



Does a Patient-Managed Insulin Intensification Strategy With Insulin Glargine and Insulin Glulisine Provide Similar Glycemic Control as a Physician-Managed Strategy? Results of the START (Self-Titration With Apidra to Reach Target) Study

A Randomized Noninferiority Trial

OBJECTIVE

Diabetes self-management is universally regarded as a foundation of diabetes care. We determined whether comparable glycemic control could be achieved by self-titration versus physician titration of a once-daily bolus insulin dose in patients with type 2 diabetes who are unable to achieve optimal glycemia control with a basal insulin.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes, an HbA_{1c} level >7% (53 mmol/mol), and either nocturnal hypoglycemia episodes or an insufficient basal insulin glargine level (with or without oral agents) to achieve a fasting plasma glucose level ≤6 mmol/L (108 mg/dL) were studied. Participants all had bolus insulin glulisine added at breakfast and were allocated to either algorithm-guided patient self-titration or physician titration. The primary outcome was an HbA_{1c} level ≤7% (53 mmol/mol) without severe hypoglycemia.

RESULTS

After a mean (SD) follow-up of 159.4 days (36.2 days), 28.4% of participants in the self-titration arm vs. 21.2% in the physician titration arm achieved an HbA_{1c} level of ≤7% (53 mmol/mol) without severe hypoglycemia (between-group absolute difference 7.2%; 95% CI −3.2 to 17.7). The lower end of this 95% confidence interval was within the predetermined noninferiority boundary of −5% (*P* non-inferiority = 0.011).

CONCLUSIONS

In stable patients with type 2 diabetes who are receiving doses of basal insulin glargine who require bolus insulin, a simple bolus insulin patient-managed titration algorithm is as effective as a physician-managed algorithm.

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Due to the progressive nature of type 2 diabetes mellitus, exogenous insulin is often required to sustain optimal metabolic control (1). This is a particular challenge in the primary care setting where the conditions of >90% of patients with type 2 diabetes are managed (2), and where there is a lack of confidence and skill in insulin intensification strategies (3). Basal insulin analogs are often added to oral

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anti-hyperglycemic agents (OADs) (4,5) with a number of successfully tested algorithms for initiation and titration (6–9). Indeed, these patient-driven basal insulin algorithms have been demonstrated to be safe and efficacious in improving glycemic control (6,7), and have been successfully implemented in the primary care practice setting (10).

Over time, basal insulin may be insufficient to maintain optimal glycemia control in patients with type 2 diabetes due to a rise of postprandial glucose levels despite normal fasting glucose levels. Hence, to achieve glycemic targets, treatment of type 2 diabetes may have to progress beyond basal insulin. Because HbA_{1c} level reflects the contribution of both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels, optimal insulin therapy should focus on both FPG and PPG (11–18). Elevated FPG level is often targeted first with basal insulin, while elevated PPG level indicates the need for bolus insulin (19). Thus, the addition of bolus insulin has been recommended when HbA_{1c} levels remain above target despite achieving an acceptable FPG with basal insulin (20).

There has been increasing acceptance of a strategy that progressively adds bolus to basal insulin (21–24). However, the optimal way to do this is not clear. It is also unclear whether a patient-driven self-titration algorithm would achieve glycemic control that was comparable to that achieved by physician-titrated preprandial insulin. This question was assessed in the Self-Titration with Apidra to Reach Target (START) randomized controlled trial.

RESEARCH DESIGN AND METHODS

START was a randomized, parallel-group, open-label, stratified multicenter clinical trial designed to determine whether patient self-titration of a preprandial insulin dose was noninferior to physician titration in people with type 2 diabetes who were unable to achieve optimal glycemia control with a basal insulin. A noninferiority design was chosen to determine whether a patient-managed basal-plus insulin titration algorithm was similar to a physician-managed basal-plus insulin titration

algorithm in patients with poorly controlled type 2 diabetes.

