Achievement of Target A1C <7.0% (<53 mmol/mol) by U.S. Type 2 Diabetes Patients Treated With Basal Insulin in Both Randomized Controlled Trials and Clinical Practice

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ABSTRACT

Objective. Many patients with type 2 diabetes do not reach glycemic goals despite basal insulin treatment. This study assessed the achievement of a target A1C <7.0% (<53 mmol/mol) after initiation of basal insulin in two settings.

Methods. This was a retrospective analysis of pooled randomized controlled trial (RCT) data, from 11 24-week studies of patients initiating basal insulin performed between 2000 and 2005 and of outpatient electronic medical record (EMR) data from the General Electric Centricity database for insulin-naive patients initiating basal insulin between 2005 and 2012. Baseline characteristics stratified by target A1C and fasting plasma glucose (FPG) attainment were compared descriptively.

Results. In the RCT dataset, 49.0% of patients failed to achieve the target A1C at 6 months versus 72.4% and 72.9% at 6 and 12 months in the EMR dataset, respectively. Despite this, in the RCT dataset, 79.4% of patients achieved the target A1C and/or an FPG <130 mg/dL. In the EMR dataset, only 47.6% and 47.3% of patients achieved an A1C <7.0% and/or FPG <130 mg/dL at 6 and 12 months, respectively. Overall, patients with an A1C >7.0% had a longer diabetes duration and were more likely to be female, nonwhite, and self-funding or covered by Medicaid. Among patients with an A1C >7.0%, more RCT patients (58.0%) had an FPG <130 mg/dL than EMR patients at 6 (27.8%) and 12 months (27.7%).

Conclusion. Unmet needs remain after basal insulin initiation, particularly in real-world settings, where many patients require further insulin titration. In both populations, patients failing to achieve the target A1C despite attaining an FPG <130 mg/dL require interventions to improve postprandial control.

Type 2 diabetes is a progressive disease and, in most patients, intensification of treatment over time is required to attain and maintain glycemic control (1). Poor glycemic control in patients with type 2 diabetes is associated with microvascular and macrovascular complications (2–4), and intensive treatment regimens that improve glycemic control can reduce the risk for the development and progression of these complications (5–9).

For most adult, nonpregnant patients with diabetes, the American Diabetes Association (ADA) recommends a target A1C of <7.0% (<53 mmol/mol) (10), ideally with a fasting plasma glucose (FPG) of 80–130 mg/dL (4.4–7.2 mmol/L) and a peak postprandial glucose (PPG) of <180 mg/dL (10.0 mmol/L) (10). Initial treatment of diabetes tends to focus on controlling FPG, which is the major driver of hyperglycemia in patients with an A1C ≥8.5% (≥69 mmol/mol) (11).

Despite advances in the management of type 2 diabetes, there remain unmet needs with regard to

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antihyperglycemic therapy. This study assessed the achievement of target A1C (defined as an A1C <7.0%) with basal insulin using both randomized controlled trial (RCT) data and "real-world" data from a retrospective analysis of electronic medical records (EMRs). It also assessed the baseline characteristics of patients with type 2 diabetes who did not achieve target glycemic control on basal insulin. The study further characterized the population of patients who did not achieve a. target A1C on basal insulin but did achieve an FPG goal of <130 mg/dL. In comparing real-world and RCT data, this study aims to better characterize patients who do not reach glycemic goals with basal insulin alone to inform future management decisions regarding treatment intensification.

Materials and Methods

Study Design and Patients

This was a retrospective analysis of pooled RCT data and data from the General Electric (GE) Centricity EMR database.

Pooled RCT Data

Clinical trial data were obtained from eligible clinical studies performed by Sanofi or predecessor companies between 2000 and 2005. The study analyzed prospective, randomized, controlled, 24-week clinical studies conducted according to Good Clinical Practice standards of patients with diabetes using insulin therapy added to lifestyle modification alone or stable oral antihyperglycemic drug (OAD) therapy. In total, 11 studies met the criteria for inclusion (Supplementary Table 1) (12–21). Data were included from patients on basal insulin (glargine or NPH) with A1C and FPG values at both baseline and 6 months. Data collected included patient demographics and clinical characteristics at baseline and measures of glycemic control at both baseline and 6 months.

