Received: 24 September 2018 | Revised: 12 December 2018 | Accepted: 2 January 2019

DOI: 10.1111/dom.13673

WILEY

ORIGINAL ARTICLE

The Diabetes Unmet Need with Basal Insulin Evaluation (DUNE) study in type 2 diabetes: Achieving HbA1c targets with basal insulin in a real-world setting

Luigi F. Meneghini MD[1,2] | Didac Mauricio MD[3] | Emanuela Orsi MD[4] | Nebojsa M. Lalic MD[5] | Anna M.G. Cali MD[6] | Jukka Westerbacka MD[6] | Peter Stella MD[6] | Christophe Candelas, DEA[7] | Valerie Pilorget MD[7] | Riccardo Perfetti MD[8] | Kamlesh Khunti MD[9] | on behalf of the DUNE investigators

[1]Division of Endocrinology, University of Texas Southwestern Medical Center, Dallas, Texas

[2]Global Diabetes Program, Parkland Health & Hospital System, Dallas, Texas

[3]Department of Endocrinology and Nutrition, CIBER of Diabetes and Associated Metabolic Diseases, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[4]Endocrine and Metabolic Diseases Unit, Fondazione Ca' Granda IRCCS, Milan, Italy

[5]Clinic for Endocrinology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia

[6]Sanofi, Paris, France

[7]Sanofi, Chilly-Mazarin, France

[8]Sanofi, Bridgewater, New Jersey

[9]Diabetes Research Centre, University of Leicester, Leicester, UK

Correspondence
Dr Luigi Meneghini MD, Department of Internal Medicine, Division of Endocrinology, University of Texas Southwestern Medical Center and Parkland Health and Hospital System, 5323 Harry Hines Blvd, Dallas, TX 75390, USA.
Email: luigi.meneghini@utsouthwestern.edu

Funding information
This study was sponsored by Sanofi. Sanofi designed and coordinated the clinical trial presented in this manuscript; Sanofi; Health Research

Aims: To describe in a real-world setting the achievement of physician-selected individualized HbA1c targets in individuals with type 2 diabetes, newly or recently initiated with basal insulin, and the association of hypoglycaemia with target achievement.

Materials and methods: A 12-week, prospective, single-arm, observational study of adults with type 2 diabetes, either newly initiated with any basal insulin or start on basal insulin within the preceding 12 months. At enrollment, eligible participants from 28 countries were treated with or without oral antihyperglycaemic drugs and/or GLP-1 receptor agonists.

Results: Individualized targets for almost all of the 3139 evaluable participants (99.7%) had been set by their physicians, with 57% of participants having HbA1c targets between 7.0% and <7.5% (53 and <58 mmol/mol). By week 12, 28% and 27% of newly and previously initiated participants, respectively, achieved individualized HbA1c targets with modest average increases in daily insulin dose of 9 and 5 U (0.10 and 0.06 U/kg), respectively, from baseline (14 and 23 U [0.17 and 0.29 U/kg], respectively). Overall, 16% of participants experienced at least one episode of hypoglycaemia. Both the incidence and frequency of hypoglycaemia, but not the severity, were positively associated with a higher likelihood of achieving individualized HbA1c targets ($P < 0.05$).

Conclusions: In this prospective real-world study, most participants using basal insulin did not achieve the individualized HbA1c targets set by their physicians. Participants who experienced symptomatic hypoglycaemia were more likely to achieve HbA1c targets than those who did not.

KEYWORDS

basal insulin, glycaemic control, hypoglycaemia, insulin therapy, observational study, type 2 diabetes

1 | INTRODUCTION

Chronic hyperglycaemia is associated with long-term complications of type 2 diabetes (T2DM),[1–3] including increased risk of cardiovascular events.[4] However, approximately one half of all individuals with T2DM do not achieve the HbA1c level of less than 7.0% (<53 mmol/mol)[5] that is recommended in clinical practice,[6,7] with lower rates of target achievement often reported for those treated with basal insulin

(BI).[8–11] For example, in two international real-world studies, only 27% to 33% of individuals with T2DM achieved HbA1c less than 7.0% (<53 mmol/mol) after initiating BI therapy.[10,11] Furthermore, failure to achieve HbA1c targets in the short term may be associated with suboptimal long-term blood glucose (BG) control, as illustrated by a recent retrospective analysis of medical records from Europe and the USA, in which those who did not achieve HbA1c less than 7.0% (<53 mmol/mol) at 3 months were less likely to achieve this target at 24 months.[10] Recent international treatment guidelines advocate setting individualized HbA1c targets that take account of the individual's characteristics, duration of diabetes, co-morbidities, life expectancy and risk of hypoglycaemia.[12–15] Furthermore, therapy intensification is recommended if individualized targets are not reached after 3 months.[5]