This trial was conducted in 47 primary care sites across Canada. Volunteer patients with type 2 diabetes (age ≥ 30 years) were recruited at each site. Patients were eligible to enter the 12-week run-in phase if they were treated for at least 3 months and either 1) were receiving treatment with basal insulin (insulin glargine, NPH insulin, or insulin detemir) as their only insulin with or without OADs and had an HbA_{1c} level $>7.0\%$ (53 mmol/mol), or 2) were insulin-naïve but taking two or three OADs and had an HbA_{1c} level $\geq 7.8\%$ (62 mmol/mol).

During the run-in phase, patients either began or self-titrated bedtime insulin glargine (glargine) doses using the INSIGHT protocol (i.e., increasing by 1 unit/day until the prebreakfast capillary glucose value was ≤ 5.5 mmol/L [99 mg/dL]) (6). Patients not receiving insulin at baseline started glargine therapy at 10 units/day (6); patients receiving glargine were started on their existing dose; patients receiving once-daily NPH insulin switched to the same dose of glargine; patients receiving twice-daily NPH insulin started glargine therapy at 80% of the total daily NPH insulin dose (but not <10 units/day); patients receiving once-daily or twice-daily insulin detemir started glargine therapy at 70% of the total daily insulin detemir dose (but not <10 units/day).

Patients entered the 24-week randomized treatment phase if their HbA_{1c} levels remained $>7.0\%$ (53 mmol/mol) and they had either 1) one or more episodes of confirmed nocturnal hypoglycemia (blood glucose level <4.0 mmol/L [72 mg/dL]; or 2) two or more measurements of FPG ≤ 6.0 mmol/L (108 mg/dL) within the previous week (i.e., there was no “glycemic room” to continue glargine uptitration). At each site, patients were randomized 1:1 to either the patient-managed or physician-managed titration algorithms using concealed allocation. Randomization was stratified by site and previous basal insulin use.

Intervention

After randomization, all patients continued receiving their fixed glargine

dose and added insulin glulisine (glulisine) before breakfast. Patients were instructed to eat their usual breakfast and were not required to log their diet. Breakfast was chosen for the following reasons: 1) to maximize patient safety by reducing the risk of nocturnal hypoglycemia; 2) to expand on the common practice that many patients receiving a basal insulin routinely test their blood glucose in the morning and that the addition of a breakfast prandial insulin self-titration algorithm requires only one extra self-monitoring test later in the same morning; 3) patient convenience of injecting at home; 4) optimization of blood glucose levels earlier in the day may help to maintain good glycemic control for the remainder of the day; and 5) it may be easier for patients to pursue self-titration sequentially with the same dosage titration algorithm to adjust for injection at subsequent meals in their future care.

Those randomized to the patient-managed arm received a pamphlet explaining the self-titration method. The starting dose of glulisine was 2 units, and they were instructed to self-titrate 1 unit/day to reach a target 2-h PPG level between 5.0 and 8.0 mmol/L (90 and 144 mg/dL). The PPG was measured 2 h after the start of breakfast. Once the target was attained, the maintenance dose was based on the monitoring of two or three 2-h PPGs per week.

Those randomized to the physician-managed arm had a starting dose of insulin glulisine of 2 units recommended to the physicians, but this dose, and the titration and self-monitoring of blood glucose schedules, were left to the physicians' discretion. Patients in this arm were required to contact their physician prior to any dose adjustment.

Primary and Secondary Outcome Measures

The primary outcome was the achievement of an HbA_{1c} level of $\leq 7\%$ (53 mmol/mol) without severe hypoglycemia 24 weeks after randomization. Secondary outcome measures included changes in HbA_{1c} level, FPG, 7-point blood glucose profile (fasting before breakfast, 2 h after

breakfast, before lunch, 2 h after lunch, before dinner, 2 h after dinner, and at bedtime), and body weight from randomization to end point. Blood glucose levels and the 7-point blood glucose profile were measured by patients using a self-monitoring of blood glucose system (FreeStyle Lite blood glucose meter plus test strips; Abbott). The change between FPG and 2-h PPG levels and the total area under the 7-point glucose profile curve were calculated.