Real-World EMR Study Data

The GE Centricity EMR database was used by >30,000 physicians as of 2007 and contains the medical records for ~30 million patients from 49 U.S. states (22). Data were extracted for patients aged ≥18 years with a supposed diagnosis of type 2 diabetes (*International Classification of Diseases*, 9th revision, Clinical Modification diagnosis codes 250.x0 or 250.x2 [23]) who initiated basal insulin between January 2005 and January 2012 and who were previously treated with OADs alone. The date of the first basal insulin prescription was termed the index date. Eligible patients had EMR data available for ≥6 months before the index date, with no prescribed insulin during this timeframe; ≥1 OAD prescription during the 6 months before the index date; and ≥1 follow-up A1C measurement at 6 or 12 months post-index date. Data on patient characteristics, treatment patterns, and clinical outcomes of patients were extracted from EMRs. Patients were also categorized by the Charlson Comorbidity Index (CCI) (24), a weighted index that predicts 1-year mortality for patients diagnosed with a range of comorbid conditions. A score of 1, 2, 3, or 6 is assigned to each condition, depending on the risk of death occurring. As the comorbidity index increases, the cumulative mortality attributable to comorbid disease also increases.

Patient Outcomes and Analysis Populations

Baseline patient data from both the pooled RCT and real-world analyses were stratified by A1C levels <7.0% or ≥7.0% at 6 months (RCT and EMR data) and 12 months (EMR data); and FPG <130 mg/dL or ≥130 mg/dL at 6 months (RCT and EMR data) and 12 months (EMR data).

Primary analyses were conducted to descriptively compare baseline demographics and clinical characteristics of patients who achieved an A1C <7.0% on a basal insulin regimen to those who did not. For patients who did not achieve a target A1C <7.0% on a basal insulin regimen, baseline demographics and clinical characteristics of those who had an FPG <130 mg/dL versus those who had an FPG ≥130 mg/dL were compared.

Statistical Analyses

All data were compared descriptively; no analyses to determine statistical significance between baseline characteristics of stratified datasets were conducted.

Results

Study Population

RCT data for 3,082 patients on basal insulin were included in the analysis; real-world EMR data for 1,612,343 patients with type 2 diabetes were initially extracted from the GE Centricity database (Supplementary Figure S1). Of the 3,082 patients in the RCT dataset, 2,600 patients were on insulin glargine or NPH insulin, of which 2,494 had A1C and FPG data available at 6 months. More patients had both A1C and FPG data at 12 months than at 6 months; hence, 12,562 and 14,038 patients from the EMR database were eligible for inclusion at 6 and 12 months, respectively.

In the RCT dataset, 1,223 patients (49.0%) failed to achieve a target A1C <7.0% at 6 months (Figure 1). Of the patients who failed to reach this target, 58.0% achieved an FPG <130 mg/dL. Therefore, the majority of patients (79.4%) in the RCT dataset achieved a target A1C and/or an FPG <130 mg/dL, indicating a reasonably appropriate titration of their basal insulin.

In the EMR dataset, 9,098 patients (72.4%) failed to achieve a target A1C <7.0% at 6 months, and 10,233 (72.9%) failed to achieve the target at 12 months. At 6 months, only 27.8% of the patients who failed to achieve the target A1C had an FPG <130 mg/dL, whereas 63.1% of patients who had a target A1C achieved an FPG level <130 mg/dL.

Only 47.6% of EMR patients achieved the target A1C level and/or an FPG <130 mg/dL at 6 months, which could be surmised as likely

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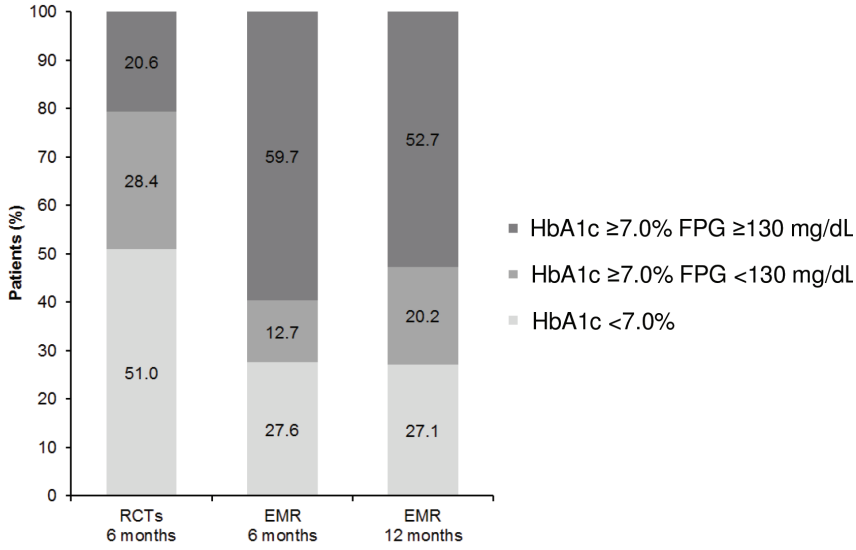

FIGURE 1. Proportion of patients stratified by achieved A1C and FPG targets at 6 and 12 months. The graph represents data from pooled RCTs from 11 24-week studies of patients initiating basal insulin between 2000 and 2005 and from outpatient EMR data from the GE Centricity database for insulin-naive patients initiating basal insulin between 2005 and 2012.

inadequate titration of basal insulin in this population.