In the case of insulin-treated individuals with T2DM, suboptimal glycaemic control may be due, in part, to ineffective treatment prescription, therapeutic inertia, non-adherence, omission and/or dose reduction in the setting of hypoglycaemia, or fear of hypoglycaemia.[16–20] For example, concerning individuals with T2DM who had received stable doses of metformin and sulfonylureas for at least 6 months, those who experienced moderate or severe hypoglycaemia reported poorer adherence to medication (46% vs 67%; $P < 0.01$) and were more likely to perceive side effects as a barrier to treatment (36% vs 14%; $P < 0.001$) than those who did not experience hypoglycaemia or experienced only mild hypoglycaemia.[21] However, it is less clear whether poor adherence to treatment as the result of hypoglycaemia impacts attainment of HbA1c targets. An inverse relationship appears to exist between rates of hypoglycaemia and HbA1c in T2DM, as reported in a meta-regression analysis of 11 randomized controlled trials involving insulin-treated participants,[22] and a study in individuals treated with sulfonylureas.[23] Walz et al reported that, despite poorer adherence, patients who experienced moderate or severe symptoms of hypoglycaemia achieved lower mean HbA1c values than patients without or with only mild symptoms (7.0% vs 7.3% [53 vs 56 mmol/mol]; $P < 0.05$).[21]

Data concerning the extent to which patients are set and achieve individualized HbA1c targets are lacking. Furthermore, the association between achievement of individualized glycaemic targets and the risk of hypoglycaemia in clinical practice with BI is currently not known. The Diabetes Unmet Need with Basal Insulin Evaluation (DUNE) study was a 12-week, prospective, observational study (February 2015-July 2016) involving individuals with T2DM, either newly (at enrollment) or recently (<12 months) initiated treatment with BI. The study aimed to describe the proportion of participants who achieved individualized or general HbA1c targets at 12 weeks, and to evaluate the impact of the frequency and severity of symptomatic hypoglycaemia on target achievement.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The DUNE study was a 12-week, single-arm, observational study with prospective follow-up at week 12 (±2 weeks). The study aimed to enroll 4000 participants with T2DM ≥18 years of age who had newly initiated treatment with BI, human or analog, at the time of enrollment, or had been treated with BI for less than 12 months (previously initiated), with or without oral antihyperglycaemic drugs and/or glucagon-like peptide 1 (GLP-1) receptor agonists. Participants were required to have HbA1c between 7.5% and 11.0% (≥58-≤97 mmol/mol) for newly initiated BI users and between 7.5% and 10.0% (≥58-≤86 mmol/mol) for previously initiated BI users, and to be willing to perform self-monitoring of blood glucose (SMBG) and to complete a patient diary. Exclusion criteria included treatment with rapid-acting or premix insulin, or physician intent to intensify treatment with a rapid-acting or premix insulin within the next 3 months. Participants were also excluded if they were more likely to have type 1 diabetes (<40 years old and had initiated insulin within 1 year of diabetes diagnosis), or if they were, or planned to become, pregnant.

To help eliminate bias, investigators were advised to include consecutive patients suitable for the study. Signed informed consent was obtained from all participants. To mirror real-world clinical practice for the management of diabetes, no fixed study visit was scheduled during the follow-up period; rather, clinical visits, including the possibility of phone visits, and treatment choices were undertaken according to local practice. At study entry, data were collected from participants concerning demographics, medical history, especially concerning diabetes complications, comorbidities and history of severe hypoglycaemia, and type of BI being used (human intermediate-acting or long-acting analog). The use and titration of concomitant antidiabetic medications other than BI during the study period was left at the discretion of the treating physicians. This study was observational, with treatment carried out according to local practice and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice.

2.2 | HbA1c targets

At baseline, an individualized long-term HbA1c target was set for each participant by their physician. In the case of those for whom an individualized target was not set, a general HbA1c target less than 7.0% [<53 mmol/mol] was defined, based on current guidelines[5] (Table 1). A separate 12-week objective was set by physicians, based on the HbA1c level they anticipated patients would be able to reach by week 12; however, the results of this objective are not the focus of this report.

2.3 | Defining participants at low or high risk of hypoglycaemia complications

Independent of any evaluation by their physicians, participants were retrospectively categorized as being at low risk or high risk of complications from a hypoglycaemic event (Table 1).