Hypoglycemic and adverse events were monitored for safety. All hypoglycemic episodes were recorded and were deemed confirmed if accompanied by a documented glucose value. Annualized rates for hypoglycemia were calculated for those who had any hypoglycemic events as the total number of episodes/total patient-years. Nocturnal and severe (required assistance and FPG level <2.0 mmol/L [36 mg/dL] or responded to counteractive treatment) episodes were noted.

Other secondary outcome measures included the dose of glulisine and health resource utilization (numbers of blood glucose test strips used, office visits, and telephone calls to physician).

Patient satisfaction with treatment was assessed with the Diabetes Treatment Satisfaction Questionnaire (an eight-item questionnaire scored from -3 to 3) (25). Physician satisfaction with the two insulin titration algorithms was assessed at the study end with a brief seven-question survey using a 7-point Likert scale scored from 3 to -3 (see the Supplementary Data).

Statistical Methods

Intent-to-treat (ITT) analysis was performed on the primary outcome for all randomized patients. The primary outcome, the proportion calculated with patients meeting the end criteria ($HbA_{1c} \leq 7.0\%$ [53 mmol/mol] with no severe hypoglycemia) in the numerator and all patients randomized to that group in the denominator. Patients missing end point data were assumed not to meet it.

The sample size of 320 randomized patients (160 patients for each titration algorithm) was based on an expected 10% difference between titration

algorithms for the primary outcome with an 80% power and a nonclinically significant difference/margin of 5%.

To define noninferiority, the 95% CI of the difference between treatment algorithms was examined, and if the lower end of the CI was -5.0% or greater, the patient-managed arm was deemed noninferior to the physician-managed arm. The noninferiority boundary of -5.0% or greater was based upon the clinically important absolute difference of 10%; one half of this absolute difference was selected as the boundary. A test for the significance of the noninferiority was performed.

Secondary outcome analyses were performed for a modified ITT population. This population included all randomized patients treated with glulisine who had results for visits at 12 or 24 weeks postrandomization. Secondary outcome between-group differences were assessed using ANCOVA, with change from randomization as the dependent variable, treatment and pooled site as the independent variables, and randomization value as the covariate. Within-group differences were analyzed using one-way ANOVA.

Poisson regression was planned for the analysis of the annualized rates for hypoglycemia; however, because of overdispersion, the analysis was performed using negative binomial regression.

The study design was approved by academic ethics review boards across Canada, including that of The University of Western Ontario. All patients provided written informed consent.

RESULTS

Site Investigator Characteristics

Forty-seven physician sites participated in the START trial. Physicians were predominately male (87.8%), had a mean age of 53.5 years (SD 8.0 years), and had been practicing for 26 years (SD 8.6 years). Most physicians practiced primary care medicine (90%) in an urban setting (75%), had access to allied health staff (75.6%), and had >150 patients with diabetes (80.5%).

Study Population

At the end of the run-in phase, 49% of patients (316 of 641 patients) were

randomized. Figure 1 outlines the disposition of patients including 170 of 641 patients who did not meet randomization requirements but were observed. The dropout rates were 6.5% (10 of 154 patients) and 11% (18 of 162 patients), respectively, for the patient-managed and physician-managed groups.

Patient baseline demographics and clinical characteristics were comparable between intervention groups (Table 1). Patients were predominantly male (60.8%) with a mean age of 60.4 years. Median follow-up time was 168 days for both the patient-managed arm and physician-managed arms.