At 12 months, 27.7% of patients not reaching the A1C target achieved an FPG <130 mg/dL, and 72.3% had an FPG ≥130 mg/dL. A total of 47.3% of patients had a target A1C <7.0% and/or an FPG <130 mg/dL at 12 months. Of the patients who achieved the target A1C, 64.0% also achieved an FPG <130 mg/dL.

Baseline Characteristics of Patients Who Did Not Achieve Target A1C on Basal Insulin

Table 1 shows baseline patient data stratified by A1C as assessed at 6 and 12 months. Ages of patients reaching and failing to reach a target A1C <7.0% were similar in the RCT (A1C ≥7.0 vs. <7.0%: 58.0 vs. 58.3 years) and EMR datasets (A1C ≥7.0 vs. <7.0%: 60.2 vs. 62.3 years at 6 months and 59.8 vs. 62.7 years at 12 months). In the RCT dataset, the proportion of women with a target A1C after 6 months was lower than the proportion of men (46.4 vs. 54.6%), but in the EMR dataset these values were similar at both time points (Table 1). The proportion of white patients achieving the target A1C was higher than the combined proportion of patients of other races (52.9 vs. 40.5%). Duration of diabetes was similar in patients achieving the target A1C and those failing to achieve the target in the RCT dataset and in the EMR dataset at both time points (Table 1).

Mean baseline BMI did not differ according to target A1C achievement in either dataset (Table 1). Mean baseline A1C was lower for patients achieving a target A1C in both datasets (Table 1). Most patients in the RCT dataset achieving a target A1C after 6 months had an FPG <130 mg/dL at baseline (57.4%) (Table 1). In the EMR dataset, the majority of patients with FPG <130 mg/dL at baseline did not achieve the target A1C at either time point (39.6 and 38.8% at 6 and 12 months, respectively, achieved the target), although attainment was higher than in the population as a whole (27.6 and 27.1% at 6 and 12 months, respectively). Mean baseline FPG was lower in patients achieving a target A1C in both datasets and all time points (Table 1). About half (51.1%) of the patients in the RCT dataset treated with insulin glargine achieved a target A1C <7.0%, as did patients treated with NPH insulin (50.1%). In the EMR dataset, the likelihood of achieving glycemic goals appeared to decrease with increasing number of OADs used at baseline.

Baseline Characteristics of Patients Not at Target A1C With FPG <130 mg/dL

Table 2 shows baseline patient data stratified by FPG levels as assessed at 6 and 12 months post-baseline in patients who did not achieve a target A1C <7.0%. Of the patients in the RCT dataset with a follow-up A1C ≥7.0%, 58.0% also had an FPG <130 mg/dL at follow-up, whereas only 6.2% of patients had such a value at baseline. A smaller proportion of the patients in the EMR dataset not reaching a target A1C reached an FPG <130 mg/dL at follow-up: 27.8 and 27.7% at 6 and 12 months, respectively. The patients who achieved an FPG <130 mg/dL tended to be slightly older for both the RCT analysis (58.8 vs. 57.0 years) and the EMR 6-month (62.3 vs. 59.6 years) and 12-month (62.4 vs. 59.0 years) follow-ups. White patients and nonwhite patients were similarly likely to have an A1C ≥7.0% despite having an FPG <130 mg/dL (57.2 vs. 56.2%, respectively). The duration of diabetes was longer for the patients in the RCT dataset achieving an FPG <130 mg/dL at follow-up (9.9 vs. 9.0 years), but there was no difference at either time point in the EMR dataset (Table 2). Self-funded patients and those covered by Medicaid were less likely to have an FPG <130 mg/dL despite failing to reach a target A1C (18.9 and 19.4%, respectively) compared to patients covered by Medicare or a commercial health plan (28.4 and 27.1%, respectively). In the EMR dataset, patients with an FPG <130 mg/dL but an A1C above target at 12 months appeared to have a higher CCI than those failing to reach target (1.07 vs. 0.99, respectively).

