Randomization was carried out by using sealed envelopes containing one-to-one treatment allocations according to strata defined by baseline use of 0, 1, or 2 oral agents and study site.

Intervention

The study consisted of a 2-week screening phase and a 24-week treatment phase (from July 19, 2002, to June 24, 2004). Patients were assessed by their physicians at baseline and at weeks 8, 12, and 24. Telephone or in-person contact was scheduled for weeks 2 and 18.

An initial meeting of investigators was held to provide physicians and their research nurses with an overview of glycemic control and the targets of treatment (HbA_{1c} <7.0%) according to Canadian diabetes guidelines[19] and information about optimization of oral therapy, initiation and titration of insulin, and the protocol and technology employed in the study (eg, meter and injection devices). Each FP site had access to a nurse and physician at a designated "mentor" expert site who were available on request to provide informal advice on diabetes management.

All patients were given a MediSense SofTact blood-glucose meter, lancets, and strips, and were taught how to monitor their own blood glucose. All oral medications, insulin, and appropriate supplies were provided at no charge to study patients.

Patients randomized to receive glargine were given and taught how to use the OptiPen Pro 1 injection device and were provided with a supply of insulin cartridges. All participants were started on an initial dose of 10 units. They were told to inject the insulin at the same time each evening (between 9:00 PM and 11:00 PM), to check their capillary glucose levels regularly, and to increase the insulin dose by 1 unit per day until fasting plasma glucose (FPG) levels were ≤5.5 mmol/L.* According to the protocol, patients were instructed to contact the study coordinator when their FPG reached 6.5 mmol/L. Increasing doses of or the addition of new oral agents to those being taken at baseline were not permitted. Oral agents being taken at baseline were continued at the baseline dose; doses were reduced if necessary by the site investigator in response to hypoglycemia.

Patients in the control arm were managed with oral agents to reach the same FPG target of ≤5.5 mmol/L. Patients in this group did not titrate doses themselves. Physicians were advised to titrate doses or add oral agents as they would in their usual clinical practice until maximal doses of 2 of the agents were reached, and then to add a third agent if necessary. If insulin was required, neutral protamine Hagedorn (NPH) insulin was used, as glargine was not available (at the time of the study, glargine had been approved in Canada, but had not yet been launched). Only metformin, sulphonylureas, secretagogues, and TZDs were available.

A dietitian reviewed dietary strategies with each patient at the randomization visit. Each patient was instructed to record results of home blood-glucose tests at least 3 times daily, insulin doses (if applicable), information related to hypoglycemia (symptoms, blood-glucose levels, treatment), and variations in blood-glucose levels at indicated points during the day. If at any point self-monitored blood-glucose levels fell below 4.0 mmol/L, patients were instructed to call their site investigators.

Outcome measures

The predefined primary outcome was the proportion of subjects in each treatment arm who had achieved 2 consecutive HbA_{1c} values ≤6.5% at end point. Before analyzing the results and before closing the study, the steering committee unanimously elected to modify the primary outcome to time to achieve 2 consecutive HbA_{1c} values ≤6.5%, and to designate the proportion of subjects who had achieved these HbA_{1c} values at end point as a secondary outcome. Other secondary outcome measures included the proportion of patients who achieved FPG levels ≤5.5 mmol/L; the proportion of patients who achieved 2 consecutive HbA_{1c} values ≤7.0%; and the incidence, rate, and severity of hypoglycemia. Patients' treatment was deemed a success or a failure according to whether they achieved target levels as defined in the protocol. Other outcomes of interest included variation throughout the day in blood-glucose levels and lipid profiles. Data on quality of life and satisfaction with diabetes treatment were also collected and are reported in detail elsewhere.[20] Post-hoc analysis sought to determine whether there were differences in outcomes in terms of the above measures between FPs' patients and the patients of diabetes experts.