2.4 | Objectives and endpoints

The study had two primary objectives: first, to describe the proportion of participants who achieved their individualized (long-term) HbA1c target at 12 weeks; second, to evaluate the association of the

TABLE 1 Definitions of HbA1c goals and participants at high risk of complications from hypoglycaemia

	Definitions
Individualized HbA1c target	Overall, long-term goal; those without an individualized target set by their physician were given a general HbA1c target of <7.0% (<53 mmol/mol)
Participants at high risk[a] of complications from hypoglycaemia	• Age ≥65 y • Duration of diabetes >15 y • Coronary heart disease • Renal function impairment • Professional driver • Myocardial infarction • Myocardial revascularization • Peripheral vascular disease • Heart failure • History of severe hypoglycaemia • Stroke • Diabetic retinopathy leading to blindness • Transient ischaemic attack • Lower extremity amputation • Severe dementia

[a]High risk if patients ≥65 years old or with evidence of any of the comorbidities/characteristics agreed by the DUNE Steering Committee.

frequency and/or severity of symptomatic hypoglycaemia with individualized HbA1c target achievement at 12 weeks. Primary endpoints were achievement of individual HbA1c target, or general HbA1c target of less than 7.0% (<53 mmol/mol), and the frequency and severity of symptomatic hypoglycaemia. Symptomatic hypoglycaemia events were classified as severe (requiring third party assistance, with or without a BG measurement) or non-severe (associated with typical hypoglycaemia symptoms and not requiring third party assistance regardless of BG measurement).[24]

Secondary endpoints included hypoglycaemia occurrence, general HbA1c goal achievement (<7.0% and <8.0% [<53 and <64 mmol/mol]) according to the level of risk of complications following hypoglycaemia, and individualized HbA1c target without symptomatic hypoglycaemia. The change from baseline to week 12 was determined for HbA1c, FPG as measured by SMBG, body weight and insulin dose. At the end of the study, a survey was administered to collect investigator opinions on whether failure to reach target was due to lack of adherence to titration/lifestyle recommendations, hypoglycaemic events, intercurrent disease or other reasons.

2.5 | Data analysis and statistics

The sample size was determined to ensure sufficient precision for evaluating the percentage of participants at HbA1c target (<7.0% [<53 mmol/mol]), assuming 27% of participants would achieve that target at 12 weeks, as reported in real-world observational studies.[8] The inclusion of 4000 patients allowed this percentage to be estimated with a precision of at least 1.5%, assuming that 15% of participants would be non-evaluable. This sample size also enabled detection of an odds ratio of at least 1.3 for the relationship between HbA1c target achievement at 12 weeks and occurrence of symptomatic hypoglycaemia (assumed to be positively associated [OR > 1]) the reference being at least one symptomatic hypoglycaemic event, with a power of at least 80% and an alpha risk of 5%, and with assumptions for the incidences of symptomatic hypoglycaemia of 20% in newly initiated participants and of 45% in previously initiated participants.

Achievement of HbA1c targets at 12 weeks was modeled as a function of symptomatic hypoglycaemia using stepwise multivariate logistic regression, adjusted according to region, age, diabetes duration, HbA1c at baseline, use of sulfonylureas and/or meglitinides at baseline, and use of GLP-1 receptor agonists at study entry.

3 | RESULTS

3.1 | Study population and baseline characteristics

3.1.1 | Study population

The study, conducted from February 2015 to July 2016, evaluated 3139 patients from 28 countries (Supporting Information Figure S1), including 1716 (54.7%) newly initiated and 1423 (45.3%) previously initiated participants. Mean treatment duration for previously initiated participants was approximately 5.7 months. Overall, 63% of participants self-titrated their insulin, compared with 37% whose titrations were determined by physicians. These proportions were similar in both newly and previously initiated groups.

3.1.2 | Baseline characteristics

There were no major clinical differences between newly and previously initiated participants in terms of age, weight, BMI, concomitant diabetes medications (other than BI), presence of at least one microvascular complication, diabetic neuropathy, diabetes-related functional impairment or estimated glomerular filtration rate (eGFR) (Table 2). The proportion of newly and previously initiated participants with a duration of diabetes longer than 10 years was 39% and 46%, respectively. Participants at high risk of complications from a hypoglycaemic event comprised more than 60% of the newly and previously initiated groups (Supporting Information Table S1).

3.2 | Individualized HbA1c target

Overall, individualized HbA1c targets were set by the investigators for 99.7% of participants, with no major differences between targets set for newly and previously initiated participants (Table 3). Individualized HbA1c targets of 7.0% to less than 7.5% (<53-<58 mmol/mol) were set for the majority of participants in both groups (Table 3). The major reasons underlying physicians' decisions to set less stringent individualized HbA1c targets were participant age, patient acceptance of the treatment constraints required to meet the HbA1c target (such as SMBG, insulin dose adjustment and lifestyle changes) and the existence of comorbidities.