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TABLE 1. Baseline Characteristics Stratified by A1C at Follow-Up

	RCT Analysis		EMR Analysis			
	6-Month Follow-Up (*N* = 2,494)		6-Month Follow-Up (*N* = 12,562)		12-Month Follow-Up (*N* = 14,038)	
	A1C <7.0%* (*n* = 1,271)	A1C ≥7.0%† (*n* = 1,223)	A1C <7.0%* (*n* = 3,464)	A1C ≥7.0%† (*n* = 9,098)	A1C <7.0%* (*n* = 3,805)	A1C ≥7.0%† (*n* = 10,233)
Baseline demographics						
Mean age, years (SD)	58.3 (9.7)	58.0 (10.4)	62.3 (12.4)	60.2 (12.4)	62.7 (12.2)	59.8 (12.3)
Sex, *n* (%)						
Female	510 (46.4)	589 (53.6)	1,699 (26.8)	4,644 (73.2)	1,918 (27.1)	5,171 (72.9)
Male	761 (54.6)	634 (45.4)	1,765 (28.4)	4,454 (71.6)	1,887 (27.2)	5,062 (72.8)
Race, *n* (%)						
White	1,101 (52.9) (*n* = 1,222)	979 (47.1) (*n* = 1,157)	NA	NA	NA	NA
Other	121 (40.5) (*n* = 1,222)	178 (59.5) (*n* = 1,157)	NA	NA	NA	NA
Mean duration of diabetes, years (SD)	8.3 (5.7) (*n* = 1,269)	9.5 (6.4) (*n* = 1,218)	3.0 (3.1)	3.2 (3.0)	3.0 (3.3)	3.1 (3.0)
Payer type, *n* (%)						
Commercial	NA	NA	740 (25.8)	2,132 (74.2)	832 (25.3)	2,459 (74.7)
Medicaid	NA	NA	72 (21.2)	268 (78.8)	83 (21.2)	309 (78.8)
Medicare	NA	NA	1,301 (30.7)	2,935 (69.3)	1,512 (31.7)	3,256 (68.3)
Self	NA	NA	39 (14.7)	226 (85.3)	38 (13.9)	235 (86.1)
Unknown	NA	NA	1,312 (27.1)	3,537 (72.9)	1,340 (25.2)	3,974 (74.8)
CCI score						
0, *n* (%)	NA	NA	1,636 (25.3)	4,819 (74.7)	1,799 (24.5)	5,556 (75.5)
1–2, *n* (%)	NA	NA	1,137 (28.3)	2,878 (71.7)	1,279 (28.8)	3,162 (71.2)
>2, *n* (%)	NA	NA	691 (33.0)	1,401 (67.0)	727 (32.4)	1,515 (67.6)
Mean (SD)	NA	NA	1.28 (1.72)	1.05 (1.56)	1.27 (1.72)	1.01 (1.51)
Clinical characteristics						
Mean BMI, kg/m^2 (SD)	31.0 (5.1) (*n* = 1,270)	30.9 (5.3)	33.9 (8.3) (*n* = 3,254)	34.4 (8.0) (*n* = 8,502)	34.0 (8.2) (*n* = 3,535)	34.3 (8.1) (*n* = 9,543)
A1C <7.0%,* *n* (%)	25 (92.6)	2 (7.4)	1,019 (58.9)	710 (41.1)	1,149 (57.1)	864 (42.9)

TABLE CONTINUED ON P. 5 →

TABLE 1. Baseline Characteristics Stratified by A1C at Follow-Up, *continued from p. 4*

	RCT Analysis		EMR Analysis			
	6-Month Follow-Up (*N* = 2,494)		6-Month Follow-Up (*N* = 12,562)		12-Month Follow-Up (*N* = 14,038)	
	A1C <7.0%* (*n* = 1,271)	A1C ≥7.0%† (*n* = 1,223)	A1C <7.0%* (*n* = 3,464)	A1C ≥7.0%† (*n* = 9,098)	A1C <7.0%* (*n* = 3,805)	A1C ≥7.0%† (*n* = 10,233)
Mean A1C % (SD)	8.5 (0.9) [69 mmol/mol]	9.1 (1.0) [76 mmol/mol]	8.1 (2.0) [65 mmol/mol] (*n* = 3,161)	9.0 (1.9) [75 mmol/mol] (*n* = 8,492)	8.0 (2.0) [64 mmol/mol] (*n* = 3,444)	9.0 (1.9) [75 mmol/mol] (*n* = 9,372)
FPG <130 mg/dL, *n* (%)	78 (57.4) (*n* = 1,252)	58 (42.6) (*n* = 1,199)	837 (39.6)	1,276 (60.4)	904 (38.8)	1,426 (61.2)
Mean FPG, mg/dL (SD)	193.0 (48.9) (*n* = 1,252)	206.2 (53.7) (*n* = 1,199)	186.1 (90.3) (*n* = 2,963)	207.4 (84.6) (*n* = 7,750)	185.9 (90.5) (*n* = 3,252)	209.5 (87.4) (*n* = 8,597)
Treatment patterns						
Number of OADs used during 6 months before index date						
1, *n* (%)	NA	NA	1,862 (31.9)	3,967 (68.1)	1,976 (30.9)	4,421 (69.1)
2, *n* (%)	NA	NA	1,191 (25.7)	3,443 (74.3)	1,336 (25.6)	3,885 (74.4)
3, *n* (%)	NA	NA	372 (19.5)	1,539 (80.5)	456 (20.6)	1,753 (79.4)
>3, *n* (%)	NA	NA	39 (20.7)	149 (79.3)	37 (17.5)	174 (82.5)
Mean (SD)	NA	NA	1.59 (0.7)	1.77 (0.8)	1.62 (0.7)	1.77 (0.8)

Percentages are row percentages; where column totals are different from those indicated at the top of the table, they are presented in the appropriate cells.
*<53 mmol/mol. †≥53 mmol/mol.NA, not applicable.