Analysis

Changes in continuous variables were evaluated using analysis of variance (ANOVA). The time for each study arm to achieve the first 2 consecutive HbA_{1c} values ≤6.5% was analyzed by constructing Kaplan-Meier curves, which were then compared using Wilcoxon tests. After inspecting the data for proportionality of hazard rates, Cox proportional hazards models were used to estimate the hazard ratio and 95% confidence interval (CI) of time to achieve the first 2 consecutive HbA_{1c} values ≤6.5%. Proportions of patients who achieved a target level by study end point were compared using Fisher exact tests. Participants who

CFPlus GO

*The patient and physician instructions and algorithms for starting insulin are available at **www.cfp.ca**. Go to the full text of this article on-line, then click on **CFPlus** in the menu at the top right-hand side of the page.

did not achieve target HbA_{1c} levels by the end of the study had their previous values carried forward.

RESULTS

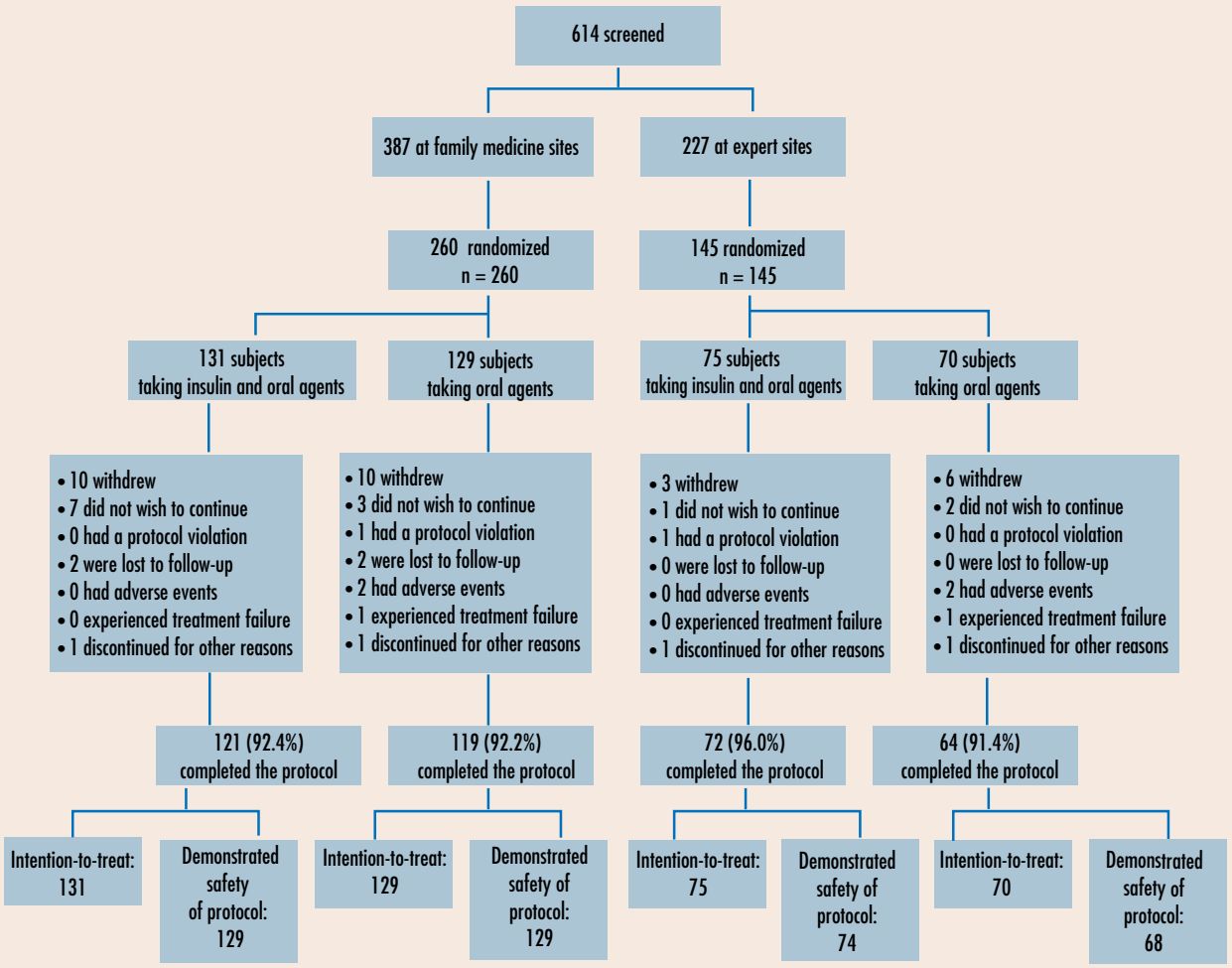
Figure 1 outlines the disposition of subjects. Reasons for failing to be randomized were comparable at expert and FP sites, with the primary reason being HbA_{1c} values out of range (74.4% and 74%, respectively). Of the 405 patients randomized, 206 were randomized to the glargine arm, and 199 to the oral-agent arm; 145 were followed by experts and 260 by FPs. More than 90% of patients in each arm completed the study.