3.3 | Insulin treatment and weight

Long-acting BI analogs were used by 80% and 76% of newly and previously initiated participants, respectively. The remaining participants used human intermediate-acting insulin (NPH). Mean daily insulin dose (standard deviation [SD]) at baseline was 14 (7) U (0.17 [0.09] U/kg) and 23 (15) U (0.29 [0.17] U/kg) for newly and previously initiated participants, respectively. The majority of newly initiated

TABLE 2 Demographic and baseline characteristics

Characteristic	Newly initiated n = 1716	Previously initiated (within 12 months) n = 1423	All (total) n = 3139
Age, y (SD)	60 (11)	61 (10)	61 (11)
Gender, female/male, %	50/50	53/47	51/49
Weight, kg (SD)	85 (18)	83 (17)	84 (17)
Body mass index, kg/m^2 (SD)	30.6 (5.6)	30.4 (5.4)	30.5 (5.5)
Mean HbA1c (SD)			
%	9.14 (1.01)	8.56 (0.77)	8.88 (0.96)
mmol/mol	76.44 (11.03)	70.01 (8.46)	73.52 (10.45)
Duration of diabetes, years (SD)	10 (7)	11 (7)	10 (7)
<1 y, %	6	5	6
1 to 5 y, %	22	20	21
5 to 10 y, %	33	29	31
>10 y, %	39	46	42
Hypoglycaemia within 6 months of study entry, n (%)			
Severe	37 (2.2)	75 (5.3)	112 (3.6)
Symptomatic	68 (4.0)	171 (12.0)	239 (7.6)
At least one diabetes medication, %	92	93	93
Metformin	80	80	80
Sulfonylureas	54	42	49
DPP-4 inhibitors	30	26	28
GLP-1 receptor agonists	5	6	6
Glinides	4	4	4
SGLT2 inhibitors	4	4	4
Thiazolidinediones	2	3	2
Alpha-glucosides inhibitors	2	1	2
Diabetes complications			
At least one complication, %	39	42	40
eGFR (mL/min/1.73 m^2), mean (SD)	84 (29)	85 (27)	84 (29)

Abbreviations: DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SD, standard deviation; SGLT, sodium-glucose co-transporter.

TABLE 3 Individualized HbA1c target set by physicians

Individualized targets set	Newly initiated (n = 1716)	Previously initiated (n = 1423)	All (total) n = 3139
Target set for the patient, % (mmol/mol)	99.9	99.5	99.7
<6.5 (<48)	1	1	1
6.5 to <7.0 (48-<53)	18	18	18
7.0 to <7.5 (53-<58)	**58**	**57**	**57**
7.5 to <8.0 (58-<64)	17	17	17
≥8.0 (≥64)	6.5	7.2	6.8
Reason for target (several possible) (%)			
Age	67	65	66
Comorbidities	36	39	38
History of severe hypoglycaemia	0.6	2.3	1.4
Patient acceptability	40	43	41
Other	9	10	9
Individualized target achievement			
Patients achieving target (%)			
Individualized target	28	27[a]	27
<7.0 % (<53 mmol/mol)			
High risk	24	21	23
Low risk	27	28	28
<8.0 % (<64 mmol/mol)			
High risk	65	64	65
Low risk	62	65	63
Patients achieving individual target without hypoglycaemia (%)	24	20	22
Physician-reported reasons for failure to reach the 12-wk objective[b] (%)			
Lack of adherence to titration	44	44	44
Lack of adherence to lifestyle recommendations	62	58	60
Hypoglycaemic events	4	5	4
Intercurrent disease	4	5	5
Other	22	27	24

[a]P = 0.504, Chi-squared test.
[b]The 12-week objective was the HbA1c level that physicians anticipated their patients would be able to reach by week 12, and may have differed from the individualized target described in the main text.

(95%) and previously initiated (89%) participants were using once-daily BI dosing; 5% and 11% of participants were using at least twice-daily dosing, respectively. The median (SD) target for fasting SMPG set by physicians, according to local practice, was 118 (15) mg/dL (7 [0.9] mmol/L). In participants for whom titration data were available (n = 3090), titration was predominantly performed every 1 to 3 days (41%) or weekly (34%). In the remaining participants, titration frequency was less than once a week. Eleven (0.6%) in the newly initiated group and 15 (1.1%) in the previously initiated group discontinued insulin use during the study because of insufficient control (0.8% overall), hypoglycaemia (0.2%), lack of adherence (0.2%), other adverse drug reactions (0.03%) or other reasons (0.4%). By week 12, the daily insulin dose increased by an average of 0.08 U/kg in both newly and previously initiated participants (Supporting Information Table S2). There was a modest increase in weight over the 12 weeks in both groups (Supporting Information Table S2).

3.4 | Achievement of HbA1c target at 12 weeks

At week 12, HbA1c had reduced from baseline by 1.4% (15 mmol/mol) in newly initiated participants, and by 0.8% (8.7 mmol/mol) in previously initiated participants (Supporting Information Table S3).

Overall, 27% of patients achieved their individualized HbA1c target, which was most commonly between 7.0% and less than 7.5% (<53-<58 mmol/mol) (Table 3). Fewer participants achieved individualized targets without experiencing hypoglycaemia (Table 3). Similar proportions in the self-titrated and physician-titrated groups achieved their individualized HbA1c target (Supporting Information Table S4).