Primary Outcome

After a mean follow-up time of 159.4 days (SD 36.2 days), the primary outcome was achieved by 28.4% of subjects in the patient-managed arm and 21.2% in the physician-managed arm, an absolute difference of 7.2% (95% CI -3.2 to 17.7). The lower end of the 95% CI for the difference, -3.2 , was within the predefined noninferiority boundary (set at -5.0% or greater), demonstrating noninferiority ($P = 0.0105$) of the patient-managed group.

Secondary Outcomes

Glycemic Control

Over the course of the study (randomization to end of treatment) HbA_{1c} , the change between FPG and 2-h PPG levels, and the total area under the 7-point glucose profile curve decreased significantly for both the patient-managed and physician-managed groups. No statistically significant differences between the titration algorithms were evident (Table 2).

There was a significant increase in FPG level in both the patient-managed and physician-managed groups, with no significant difference between algorithms (Table 2).

Medication Dose

Glargine dose did not significantly increase within or between groups after the run-in phase: mean units at randomization, and 12 and 24 weeks were 59.2, 58.1, and 59.8 units, respectively, for the patient-managed group and 53.1, 53.6, and 53.0 units, respectively, for the physician-managed group.

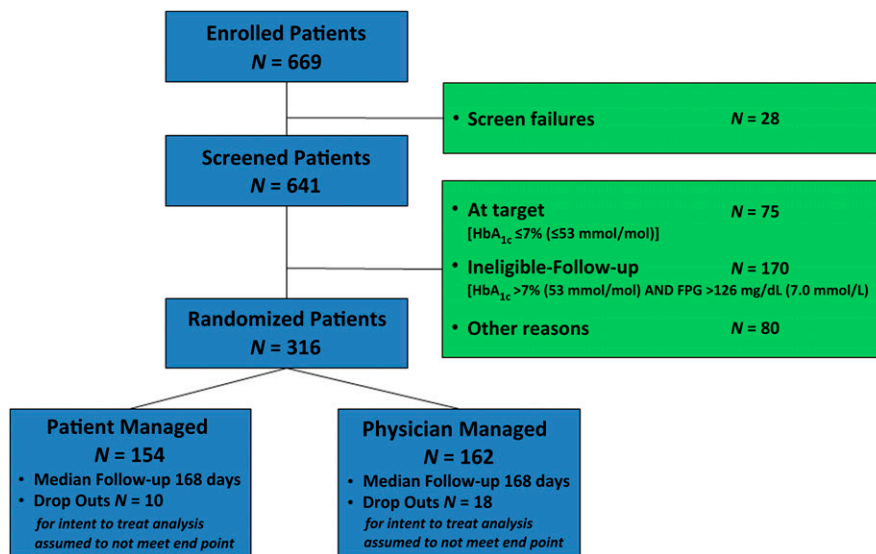


Figure 1—Disposition of patients.

After randomization, mean glulisine dose significantly increased for patients in both groups ($P = 0.0001$). The patient-managed group increased from 2.0 ± 0.47 to 16.3 ± 17.57 units, and the physician-managed group increased

from 2.5 ± 1.11 to 12.0 ± 11.29 units. This increase was significantly higher by the end of treatment for patient-managed patients with an adjusted mean difference of 5.6 (SE 1.77) (95% CI 2.1–9.1, $P = 0.0018$).

Quality of Life

No significant differences in quality of life were evident between groups as assessed by the patient total satisfaction score and perceived hyperglycemia/hypoglycemia. Patients ranked their mean satisfaction as “high” (of 18) by the end of their treatment (patient-managed group 13.39 ± 5.32 ; physician-managed group 13.26 ± 5.90).

Resource Utilization

There were no between-group differences in the number of blood glucose testing strips used and visits to a healthcare professional. The number of telephone calls made to the physician’s office were significantly lower for patients managing their own treatment, with an adjusted mean difference of -0.74 calls (SE 0.20) (95% CI -1.14 to -0.35 , $P = 0.0001$).