Table 1 outlines baseline demographics and characteristics by treatment arm and type of physician. Mean baseline HbA_{1c} value was 8.6% and mean FPG level was 10.7 mmol/L. There were no significant differences in any baseline parameters between FPs' patients and experts' patients.

Primary results of the INSIGHT study are reported in detail elsewhere.[18] Briefly, 206 participants were allocated to glargine and 199 to oral agents. Compared with controls, patients in the glargine group were 1.68 times more likely to achieve 2 consecutive HbA_{1c} levels ≤6.5% (95% CI 1.00 to 2.83, P=.049); to reduce their HbA_{1c} values by 1.55% versus 1.25% (P=.005), achieving adjusted means of 7.0% versus 7.2% (P=.0007); to have lower FPG (P=.0001), non–high-density lipoprotein cholesterol (P=.02), and triglyceride (P=.02) levels; to have greater increases in treatment satisfaction (P=.045); and to have a mean of 1.9 kg greater increase in weight (P<.0001). No differences in hypoglycemia were noted.

Post-hoc analysis of primary findings by physician type showed that the trend of the treatment effect in favour of glargine was the same for patients of FPs and experts and that there was no statistically significant interaction between FPs or experts and treatment for the primary outcome (**Table 2**). Mean reductions in HbA_{1c} values (FPs: -1.45%, experts -1.33%; P=.2789), FPG levels (FPs: -3.30 mmol/L, experts -2.85 mmol/L; P=.1251),

Figure 1. Disposition of subjects



and rates of hypoglycemia (FPs: 109/260, -41.9%; experts: 75/145, -51.7%; *P*=.0616) were comparable among patients of both FPs and experts. Both FPs' and experts' patients achieved significantly greater reductions in FPG levels with glargine than with oral agents (FPs: -4.14 vs -2.45 mmol/L, *P*=.0001; experts: -3.47 vs -2.19 mmol/L, *P*=.0013) (**Figure 2A**). Family physicians' patients, however, also achieved significantly greater reductions in HbA_{1c} values with glargine than with oral agents (FPs: -1.64 vs -1.26%, *P*=.0058; experts: -1.41 vs -1.24%, *P*=.3331) (**Figure 2B**). The final mean dose of insulin was higher among FPs' patients than among experts' patients (41.74 vs 31.66 units, 95% CI 1.98 to 18.17; *P*=.015). **Figure 3A** shows median doses of insulin glargine over time for patients of both FPs and experts. **Figure 3B** shows mean number of oral agents prescribed in each treatment arm.