Participants at high risk of complications following hypoglycaemia were significantly more likely ($P < 0.0001$) to have higher HbA1c targets set by their physicians, compared with those at low risk (Supporting Information Table S5). The overall proportion of low-risk participants who achieved HbA1c less than 7.0% (<53 mmol/mol) was lower than the proportion of high-risk participants who achieved HbA1c less than 8.0% (<64 mmol/mol) (Table 3). The majority of participants with an individualized HbA1c target less than 7.0% (<53 mmol/mol) did not achieve the target, irrespective of risk status. In contrast, most participants with an individualized HbA1c target less than 8.0% (<64 mmol/mol) did achieve this target (Supporting Information Table S5).

3.5 | Self-reported hypoglycaemia

Symptomatic hypoglycaemia within the last month prior to study entry was reported by 4% and 12% of newly and previously initiated participants, respectively. Severe hypoglycaemia within the last 6 months prior to study entry was reported in 2% and 5% of newly and previously initiated participants, respectively. During the 12-week study period, symptomatic hypoglycaemia was reported in 14% and 18% of newly and previously initiated participants, respectively (Table 4), corresponding to a rate of 1.5 and 2.2 events per participant per year, respectively. The incidence of severe hypoglycaemia during the study period was very low in both newly and previously initiated participants.

TABLE 4 Self-reported hypoglycaemia

	Newly initiated (n = 1716)	Previously initiated (within 12 mo) (n = 1423)	All (total) (n = 3139)
Participants with at least one symptomatic hypoglycaemic event (%)	14	18	16
Number of symptomatic hypoglycaemic events per participant, mean (SD), range	0.37 (1.36), 0 to 21	0.55 (1.96), 0 to 39	0.45 (1.66), 0 to 39
Frequency of symptomatic hypoglycaemia (%)			
0	86	82	84
1	6	7	6
2 to 4	7	8	8
>4	2	3	2
Severity of symptomatic hypoglycaemia (%)			
Absence of symptomatic hypoglycaemia	85.8	81.7	84.0
Non-severe symptomatic hypoglycaemia	13.7	17.0	15.2
Severe hypoglycaemia	0.5	1.3	0.8

3.6 | HbA1c target achievement at 12 weeks – multivariate model

Participants who did not experience a symptomatic hypoglycaemic event were significantly less likely to achieve their HbA1c target than those who had experienced an event ($P < 0.001$) (Table 5). Factors that were significantly associated with target achievement in this model included higher individualized HbA1c target set by physicians at study entry ($P < 0.001$) and use of long-acting BI analog vs human intermediate-acting insulin ($P < 0.05$) (Supporting Information Table S6). By comparison, factors negatively associated with target achievement included longer duration of diabetes ($P < 0.001$) and higher HbA1c at study entry ($P < 0.001$) (Supporting Information Table S6). The frequency of symptomatic hypoglycaemia was also significantly associated with target achievement. Compared with participants who did not experience any events, those who experienced one, two to four or more than four events were significantly more likely ($P < 0.05$) to achieve target HbA1c (Table 5).

Achievement of individualized HbA1c targets without symptomatic hypoglycaemia was significantly less likely with increasing duration of diabetes (>10 vs <1 year; OR [95% CI], 0.37 [0.25-0.54]; $P < 0.001$) and with higher HbA1c levels at study entry (≥9.6% vs <8.0% [≥81 vs <64 mmol/mol]; OR [95% CI], 0.42 [0.31-0.56]; $P < 0.001$). Participants for whom higher HbA1c targets were set at study entry were more likely to achieve individualized targets without hypoglycaemia compared with participants for whom lower targets were set (eg, ≥7.5%-<8.0% vs <7.0% [≥58-<64 vs ≥53 mmol/mol]; OR [95% CI], 3.09 [1.89-5.07]; $P < 0.001$).

TABLE 5 Multivariate logistic regression model of individual HbA1c target[a] achievement at 12 weeks

Multivariate model[b]		OR (95% CI)	P value
Symptomatic hypoglycaemia	Yes	Reference	<0.001[c]
	No	0.645 (0.513 to 0.810)	<0.001
Frequency of symptomatic hypoglycaemic events	0	Reference	0.002[3]
	1	1.411 (1.004 to 1.983)	0.047
	2 to 4	1.585 (1.160 to 2.166)	0.004
	>4	1.946 (1.091 to 3.473)	0.024
Number of symptomatic hypoglycaemic events	n	1.088 (1.030 to 1.149)	0.002

[a]Proportion of patients in target range: 1%, <6.5% (<48 mmol/mol); 18%, 6.5% to <7.0% (48-<53 mmol/mol); 57%, 7.0% to <7.5% (53-<58 mmol/-mol); 17%, 7.5% to <8.0% (58-<64 mmol/mol); 7%, ≥8.0% (≥64 mmol/mol).
[b]Modeling was adjusted for region, age, duration of diabetes, baseline HbA1c, use of sulfonylureas and/or metiglinides at study entry, and use of GLP-1 receptor agonists at study entry.
[c]Reference *P* values reflect the global association between the hypoglycaemia factor and HbA1c target achievement; all other *P* values are compared to the reference.