Body Weight

Mean body weight significantly increased ($P < 0.001$) from randomization to the end of treatment for both the patient-managed (98.54 ± 21.15 – 100.56 ± 21.68 kg) and physician-managed (99.09 ± 22.86 – 100.23 ± 23.50 kg) groups. Between-group analysis showed a significantly higher increase at the end of treatment for the patient-managed group, with an adjusted mean difference of 0.87 kg (SE 0.44) (95% CI 0.00–1.73, $P = 0.0494$).

Safety Hypoglycemia

There was no difference between the groups for the proportion of patients

Table 1—Patient baseline demographics and clinical characteristics by titration algorithm, all randomized patients (n = 316)

Demographics and characteristics	Patient-managed group (N = 154)	Physician-managed group (N = 162)	P value
Age, mean (SD), years	60.4 (10.0)	60.2 (9.8)	0.72
Male, n (%)	90 (58.4)	102 (63.0)	0.50
Caucasian, n (%)	142 (92.2)	137 (84.6)	0.04
BMI (kg/m ²)	34.1 (7.2)	34.3 (7.9)	0.74
Duration of diabetes, mean (SD), years	12.1 (8.0)	12.2 (8.6)	0.86
HbA _{1c} at randomization, mean (SD)			
%	8.2 (0.8)	8.3 (1.3)	0.86
mmol/mol	66 (8.7)	67 (14.2)	
Insulin-naïve patients, n (%)	75 (48.7)	81 (50.0)	
or			0.94
Patients on basal insulin at screening, n (%)	79 (51.3)	81 (50.0)	
Duration of basal insulin therapy, mean (SD), years	2.2 (3.4)	2.5 (2.7)	0.42
Patients on oral antihyperglycemic medications at screening, n (%)	149 (96.8)	159 (98.1)	0.49
Duration of OADs, mean (SD), years	8.4 (6.6)	8.5 (6.8)	0.93
OADs at screening, mean (SD), n	2.1 (0.7)	2.0 (0.7)	0.47
Patients with diabetes-related complications at screening, n (%)			
Nephropathy, n (%)	47 (30.5)	57 (35.2)	0.38
Retinopathy, n (%)	21 (13.6)	24 (14.8)	0.76
Foot ulcers, n (%)	15 (9.7)	12 (7.4)	0.46
Neuropathy, n (%)	3 (1.9)	4 (2.5)	0.75
Neuropathy, n (%)	19 (12.3)	39 (24.1)	0.01
Cardiovascular disease, n (%)	37 (24.0)	37 (22.8)	0.80
Cerebrovascular disease, n (%)	5 (3.2)	9 (5.6)	0.32
Peripheral vascular disease, n (%)	4 (2.6)	5 (3.1)	0.79

Table 2—Within-group and between-group change from randomization to end of treatment for glycemic control (modified ITT patients)

Glycemic control	Group	Descriptive statistics		Change at end of treatment (within-group <i>P</i> value)	Change at end of treatment between groups	
		Randomization	End of Treatment		95% CI	Between-group <i>P</i> value*
HbA _{1c} %	PM (N = 154)	8.2 (0.8)	7.7 (0.9)	0.0001	−0.27 to 0.13	0.49
mmol/mol		66 (8.3)	60 (9.5)			
%	HCPM (N = 159)	8.3 (1.06)	7.8 (1.2)	0.0001	−0.27 to 0.13	0.49
mmol/mol		67 (11.6)	62 (13.3)			
Difference between FPG and 2-h PPG levels (mmol/L)	PM (N = 121) [†]	3.7 (2.7)	1.4 (3.0)	0.0001	−1.13 to 0.49	0.43
	HCPM (N = 129)	4.4 (3.2)	1.8 (3.2)	0.0001		
FPG mmol/L	PM (N = 121)	6.2 (2.1)	6.8 (2.2)	0.039	−0.33 to 0.76	0.44
mg/dL		112.1 (37.1)	122.0 (39.2)			
mmol/L	HCPM (N = 129)	6.0 (1.7)	6.6 (2.1)	0.0097	−0.33 to 0.76	0.44
mg/dL		108.4 (31.0)	119 (38.5)			
Total area under 7-point glucose profile (mmol/L* h)	PM (N = 121)	215.2 (40.7)	202.9 (40.0)	0.0045	−10.42 to 9.60	0.94
	HCPM (N = 129)	225.6 (49.8)	206.0 (44.8)	0.0001		