Table 1. Baseline characteristics of study patients

CHARACTERISTIC	PATIENTS TAKING GLARGINE AND ORAL AGENTS		PATIENTS TAKING ORAL AGENTS ONLY		*P* VALUE OF INTERACTION BETWEEN FAMILY PHYSICIANS AND EXPERTS BY TREATMENT
	FOLLOWED BY FAMILY PHYSICIANS N=131	FOLLOWED BY EXPERTS N=75	FOLLOWED BY FAMILY PHYSICIANS N=129	FOLLOWED BY EXPERTS N=70	
No. who took any drug (%)	129 (98.5)	74 (98.7)	129 (100)	68 (97.1)	...
No. who had any follow-up of HbA_{1c} levels (%)	124 (94.7)	73 (97.3)	126 (97.7)	67 (95.7)	...
Mean age in years (SD)	56.6 (9.89)	55.8 (8.65)	57.6 (10.84)	55.3 (8.47)	.492
No. of men (%)	87 (66.4)	51 (68.0)	86 (66.7)	43 (61.4)	.489
No. of women (%)	44 (33.6)	24 (32.0)	43 (33.3)	27 (38.6)	
Mean age in years at diagnosis of diabetes mellitus (SD)	49.6 (10.23)	48.3 (8.35)	50.3 (10.41)	46.7 (9.39)	.251
Mean duration in years of diabetes mellitus (SD)	7.4 (5.68)	7.9 (4.98)	7.7 (6.54)	9.2 (6.46)	.436
Mean weight in kg (SD)	89.89 (16.16)	86.48 (14.65)	90.78 (16.88)	87.84 (16.38)	.886
Mean body mass index (SD)	31.38 (4.72)	30.58 (3.83)	31.60 (4.62)	31.24 (4.57)	.639
Mean HbA_{1c} level (SD)	8.63 (1.06)	8.53 (0.93)	8.53 (0.96)	8.53 (0.97)	.624
Mean FPG level in mmol/L (SD)	10.90 (2.96)	10.21 (2.20)	10.90 (2.77)	10.25 (2.54)	.951
No. of patients taking metformin alone (%)	25 (19.08)	17 (22.67)	32 (24.81)	10 (14.29)	.256
No. of patients taking secretagogue alone (%)	30 (22.90)	9 (12)	31 (24.03)	11 (15.71)	.256
No. of patients taking metformin and secretagogue (%)	48 (36.64)	39 (52)	42 (32.56)	43 (61.43)	.256
No. of drug-naive patients (%)	28 (21.37)	10 (13.33)	24 (18.60)	6 (8.57)	.256

FPG—fasting plasma glucose, HbA_{1c}—glycated hemoglobin.

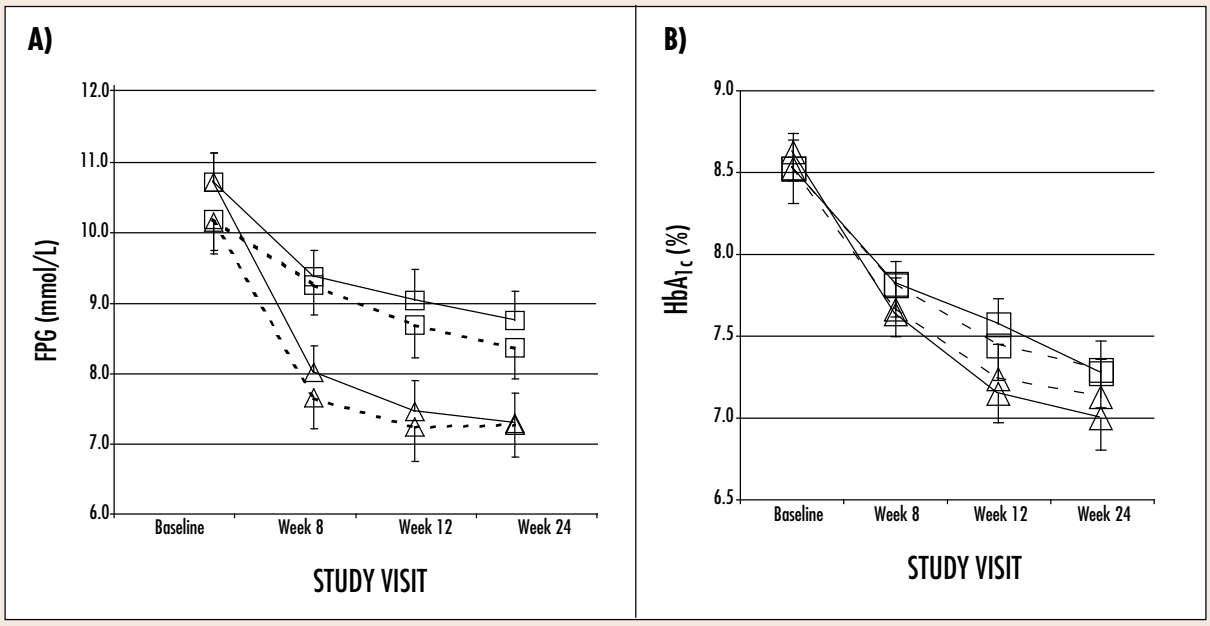
Table 2. Number and percentage of patients achieving HbA_{1c} levels ≤6.5% and sustaining them (2 or more consecutive values) at ≤7%: *Intention-to-treat population*.