3.7 | Predictive factors for treatment failure – multivariate model

Multivariate analysis was conducted to identify factors predictive of treatment failure, defined as failure to achieve individualized and general HbA1c target at week 12). While experience of severe hypoglycaemia during the last 6 months prior to study entry (OR [95% CI], 0.77 [0.49-1.21]) was not significantly associated with treatment failure, a significant positive association was observed for duration of diabetes (1–5 vs <1 year; OR [95% CI], 2.33 [1.60-3.41]) and for HbA1c at study entry (8.01%-8.70% vs <8.01%; OR [95% CI], 1.62 [1.27-2.08]) with treatment failure.

4 | DISCUSSION

The DUNE study was an observational, multinational, prospective real-life study that assessed the achievement of HbA1c targets set by physicians based on individual patient characteristics. The study further explored the relationship between the occurrence of hypoglycaemia and achievement of individualized HbA1c targets. Based on prespecified criteria, over 60% of DUNE participants were deemed at "high risk" of complications from hypoglycaemia because of their age (>65 years), health status (vascular complications or co-morbidities) or occupation (commercial/truck driver).

While there were substantial reductions in HbA1c during the 12-week study in both newly and previously initiated patients, most participants failed to achieve their individualized HbA1c target, set at <7.5% (<58.5 mmol/mol) for 76% of patients. This may be related, in part, to insufficient insulin dose titration during the 12 weeks of treatment, as indicated by the 9 U and 5 U dose increases reported in the newly or previously initiated groups, respectively; such absence of intensive titration (titration inertia) has been reported previously in real-world clinical practice.[25] Notably, 63% of participants in this study were reportedly self-titrating their insulin, whereas, in wider clinical practice settings, it is likely that titration is largely determined by physicians.[26] Overall, however, no major difference in individualized HbA1c target achievement was observed between participant-driven or physician-driven titration, in either newly or previously initiated participants. While only 27% of participants achieved their individual HbA1c target by week 12, this is consistent with observations from other real-world studies.[8,25] By comparison, in treat-to-target trials with defined titration algorithms, close follow-up and careful monitoring, the proportion of participants achieving HbA1c targets of less than 7.0% (<53 mmol/mol) with BIs has been reported to be as much as 40% to 50%.[27–29] Importantly, mean daily insulin doses at the end of these treat-to-target studies reached between approximately 40 and 100 U/d,[27–29] considerably higher than those reached in this study.

It has been suggested that the experience of hypoglycaemia may result in increased fear of future hypoglycaemic events and, consequently, a worsening in glycaemic control as the result of changes in adherence to medication.[19,30] However, it has also been reported that, despite the fact that hypoglycaemia results in poorer adherence, participants experiencing hypoglycaemia achieved lower HbA1c levels than those who did not experience hypoglycaemia.[21] Lower baseline HbA1c has also been independently associated with HbA1c target achievement and risk of hypoglycaemia.[31] Each 1% increase in baseline HbA1c reduced the likelihood of achieving an HbA1c target by 46% and increased the risk of experiencing at least one episode of confirmed hypoglycaemia by 17%.[31] Similarly, in the DUNE study, there was a significant positive association between experiencing symptomatic hypoglycaemia and HbA1c target achievement, and between lower baseline HbA1c and 12-week HbA1c target achievement. Hypothetically, this association might be explained by the fact that participants who achieved target HbA1c were at greater risk of hypoglycaemia, given their lower average BG levels. While more intensive insulin titration can also lead to greater risk of hypoglycaemia, we observed very modest increases in insulin use in our study.

The DUNE study may have been limited by several factors. Firstly, as mentioned earlier, a high proportion of participants reportedly self-titrated, which may not be applicable beyond the clinical practice settings represented in this real-world study.[26] Furthermore, hypoglycaemia data were collected by physicians only at week 12, based on patient diaries, which may be subject to recall bias.[32] The short observational period may also reduce the generalizability of results, and the association between hypoglycaemia and target achievement may not necessarily have persisted over a longer observational period. The 3-month study period may have been insufficient to allow participants with higher baseline HbA1c levels to reach glycaemic targets. However, a recent real-world clinical study reported that decline in HbA1c occurs, for the most part, during the first 3 months of insulin titration, with limited further decline thereafter,[10] suggesting that the HbA1c levels reached during the DUNE study would reflect longer-term levels. Additionally, the decline in HbA1c during the first 3 months may reflect the period when titration occurs most often during routine practice.[25]

It is of interest that the rates of symptomatic hypoglycaemia during the study period in both newly initiated (14%) and previously initiated (18%) participants were lower than predicted (45% and 20%, respectively) based on conservative estimates from previous randomized clinical trials.[28,33] This suggests that such randomized trials have limited applicability to real-life clinical practice. For example, in treat-to-target trials, the lower HbA1c values were achieved with intensive titration. By contrast, the limited increases in insulin dose in this study may have further contributed to the observed low incidence and rates of hypoglycaemia. The low rate of hypoglycaemia in the DUNE study could have impacted the reported association between HbA1c target achievement and the occurrence, frequency and severity of hypoglycaemia.