TABLE 2. Baseline Characteristics of Patients Not Meeting the Target A1C <7.0% (<53 mmol/mol) Stratified by FPG Level at Follow-Up

	RCT Analysis		EMR Analysis			
	6-Month Follow-Up (*N* = 1,223)		6-Month Follow-Up (*N* = 6,969)		12-Month Follow-Up (*N* = 8,603)	
	FPG <130 mg/dL (*n* = 709)	FPG ≥130 mg/dL (*n* = 514)	FPG 4130 mg/dL (*n* = 1,938)	FPG 4130 mg/dL (*n* = 5,031)	FPG 4130 mg/dL (*n* = 2,382)	FPG 4130 mg/dL (*n* = 6,221)
Baseline demographics						
Mean age, years (SD)	58.8 (10.1)	57.0 (10.6)	62.3 (11.8)	59.6 (12.6)	62.4 (11.6)	59.0 (12.4)
Sex, *n* (%)						
Female	337 (57.2)	252 (42.8)	990 (27.7)	2,583 (72.3)	1,177 (27.0)	3,182 (73.0)
Male	372 (58.7)	262 (41.3)	948 (27.9)	2,448 (72.1)	1,205 (28.4)	3,039 (71.6)

TABLE CONTINUED ON P. 6 →

TABLE 2. Baseline Characteristics of Patients Not Meeting the Target A1C <7.0% (<53 mmol/mol) Stratified by FPG Level at Follow-Up, ***continued from p. 5***

	6-Month Follow-Up (*N* = 1,223)		6-Month Follow-Up (*N* = 6,969)		12-Month Follow-Up (*N* = 8,603)	
	FPG <130 mg/dL (*n* = 709)	FPG ≥130 mg/dL (*n* = 514)	FPG 4130 mg/dL (*n* = 1,938)	FPG 4130 mg/dL (*n* = 5,031)	FPG 4130 mg/dL (*n* = 2,382)	FPG 4130 mg/dL (*n* = 6,221)
Race, n (%)						
White	560 (57.2) (*n* = 660)	419 (42.8) (*n* = 497)	NA	NA	NA	NA
Other	100 (56.2) (*n* = 660)	78 (43.8) (*n* = 497)	NA	NA	NA	NA
Mean duration of diabetes, years (SD)	9.9 (6.6) (*n* = 705)	9.0 (6.0) (*n* = 513)	3.1 (3.2)	3.1 (2.9)	3.2 (3.0)	3.1 (3.0)
Payer type, *n* (%)						
Commercial	NA	NA	430 (27.1)	1,154 (72.9)	551 (27.4)	1,463 (72.6)
Medicaid	NA	NA	40 (19.4)	166 (80.6)	56 (20.7)	214 (79.3)
Medicare	NA	NA	657 (28.4)	1,659 (71.6)	850 (30.3)	1,956 (69.7)
Self	NA	NA	34 (18.9)	146 (81.1)	34 (17.0)	166 (83.0)
Unknown	NA	NA	777 (29.0)	1,906 (71.0)	891 (26.9)	2,422 (73.1)
CCI score						
0, *n* (%)	NA	NA	1,042 (28.2)	2,651 (71.8)	1,248 (26.7)	3,419 (73.3)
1–2, *n* (%)	NA	NA	578 (26.2)	1,624 (73.8)	750 (28.1)	1,915 (71.9)
>2, *n* (%)	NA	NA	318 (29.6)	756 (70.4)	384 (30.2)	887 (69.8)
Mean (SD)	NA	NA	1.07 (1.59)	1.05 (1.57)	1.07 (1.54)	0.99 (1.52)
Clinical characteristics						
Mean BMI, kg/m^2 (SD)	30.6 (5.4)	31.4 (5.2)	33.1 (7.5) (*n* = 1,795)	34.74 (8.0) (*n* = 4,706)	33.3 (8.0) (*n* = 2,220)	34.71 (8.2) (*n* = 5,809)
A1C <7.0%,* n (%)	1 (50.0)	1 (50.0)	172 (31.3)	377 (68.7)	244 (33.2)	490 (68.8)
Mean A1C, % (SD)	9.1 (1.0) [76 mmol/mol]	9.2 (1.1) [77 mol/mol]	8.8 (1.8) [73 mmol/mol] (*n* = 1,816)	9.1 (1.9) [76 mmol/mol] (*n* = 4,668)	8.7 (1.8) [72 mmol/mol] (*n* = 2,188)	9.2 (2.0) [77 mmol/mol] (*n* = 5,698)
FPG <130 mg/dL, *n* (%)	43 (74.1) (*n* = 694)	15 (25.9) (*n* = 505)	431 (41.0)	620 (59.0)	551 (43.0)	731 (57.0)
Mean FPG, mg/dL (SD)	198.7 (53.1) (*n* = 694)	216.4 (52.9) (*n* = 505)	185.5 (78.5) (*n* = 1,775)	214.1 (84.4) (*n* = 4,572)	183.9 (81.1) (*n* = 2,158)	217.9 (86.9) (*n* = 5,571)