HbA_{1c} LEVELS	FOLLOWED BY FAMILY PHYSICIANS				FOLLOWED BY EXPERTS				
	GLARGINE AND ORAL AGENTS N (%)*	ORAL AGENTS N (%)*	HAZARD RATE (95% CI)	*P*†	GLARGINE AND ORAL AGENTS N (%)*	ORAL AGENTS N (%)*	HAZARD RATE (95% CI)	*P*†	*P*‡
Sustained at ≤6.5%	27 (20.6)	17 (13.2)	1.69 (0.92-3.09)	.092	11 (14.7)	6 (8.6)	1.74 (0.64-4.69)	.2779	.956
Sustained at ≤7.0%	63 (48.1)	39 (30.2)	1.86 (1.25-2.77)	.002	33 (44.0)	23 (32.9)	1.36 (0.80-2.32)	.2566	.351
First reading ≤6.5%	47 (35.9)	42 (32.6)	1.21 (0.79-1.84)	.38	20 (26.7)	11 (15.7)	1.61 (0.77-3.37)	.2045	.505
First reading ≤7.0%	91 (69.5)	67 (51.9)	1.65 (1.20-2.27)	.002	45 (60.0)	36 (51.4)	1.19 (0.77-1.84)	.4404	.220

HbA_{1c}—glycated hemoglobin, CI—confidence interval.
*N—Actual number of subjects, %—Kaplan-Meier estimated percentage.
†Within-arm comparison.
‡Of interaction between family physician and expert care.

There was no statistically significant difference in weight gain between patients in each treatment arm. Experts' patients taking glargine gained 1.57 kg, while those taking oral agents gained 0.66 kg (a difference of 0.92 kg, 95% CI -0.29 to 2.13, *P*=.1369). Nor was there a significant difference in weight gain seen in the

Figure 2. Glycemic control by treatment arm at study visits at baseline, week 8, week 12, and week 24 (mean and 95% confidence intervals): *A) FPG levels. B) HbA_{1c} levels.*



FPG—fasting plasma glucose, HbA_{1c}—glycated hemoglobin.