Despite its limitations, the DUNE study benefitted from having a large global real-world population with a comprehensive, prospective collection of data concerning patient characteristics at baseline, thus providing novel insights into real-life practice, particularly in that individualized targets for most patients appear to be set by their physicians. Given that individualized targets were often set higher than the general HbA1c goal of less than 7.0% (<53 mmol/mol), this definition of glycaemic control, often used in clinical studies,[6–10] might need to be reconsidered for real-world studies. The overall profile of individualized HbA1c targets set or achieved in our study population was

similar regardless of retrospective stratification of participants as being at high or low risk for hypoglycaemia complications, assessed independently from physician evaluations; therefore, the results should be translatable to other real-world scenarios.

As participants who did not experience symptomatic hypoglycaemia were less likely to achieve glucose targets, factors other than experiencing hypoglycaemia, or the fear thereof, may have contributed to the failure to achieve targets. For example, multivariate analyses showed that individuals with a longer duration of diabetes and a higher HbA1c level at study entry were significantly less likely to achieve target HbA1c levels. Although unlikely, it may also be possible that the experience of hypoglycaemia itself contributed to lower HbA1c levels, with more frequent events leading to a disproportionately lower overall average HbA1c level. Alternatively, patients who achieved lower HbA1c levels may have been at higher risk of experiencing hypoglycaemia. Further studies are required to better understand the association between hypoglycaemia and HbA1c target attainment, and to determine why so many individuals with T2DM are failing to achieve glycaemic targets in real-life settings. The observed limited increase in insulin dose suggests that there may be an opportunity for individuals with T2DM and their physicians to titrate insulin more effectively to achieve desired glycaemic goals. Alternatively, the use of newer glucose-lowering drugs with reduced risks of hypoglycaemia as compared to BI may help individuals achieve glucose targets. To this end, further research and updated treatment guidelines are required to define the most appropriate options for the intensification of glucose-lowering drugs and the optimal timing of insulin initiation and titration.

ACKNOWLEDGMENTS

The authors thank the study participants, trial staff and investigators for their participation (participating physicians are listed in Appendix S1). K. K. acknowledges support from The National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care—East Midlands (CLAHRC-EM) and the NIHR Leicester Biomedical Research Centre.

Editorial and writing assistance was provided by Arthur Holland, PhD, of Fishawack Communications Ltd and was funded by Sanofi.

Conflict of interest

L. M. has served on advisory panels for Novo Nordisk, Sanofi, and AstraZeneca, and has received consulting fees from Sanofi. D. M. has served on advisory panels for Sanofi, Praxis Pharmaceutical, AstraZeneca, Novo Nordisk and MSD, and has received speakers' bureau fees from Menarini, GlaxoSmithKline, Eli Lilly, Sanofi, Novartis, Novo Nordisk and MSD. E. O. has served on advisory panels for Boehringer Ingelheim and Eli Lilly, and has received speakers' bureau fees from Sanofi, Takeda, Johnson & Johnson, Novo Nordisk and AstraZeneca. N. L. has no conflicts of interest to declare. A. C., J. W., P. S., C. C., V. P. and R. P. are all employees of and stock/shareholders in Sanofi. K. K. has served on advisory panels, is a board member of, and has received consulting and speakers' bureau fees from Bayer, Novartis, Novo Nordisk, Sanofi, Eli Lilly, Servier and MSD, and has received research support from Novartis, Novo Nordisk, Sanofi, Eli Lilly, Pfizer, Boehringer Ingelheim and MSD.

Author contributions

L. M., D. M., A. C., J. W. and K. K. were involved in study concept and design. C. C. performed the statistical analyses of data. All authors participated in the interpretation of data and in the writing, reviewing and editing of the manuscript, and all had final responsibility for approving the published version. L. M. 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.