TABLE CONTINUED ON P. 7 →

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TABLE 2. Baseline Characteristics of Patients Not Meeting the Target A1C <7.0% (<53 mmol/mol) Stratified by FPG Level at Follow-Up, *continued from p. 6*

	RCT Analysis				EMR Analysis			
	6-Month Follow-Up (*N* = 1,223)		6-Month Follow-Up (*N* = 6,969)		12-Month Follow-Up (*N* = 8,603)			
	FPG <130 mg/dL (*n* = 709)	FPG ≥130 mg/dL (*n* = 514)	FPG 4130 mg/dL (*n* = 1,938)	FPG 4130 mg/dL (*n* = 5,031)	FPG 4130 mg/dL (*n* = 2,382)	FPG 4130 mg/dL (*n* = 6,221)
Treatment patterns						
Number OADs used during 6 months before index date						
1, *n* (%)	NA	NA	864 (28.8)	2,141 (71.2)	1,045 (28.1)	2,674 (72.0)
2, *n* (%)	NA	NA	705 (26.6)	1,944 (73.4)	851 (26.3)	2,388 (73.7)
3, *n* (%)	NA	NA	340 (28.4)	856 (71.6)	436 (29.2)	1,058 (70.8)
>3, *n* (%)	NA	NA	29 (24.4)	90 (75.6)	50 (33.1)	101 (66.9)
Mean (SD)	NA	NA	1.8 (0.8)	1.8 (0.8)	1.8 (0.8)	1.8 (0.8)

*Percentages are row percentages; where column totals are different from those indicated at the top of the table, they are presented in the appropriate cells. *<53 mmol/mol. NA, not applicable.*

Mean A1C was similar for patients not achieving target regardless of their FPG status in the RCT dataset (Table 2); however, in the EMR dataset, patients with an FPG <130 mg/dL had a lower mean A1C (8.8% [73 mmol/mol] vs. 9.1% [65 mmol/mol] at 6 months and 8.7% [72 mmol/mol] vs. 9.2% [77 mmol/mol] at 12 months). The majority of patients in the RCT dataset who had baseline FPG <130 mg/dL (74.1%) also had a follow-up FPG <130 mg/dL, despite failing to reach the target A1C. However, in the EMR dataset, the majority of those patients who had well-controlled FPG at baseline and failed to reach target A1C had an FPG ≥130 mg/dL at follow-up (59.0 and 57.0% at 6 and 12 months, respectively). In the RCT dataset, the majority of patients treated with insulin glargine or NPH insulin were more likely to have an FPG <130 mg/dL and to not reach a target A1C (57.7 and 59.3%, respectively).

Discussion

A large proportion of patients initiating basal insulin in both the RCT and EMR analyses failed to reach a target A1C <7.0% at 6 or 12 months post-baseline. There is evidence to suggest that using a less stringent A1C target of <7.5% could result in reduced risk of cardiac complications and mortality in some patients (25). However, such risk would likely be confined to those who require antihyperglycemic agents that increase the risk for hypoglycemia and weight gain to achieve the desired glycemic target. Guidelines from the ADA recommend applying an A1C goal of <7.0%, and this is considered to be a reasonable target for most patients, with the application of a less stringent target A1C of <8.0% being more appropriate for patients with an increased risk for hypoglycemia and especially those with cardiovascular disease complications (10). It is possible that using a spectrum of targets ranging from 7.0 to 8.5% may yield different results; however, at present,

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these analyses are beyond the scope of this article and might be used as a basis for future studies.