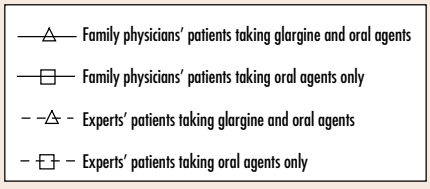
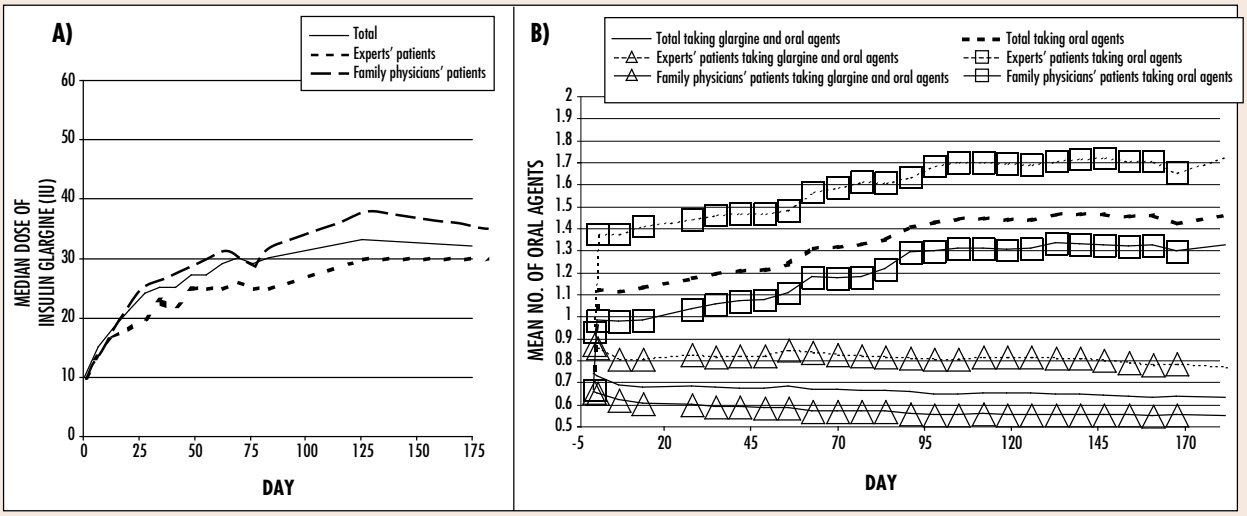


Figure 3. Medication use by day and type of physician: *A) Median dose of insulin glargine. B) Mean number of oral agents taken.*



interaction between type of physician and treatment (P=.0844). Family physicians' patients taking oral agents lost a mean 0.22 kg, while those taking glargine gained a mean 2.22 kg (a difference of 2.44 kg, 95% CI 1.46 to 3.44, P=.0001).

There was no significant difference in any lipid measurements between FPs' patients taking glargine and those taking oral agents, and no significant interaction between FPs' and experts' patients in lipid measurements.

There was significantly less 24-hour variation in blood-glucose values (as measured by the standard deviation in 24-hour 7-point glucose profiles) among FPs' patients taking glargine than among those taking oral agents (glargine -0.19 vs oral agents -0.52, difference 0.34; 95% CI 0.04 to 0.63; P=.0156). The difference in values between treatment arms among experts' patients was not significant (glargine 0.12 vs oral agents -0.19, difference 0.31; 95% CI -0.11 to 0.73; P=.3412) nor was the interaction by type of physician significant (P=.6001).

DISCUSSION

The INSIGHT trial compared use of a simple patient-driven protocol for initiation and self-titration of basal insulin therapy using insulin glargine with usual clinical care with oral agents for controlling HbA_{1c} levels.[18] Family physicians used the INSIGHT protocol as successfully as diabetes experts in terms of mean reductions in HbA_{1c} and FPG levels, rates of hypoglycemia, and lipid profiles. Patients of FPs who used basal insulin glargine had significantly less variation in blood-glucose levels over 24 hours and achieved significantly greater reductions in HbA_{1c} values than those on oral agents did.

Failure to sufficiently intensify treatment to achieve glycemic targets has been termed *clinical inertia*.[21] In a national Canadian cross-sectional survey of treatment of type 2 diabetes in primary care, Harris and colleagues[10] found that only 51% of patients had HbA_{1c} values <7.0% when only 6% were taking insulin alone and another 6% were taking insulin in combination with oral agents. When physicians were asked whether they had a plan to achieve glycemic targets in these patients, of the 56% who responded that they would intensify pharmacologic therapy or refer for specialist care, only 10% planned to increase the dose of insulin, and only 6% planned to add insulin. Shah and colleagues[22] evaluated whether specialists had less clinical inertia when caring for their diabetic patients. The authors found that 45.1% of patients under specialist care and 37.4% of patients under primary care had had their drug regimens intensified (P=.009). Most of this difference was attributed to the finding that specialists were 5 times more likely to initiate insulin than primary care physicians were. Hence, there is a need to develop and evaluate strategies to facilitate safe and efficacious use of insulin by FPs, to address gaps in knowledge, and to increase FPs' confidence in starting and titrating insulin.