Data are mean (SD), unless otherwise stated. PM, patient-managed; HCPM, health care professional–managed. *These are between-group results where change from randomization to the end of treatment was compared between PM and HCPM groups using ANCOVA. Change from randomization was the dependant variable, with treatment and pooled site as the classified independent variables, and randomization value as the covariate. †A total of 33 patients in the PM group and 30 patients in the HCPM group did not provide 7-point glucose readings.

who experienced a minimum of one hypoglycemic event (Table 3). Annualized symptomatic hypoglycemic events were 7.1 confirmed events per person per year in the patient-managed group, and 6.2 in the physician-managed group ($P = 0.5074$). The annualized rates for only those patients with at least one confirmed hypoglycemic event were 11.1 and 10.4, and were not significantly different ($P = 0.6531$). The majority of hypoglycemic events, 58.3% and 62.7%, respectively, for the patient-managed and physician-managed groups, occurred between 6:00 A.M. and noon.

Physician Satisfaction

Forty-one physicians responded to the satisfaction survey (return rate 87%), with a mean satisfaction score of 14.0 ± 7.21 (range −6 to 21). By the end of the trial, the majority of physicians (61%) reported a very high level of confidence initiating and intensifying insulin therapy.

CONCLUSIONS

This large, prospective, multicenter randomized controlled trial demonstrated that similar glycemia control can be achieved by patients using a simple breakfast preprandial insulin titration approach when compared with a physician-managed strategy. The self-titration intervention

was designed to capitalize on the common practice that most patients receiving a basal insulin routinely test their blood glucose in the morning (6), and the addition of a breakfast prandial insulin self-titration algorithm requires only one extra self-monitoring test later in the same morning, hence maximizing patient convenience. In addition, the START study was performed in primary care practices, highlighting the feasibility of an insulin intensification strategy in this setting.

In the START study, patients responsible for managing their insulin titration were more aggressive at titrating glulisine when compared with the physician-managed group (16.3 vs. 12 units, $P = 0.0018$). As well, the START study modified basal-bolus strategy significantly improved HbA_{1c} levels for both groups. This improvement was despite rising FPG levels after randomization when, by protocol, the dose of basal insulin was fixed. This highlights the relative contribution of breakfast PPG to overall control.

Furthermore, patients were satisfied with their treatment despite increases in body weight and at least one confirmed hypoglycemic episode occurring in the majority of patients (63.6% and 58.6%). The proportion of episodes defined in the START study as <3.1 mmol/L (55.8 mg/dL) were 33.8%

and 30.9% similar to Lankisch et al. (22), who reported 34.2% when defined as <3.3 mmol/L (59.4 mg/dL).

These findings build on other studies comparing patient and physician insulin titration approaches. Selam and Meneghini (26) compared a patient algorithm to a standard care physician adjustment of basal insulin for patients receiving basal-bolus insulin therapy. Patients using the algorithm increased their dose to a significantly greater extent and achieved significantly greater reductions in FPG levels. There were no significant differences in the patient versus physician titration for reduction in HbA_{1c} levels or the rate of hypoglycemic events. Davies et al. (7) compared patient- and physician-titrated basal insulin algorithms for patients suboptimally controlled and found no significant difference in the rate of severe hypoglycemia; however, the physician-titrated group had a significantly lower overall incidence of hypoglycemia. The patient titration group resulted in a significantly increased dose of basal insulin and greater reduction in levels of HbA_{1c} and FPG. Combined with the results of the START trial, these studies demonstrate that patients can successfully titrate both basal and bolus insulin.