There were several demographic differences between patients achieving and those not achieving the target A1C. RCT data suggested that women were less likely to achieve the target A1C. Similar results have been seen in international real-world studies (26–28); however, this pattern was not observed in our EMR dataset. A higher proportion of white versus nonwhite patients achieved a target A1C <7.0%. Racial differences in A1C have been reported elsewhere, with black and ethnic minority patients displaying higher A1C levels across the full glycemic spectrum, including those with type 2 diabetes (29–31). In the RCT dataset, patients achieving the target A1C tended to have a longer duration of disease than those in the EMR dataset (approximate duration 9 and 3 years, respectively). Longer disease duration has previously been shown to be associated with higher A1C (31). It may be that duration-dependent effects on glycemic control, such as β-cell dysfunction, are more evident in those with a longer duration of disease. β-Cell dysfunction is known to accelerate as type 2 diabetes progresses (32). The differences in the proportion of patients achieving a target A1C <7.0% among payers are of interest given that A1C is one of the Healthcare Effectiveness Data and Information Set quality measures, thus linking goal attainment to reimbursement (33). Furthermore, in the EMR dataset, there was an inverse relationship between the number of OADs used by patients at baseline and the likelihood of those patients of achieving glycemic goals. A higher number of OADs taken could be reflective of the progression and complexity of these patients' disease.

A previous study has shown that patients with a higher CCI (reflecting a higher probability of 1-year mortality) have worse glycemic control (31). However, a study conducted by Hudon et al. (34) showed no apparent relationship between the presence of comorbidities and achievement of glycemic control, as measured with the Cumulative Illness Rating Scale (CIRS) (34). The CIRS measurement includes all comorbidities and their severity, rather than individual conditions. Similar to results obtained by Riddle et al. (35), patients in our study failing to reach the target A1C at follow-up tended to have a higher A1C at baseline compared to those who did reach the target. Similarly, mean baseline FPG was lower for patients who achieved the target A1C than for those who did not. Furthermore, Bloomgarden et al. (36) showed that baseline glycemic status strongly influenced FPG and A1C reduction after treatment, irrespective of the drug class used.

For the RCT analysis, about half of the patients on insulin glargine or NPH insulin achieved an A1C <7.0% at follow-up; among the patients in the EMR dataset, substantially fewer patients achieved an A1C <7.0% at follow-up (27.6 and 27.1% at 6 and 12 months, respectively), and more OADs were prescribed to those patients who did not reach the target A1C. This may be related to an effort to delay or avoid addressing postprandial hyperglycemia with prandial insulin or glucagon-like peptide 1 (GLP-1) receptor agonists and thus may support a recommendation for earlier intensification of basal insulin therapy. Alternatively, use of more OADs may be indicative of greater disease severity, which has been shown to be associated with worse target A1C attainment (31).

The majority of patients in the RCT dataset with an A1C ≥7.0% did not achieve the target A1C despite having an FPG <130 mg/dL, indicating that they had reasonably adequate titration of the basal insulin and therefore likely required intervention to improve prandial glycemic excursions. In the EMR dataset, the majority of patients not achieving the target A1C had a follow-up FPG ≥130 mg/dL, indicating frequent failure of adequate basal insulin titration. However, a sizable minority failed to achieve a target A1C despite having an FPG <130 mg/dL and would therefore require prandial therapy to achieve the target A1C (37).

The results of this study indicated that appropriate titration of basal insulin is an unmet need in many patients with type 2 diabetes in real-world practice (~55%) and even in some of those enrolled in RCTs (21%), where medication regimens are closely monitored. In those patients with an A1C ≥7.0% and an FPG ≥130 mg/dL, further basal insulin titration is likely needed. Small but frequent dose increments have been shown to predict success of basal insulin titration (38).

PPG control is also an important unmet need in a significant proportion of the type 2 diabetes population. We observed that a substantial number of patients with an A1C ≥7.0% also had an FPG <130 mg/dL, possibly as a result of elevated PPG levels or worse evening and nocturnal glycemic control, which were not specifically detected by monitoring FPG. Furthermore, it has been demonstrated previously that many patients have difficulties in maintaining their recommended target A1C despite having near-normal FPG levels (39). These patients would usually benefit from pharmacologic treatment targeting PPG.

Combining basal insulin therapy with thiazolidinediones, metformin, or sulfonylureas can have beneficial effects on A1C, FPG, and PPG control, and continued OAD use after insulin initiation may help to maintain glycemic stability (40). However, combining sulfonylureas with insulin can increase the risk for hypoglycemia (41) and weight gain, while combination with thiazolidinediones can be associated with increased weight and fluid retention (42). Another option is the addition of a GLP-1 receptor agonist. Both short- and long-acting GLP-1 receptor agonists may help

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to improve PPG and FPG control, with the shorter-acting GLP-1 receptor agonists having a predominant effect on PPG excursions, whereas the longer-acting agents demonstrate a predominant effect on FPG (43). Furthermore, ADA guidelines recommend that a GLP-1 receptor agonist should be added when A1C cannot be controlled with basal insulin alone, despite reaching target FPG levels (44). Lastly, two titratable fixed-ratio coformulations of a basal insulin analog and a once-daily GLP-1 receptor agonist, insulin glargine/lixisenatide (iGlarLixi) and insulin degludec/liraglutide (iDegLira), have recently been approved by the U.S. Food and Drug Administration for patients with type 2 diabetes uncontrolled on basal insulin or the respective GLP-1 receptor agonist component (45,46). Use of one or more of these therapies may obviate the need for prandial insulin treatment in many patients with type 2 diabetes.