Family physicians in our study achieved glycemic targets in their patients as effectively as experts did, and their confidence in the protocol was evident in the fact that their patients had a higher median dose of insulin than experts' patients had. These findings suggest that the simple patient-driven protocol gave FPs (and their patients) the necessary framework and support to use insulin confidently.

The significant difference in weight gain between patients in the 2 arms at family practice sites might be associated with the fact that FPs were more aggressive in their use of insulin while experts used more oral agents. Most weight gain with insulin therapy occurs during the first 2 years.[1] We do not know how weight would have changed over time had the patients been followed beyond the 24 weeks of this trial. These results highlight the fact that all patients with type 2 diabetes must continue to receive counseling on lifestyle and exercise in order to avoid excess weight gain.

A total of 92% of patients in the FP basal insulin arm completed the study, suggesting patients found the protocol user friendly and easy to follow. In the Treat-to-Target trial,[23] adherence to the treatment protocol also exceeded 90%; however that was a physician-driven regimen.

While glargine was the insulin used in the INSIGHT trial, it is reasonable to believe that any other basal insulin analogue including NPH insulin could be substituted in the protocol. In practice, the choice of insulin is often dictated by insurance coverage or patients' financial circumstances. While basal insulin analogues are more expensive than NPH insulin, evidence suggests that, when basal insulin is added to oral agents, an insulin analogue should be considered rather than NPH insulin to reduce the risk of nocturnal hypoglycemia.[2]

Limitations

This was an unblinded, open-label trial, so it is possible that more intensive glycemic control was targeted at the glargine group than at the oral-agent group. The fact that the doses of both oral agents and insulin were increased in similar proportions of participants between weeks 0 and 8, 8 and 12, and 12 and 24, however, suggests this was not the case. Patients in the oral-agent arm were likely being followed up frequently and might, therefore, have had more aggressive management than they would have had in routine care. Because the trial also had a relatively short (6-month) follow-up period, the degree of glycemic control that would have been seen over the longer term is uncertain. In addition, FPs in this study had access to more resources than might be available to some primary practices, and patients did not face the financial barriers that nonstudy patients might face (eg, cost of purchasing meters, testing supplies, insulin, and oral agents).

Conclusion

Results of this trial provide evidence that when FPs are given a practical patient-driven approach to initiating insulin, they are able to manage insulin therapy confidently and effectively. This study targeted known barriers to insulin initiation in family practice, such as the perceived complexity of starting insulin, time constraints, lack of access to nurses, and patients' acceptance of the regimen. In most settings, FPs could easily implement the simple patient-driven bedtime basal insulin initiation protocol used in this study.

Acknowledgment

We thank **Maher Issa, Erwan Granger, John Stewart** *of Sanofi-Aventis, and* **Susan Webster-Bogaert** *of the Centre for Studies in Family Medicine for their assistance with study design and data analysis.*

Contributors

Dr Harris, **Dr Yale, Ms Dempsey,** *and* **Dr Gerstein** *contributed to concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.*

Competing interests

The INSIGHT trial was supported by research grants from Sanofi-Aventis Canada in Montreal, Que. Oral agents, glargine insulin (Lantus), blood-glucose testing meters, and all supplies were given free of charge to patients by Sanofi-Aventis Canada. **Dr Harris** *has received honoraria for attending advisory board meetings and for making continuing medical education presentations from Sanofi-Aventis Canada, and has received grant funding for diabetes research.* **Dr Yale** *has received research funding and honoraria for speaking and consulting for Sanofi-Aventis, Eli Lilly, Novo-Nordisk, and GlaxoSmithKline. At the time of the study,* **Ms Dempsey** *was an employee of Sanofi-Aventis Canada, which sponsored this study.* **Dr Gerstein** *has received honoraria for speaking and consulting for Sanofi-Aventis, the manufacturer of insulin glargine. He has also received research grants from this company for studies using this drug.*