Studies have identified that patients in the primary care setting often fail to

Table 3—Hypoglycemia event rates by titration algorithm

Type of symptomatic hypoglycemic episodes	PM	HCPM	Between-group difference (95% CI)	P value
Patients with at least one symptomatic hypoglycemic episode (%) ^a				
All hypoglycemic episodes	67.5	61.1	−17.0 to 4.1	0.23
All confirmed hypoglycemic episodes	63.6	58.6	−15.7 to 5.7	0.36
Episodes at <3.1 mmol/L (55.8 mg/dL)	33.8	30.9	−13.2 to 7.4	0.58
Nocturnal	26.0	28.4	−7.4 to 12.2	0.63
Severe	1.9	1.9	−3.1 to 2.9	0.95
Annualized episode rate, based on negative binomial regression ^a				
All hypoglycemic episodes	8.9	8.1	0.62 to 1.32	0.61
All confirmed hypoglycemic episodes	7.1	6.2	0.60 to 1.29	0.51
Episodes at <3.1 mmol/L (55.8 mg/dL)	1.4	3.6	0.45 to 1.25	0.27
Nocturnal	0.9	0.8	0.53 to 1.58	0.75
Severe	0.02	0.03	0.24 to 9.32	0.68
Annualized episode rate for patients having at least one event, based on negative binomial regression ^b				
All hypoglycemic episodes	13.2	13.0	0.76 to 1.28	0.93
All confirmed hypoglycemic episodes	11.1	10.4	0.71 to 1.24	0.65
Episodes at <3.1 mmol/L (55.8 mg/dL)	2.9	2.3	0.52 to 1.26	0.34
Nocturnal	3.5	2.9	0.58 to 1.15	0.25
Severe	1.3	1.7	0.32 to 5.62	0.69

PM, patient-managed; HCPM, health care professional-managed. ^aPatient-managed, N = 154; HCP-managed, N = 162. ^bPatient-managed, N = 104; HCP-managed, N = 99.

achieve optimal targets because of clinical inertia involving insulin titration (3). A stepwise approach recommended by Raccach et al. (24) may help to overcome patient (27–29) and physician (27,30) barriers to the initiation and titration of insulin. The START study used an empowerment approach (31) to patient care by supporting patients to make autonomous, informed decisions about their diabetes self-management. Patient understanding and involvement in their treatment (24), and a collaborative relationship between the physician and patient is important to improve compliance and achieving glycemic goals (32,33).

This study also highlights the need for a basal-plus strategy for patients similar to these study patients within a primary care practice, because 56% of patients (315 of 561 patients) to whom basal insulin was prescribed required prandial insulin intensification after the 12-week run-in phase. This is consistent with the value of 30–50% reported elsewhere (24). In addition, for those who do initially achieve target on basal insulin

alone, ~25% will eventually require bolus insulin (34). Because only 21% and 28% of patients in this trial achieved optimal control with no severe hypoglycemia highlights the fact that additional bolus therapy at other meals may be required.

Limitations

The START study was an open-label trial, and both physicians and patients were aware of the patient's randomization status and may have cointervened in unmeasured ways depending on their biases regarding patient-directed versus physician-directed insulin titration.

The glargine dose at randomization was maintained and may have diminished the opportunity for optimal glycemic control, but because this protocol occurred for both groups it affected both groups equally and was unlikely to affect the primary outcome. Nevertheless, this study provides preliminary data to demonstrate the feasibility and safety of implementing insulin intensification in a primary care clinical environment.

In summary, the START study offers a potential strategy to mitigate clinical inertia involving insulin intensification in the primary care setting and resulted in an overall improvement in glycemic control. A patient-driven algorithm for basal insulin plus bolus insulin at breakfast is a simple, safe, and effective strategy to improve glycemic outcomes without severe hypoglycemia in the primary care environment.

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