Differences in baseline characteristics between the two populations of patients with type 2 diabetes highlight the potential benefits of bridging the gap between RCT and EMR data to fully understand unmet needs in real-world patient care. One potential approach to achieving this "bridging" would be through the increased use of hybrid/pragmatic real-world studies (47). Indeed, many health care professionals express concern that patients recruited for RCTs frequently may not reflect real-world patient-care populations (48). In practice, the value and choice of antihyperglycemic agents are not determined solely by their efficacy (49). Factors such as patients' and health care professionals' concerns about potential side effects (e.g., hypoglycemia), constraints on treatments approved by payers, ease of use, and complexity of treatment regimen (which may often be better determined using prospective real-world studies) are also of great importance. Although prospective real-world studies can be challenging undertakings, there is recent evidence that large-scale, prospective, real-world studies can provide a wealth of information that is very relevant to health care professionals (50,51).

As with all retrospective, observational studies, EMR data may be subject to selection bias and confounding. In particular, because the data are not randomized, clinicians may choose different therapies for different patients based on patient characteristics or clinicians' preferences, and this may affect the outcomes. The intensive monitoring of patients in RCTs, as well as mandated management algorithms and patient awareness through increased self-monitoring of plasma glucose, may lead to reporting of laboratory parameters at greater frequencies, as well as better outcomes, than are measured in real-world practice. With regard to the RCT data in our study, these were limited to studies performed by Sanofi or predecessor companies, and patient inclusion criteria, treatments, and outcomes may not always be generalizable to the broad population of those with diabetes seen in real-world practices. Additionally, this study only analyzed the impact of insulin glargine U100 and NPH insulin in RCTs; different outcomes may have been observed with longer-acting second-generation insulins. For example, RCTs comparing the first- and second-generation insulin analogs (for example, insulin glargine 100 units/mL vs. insulin glargine 300 units/mL) demonstrated similar A1C reductions with decreased hypoglycemia (52,53).

With regard to the EMR analysis, patients were identified based on primary care physician prescription order data, and we could not control for heterogeneity in the population receiving basal insulin. Furthermore, prescribed insulin dosages may not be disclosed, prescription orders may not be filled, and filled prescriptions may not be taken with regularity by patients. Differences in patient demographics and outcome data collected for the RCTs and the data available in the EMR databases mean that comparisons between the two datasets were not possible for all data elements, and such differences could be confounding factors in the analysis. Similarly, differences in study group sizes and demographics among RCTs were potential confounding factors, which is a detriment of performing retrospective analysis rather than a prospective, specifically designed trial. Additionally, EMR data had a 12-month follow-up, which was not available in the RCT dataset, preventing longer-term comparison. Finally, although the time periods analyzed differed between the RCTs and EMR (2000–2005 and 2005–2012, respectively), we do not feel that this would have significantly affected the findings of this study.

In conclusion, large numbers of patients with type 2 diabetes, both in real-world clinical practice and in RCTs, do not reach glycemic goals despite treatment with OADs and basal insulin. The patterns of FPG control found in our study highlights a frequent unmet need to optimally titrate basal insulin. In those patients with well-controlled FPG but inadequately controlled A1C, there is an unmet need to address PPG. Both efficacy studies in RCTs and real-world effectiveness studies provide evidence to facilitate health care professionals' decision-making and to enable payers and formulary decision-makers to assess the real-world impact of antihyperglycemic therapies. Differences in baseline characteristics and target A1C achievement between the two populations of patients with type 2 diabetes highlight the importance of bridging the gap between RCT and EMR data to fully understand unmet needs in real-world patient care. Obtaining glucose profiles and targeting therapy to address both FPG and PPG, in addition to A1C, is necessary to make appropriate therapeutic choices for patients not reaching glycemic goals. Understanding the differences between patients who

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achieve target A1C and FPG goals and those who do not could assist in individualizing treatment regimens and optimizing patient outcomes.

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Duality of Interest

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Author Contributions

L.B., S.A.B., and P.C. critically reviewed the concept, interpreted the results of the analyses, reviewed the manuscript drafts, and provided comments. R.Z., J.M., and K.L.D. co-developed the analysis plan, performed the analyses, interpreted the results of the analyses, prepared the study report, reviewed manuscript and provided comments. M.R.D. and A.D. co-developed the concept, co-developed the analysis plan, interpreted the results of the analyses, reviewed manuscript and provided comments. L.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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