ORCID

Luigi F. Meneghini https://orcid.org/0000-0003-4539-2725
Didac Mauricio https://orcid.org/0000-0002-2868-0250

REFERENCES

1. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.
2. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ*. 1998;316:823-828.
3. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke*. 1996;27:63-68.
4. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2015;14:100.
5. American Diabetes Association. Standards of medical care in diabetes-2017: summary of revisions. *Diabetes Care*. 2017;40:S4-S5.
6. Stone MA, Charpentier G, Doggen K, et al. Quality of care of people with type 2 diabetes in eight European countries: findings from the Guideline Adherence to Enhance Care (GUIDANCE) study. *Diabetes Care*. 2013;36:2628-2638.
7. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36:2271-2279.
8. Dalal MR, Grabner M, Bonine N, Stephenson JJ, DiGenio A, Bieszk N. Are patients on basal insulin attaining glycemic targets? Characteristics and goal achievement of patients with type 2 diabetes mellitus treated with basal insulin and physician-perceived barriers to achieving glycemic targets. *Diabetes Res Clin Pract*. 2016;121:17-26.
9. Kostev K, Dippel FW, Rathmann W. Glycemic control after initiating basal insulin therapy in patients with type 2 diabetes: a primary care database analysis. *Diabetes Metab Syndr Obes*. 2015;8:45-48.
10. Mauricio D, Meneghini L, Seufert J, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. *Diabetes Obes Metab*. 2017;19:1155-1164.
11. Khunti K, Caputo S, Damci T, et al. The safety and efficacy of adding once-daily insulin detemir to oral hypoglycaemic agents in patients with type 2 diabetes in a clinical practice setting in 10 countries. *Diabetes Obes Metab*. 2012;14:1129-1136.
12. American Diabetes Association. Standards of medical care in diabetes-2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.
13. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140-149.

14. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35:1364-1379.
15. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013. *Endocr Pract*. 2013;19:327-336.
16. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet Med*. 2012;29:682-689.
17. Garber AJ. The importance of titrating starting insulin regimens in patients with type 2 diabetes. *Diabetes Obes Metab*. 2009;11(suppl 5):10-13.
18. Brod M, Rana A, Barnett AH. Adherence patterns in patients with type 2 diabetes on basal insulin analogues: missed, mistimed and reduced doses. *Curr Med Res Opin*. 2012;28:1933-1946.
19. Ahren B. Avoiding hypoglycemia: a key to success for glucose-lowering therapy in type 2 diabetes. *Vasc Health Risk Manag*. 2013;9:155-163.
20. Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. *Diabetes Obes Metab*. 2018;20:488-496.
21. Walz L, Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wandell P. Impact of symptomatic hypoglycemia on medication adherence, patient satisfaction with treatment, and glycemic control in patients with type 2 diabetes. *Patient Prefer Adherence*. 2014;8:593-601.
22. Mullins P, Sharplin P, Yki-Jarvinen H, Riddle MC, Haring HU. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven Phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther*. 2007;29:1607-1619.
23. Kalra S, Deepak MC, Narang P, Singh V, Maheshwari A. Correlation between measures of hypoglycemia and glycemic improvement in sulfonylurea treated patients with type 2 diabetes in India: results from the OBSTACLE hypoglycemia study. *J Postgrad Med*. 2014;60:151-155.
24. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40:155-157.
25. Khunti K, Damci T, Meneghini L, Pan CY, Yale JF, SOLVE Study Group. Study of Once Daily Levemir (SOLVE): insights into the timing of insulin initiation in people with poorly controlled type 2 diabetes in routine clinical practice. *Diabetes Obes Metab*. 2012;14:654-661.
26. Khunti K, Davies MJ, Kalra S. Self-titration of insulin in the management of people with type 2 diabetes: a practical solution to improve management in primary care. *Diabetes Obes Metab*. 2013;15:690-700.
27. Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/-mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care*. 2014;37:2755-2762.
28. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17:386-394.
29. Pan C, Gross JL, Yang W, et al. A multinational, randomized, open-label, treat-to-target trial comparing insulin degludec and insulin glargine in insulin-naive patients with type 2 diabetes mellitus. *Drugs R D*. 2016;16:239-249.
30. Mitchell BD, Vietri J, Zagar A, Curtis B, Reaney M. Hypoglycaemic events in patients with type 2 diabetes in the United Kingdom: associations with patient-reported outcomes and self-reported HbA1c. *BMC Endocr Disord*. 2013;13:59.
31. Riddle MC, Vlajnic A, Zhou R, Rosenstock J. Baseline HbA1c predicts attainment of 7.0% HbA1c target with structured titration of insulin glargine in type 2 diabetes: a patient-level analysis of 12 studies. *Diabetes Obes Metab*. 2013;15:819–825.
32. Khunti K, Alsifri S, Aronson R, et al. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab*. 2016;18:907-915.
33. Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care*. 2014;37:3235-3243.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Meneghini LF, Mauricio D, Orsi E, et al. The Diabetes Unmet Need with Basal Insulin Evaluation (DUNE) study in type 2 diabetes: Achieving HbA1c targets with basal insulin in a real-world setting. *Diabetes Obes Metab*. 2019;21:1429–1436. https://doi.org/10.1111/dom.13673