Correspondence to: **Dr Stewart Harris**, *Department of Family Medicine, Schulich School of Medicine & Dentistry, Centre for Studies in Family Medicine, University of Western Ontario, 245—100 Collip Circle, London, ON N6G 4X8; telephone 519 858-5028; fax 519 858-5029; e-mail* **sharris1@uwo.ca**

References

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2003;27(Suppl 2):S1-152.
3. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2006;29(Suppl 1):S4-42.
4. International Diabetes Federation. *Global guideline for type 2 diabetes*. Brussels, Belg: International Diabetes Federation; 2005. Available from: **www.idf.org**. Accessed 2006 April 17.
5. Jaakkimainen L, Biaju RS, Kopp A. Sources of physician care for people with diabetes. In: Hux JE, Booth G, Slaughter P, Laupacis A, editors. *Diabetes in Ontario: an ICES practice atlas*. Toronto, ON: Institute for Clinical Evaluative Sciences; 2003. p. 9.181-92.
6. Harris S, Stewart M, Brown JB, Wetmore S, Faulds C, Webster-Bogaert S, et al. Type 2 diabetes in family practice: room for improvement. *Can Fam Physician* 2003;49:778-85.
7. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. *Diabetes Care* 1999;22(3):403-8.
8. Worrall G, Freake D, Kelland J, Pickle A, Keenan T. Care of patients with type II diabetes: a study of family physicians' compliance with clinical practice guidelines. *J Fam Pract* 1997;44:374-81.
9. Toth EL, Majumdar SR, Guirguis LM, Lewanczuk RZ, Lee TZ, Johnson JA. Compliance with clinical practice guidelines for type 2 diabetes in rural patients. Treatment gaps and opportunities for improvement. *Pharmacotherapy* 2003;23:659-65.
10. Harris SB, Ekoé J-M, Zdanowicz Y, Webster-Bogaert S. Glycemic control and morbidity in the Canadian primary care setting. *Diabetes Res Clin Pract* 2005;70:90-7.
11. Koro CE, Bowlin SJ, Boureouis N, Fedder DO. Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care* 2004;27(1):17-20.
12. Beaton SJ, Nag SS, Gunter MJ, Gleeson JM, Sahhan SS, Alexander CH. Adequacy of glycemic, lipid and blood pressure management for patients with diabetes in a managed care setting. *Diabetes Care* 2004;27(3):694-8.
13. Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obesity* 2002;26(Suppl 3):S18-24.
14. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26:57-65.
15. Riddle MC. The underuse of insulin therapy in North America. *Diabetes Metab Res Rev* 2002;18(Suppl 3):S42-9.
16. LeRoith D, Levetan CS, Hirsch IB, Riddle MC. Type 2 diabetes: the role of basal insulin therapy. *J Fam Pract* 2004;53(3):1-9.
17. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy. The basis of patient reluctance. *Diabetes Care* 1997;20(3):292-8.
18. Gerstein HF, Yale J-F, Harris SB, Issa M, Stewart J, Dempsey E. 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. *Diabet Med* 2006;23:736-42.
19. Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, et al. 1998 clinical practice guidelines for the management of diabetes in Canada. *CMAJ* 1998;159(Suppl 8):S1-29.
20. Houlden R, Ross S, Harris S, Yale J-F, Sauriol L, Gerstein HC. Treatment satisfaction and quality of life using an early insulinization strategy with insulin glargine compared to an adjusted oral agent therapy in the management of type 2 diabetes: the Canadian INSIGHT study. *Diabetes Res Clin Pract* 2007;78(2):254-8.
21. Philips LS, Branch WT Jr, Cook CB, Doyle JP, Kebb IM, Gallina DL, et al. Clinical inertia. *Ann Intern Med* 2001;135:825-34.
22. Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control. Do specialists differ from primary care physicians? *Diabetes Care* 2005;28(3):600-6.
23. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The Treat-to-Target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26(11):3080-6.