DUNE
Diabetes Unmet Needs with basal insulin Evaluation

Achievement of HbA_{1c} targets in the Diabetes Unmet Need with basal insulin Evaluation (DUNE) real-world study

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INTRODUCTION

- Treatment guidelines advocate the achievement of individualized HbA_{1c} targets to reduce the glycaemic burden in people with type 2 diabetes (T2DM).[1–4]
- Approximately half of all people with T2DM are unable to achieve glycaemic targets (HbA_{1c} <7.0 % [<53 mmol/mol]) in clinical practice, with even lower rates for those treated with basal insulin (BI).[5–7]
- In addition, not achieving HbA_{1c} targets in the short-term is associated with suboptimal long-term blood glucose control.[8]
- In insulin-treated people with T2DM, suboptimal glycaemic control may be due, in part, to non-adherence, lack of dose titration or omission and/or dose reduction in the setting of a fear of hypoglycaemia.[9–12]
- The association between achievement of individualized glycaemic targets and hypoglycaemia risk in the real-world setting is unknown.

OBJECTIVE

To assess individualized HbA_{1c} target achievement and its potential association with the occurrence, frequency, and severity of symptomatic hypoglycaemia in a real-world setting.

METHODS

- **Design:** the Diabetes Unmet Need with basal insulin Evaluation (DUNE) study was a 12-week, single-arm, prospective, observational study (February 2015 to July 2016).
  - Treatment was carried out according to local practice.
- **Study population:**
  - Key inclusion criteria:
    - Age ⩾18 years and having T2DM in people either newly initiated with BI at the time of enrolment, or treated with BI for <12 months (previously initiated) with or without oral antihyperglycaemic drugs and/or glucagon-like peptide-1 receptor agonists.
    - HbA_{1c} ⩾7.5 and ⩽11.0 % (⩾58 and ⩽97 mmol/mol) for newly initiated BI users, and ⩾7.5 and ⩽10.0 % (⩾58 and ⩽86 mmol/mol) for previously initiated BI users.
  - Key exclusion criteria:
    - Treatment with rapid-acting or premix insulin or physician plans to intensify the treatment with a rapid-acting or premix insulin within the next 3 months.
- **Primary endpoints:**
  - Achievement of individual HbA_{1c} target at 12 weeks (if an individual target is not defined at baseline, a general HbA_{1c} target of <7.0 % [<53.0 mmol/mol] will be considered as relevant).
  - The impact of symptomatic hypoglycaemia according to its frequency and severity on short-term HbA_{1c} target achievement at 12 weeks.
- **Secondary endpoints:**
  - Achievement of the general HbA_{1c} target of <7.0 % (<53.0 mmol/mol) and <8.0 % (<63.9 mmol/mol) at week 12, according to level of risk of hypoglycaemia complications.[13]
  - HbA_{1c} and basal insulin dose changes from baseline.
  - Hypoglycaemia – any symptomatic, severe, and documented symptomatic events (glycaemic thresholds: 54 and 70 mg/dL [3.0 and 3.9 mmol/L]).
- **Data analysis and statistics:**
  - The number and proportion of patients achieving individualized HbA_{1c} targets at 12 weeks was summarized using a 95% confidence interval, with a precision of at least 1.5%.
  - The relationship between HbA_{1c} target at 12 weeks and symptomatic hypoglycaemia was analyzed using univariate and multivariate logistic regression.
  - The multivariate analysis was adjusted on the baseline characteristics of region, age, duration of diabetes, HbA_{1c}, use of sulphonylureas and/or glinides, and use of glucagon-like peptide-1 receptor agonists. Other factors included in the model were selected by stepwise analysis.

RESULTS

- **Study participants:**
  - The evaluable study population included 3139 participants from 28 countries (**Table 1**).
- **Individualized HbA_{1c} target:**
  - Of the evaluable participants, 99.7% were set individualized HbA_{1c} targets by their physicians (0.3% were not set individualized targets and were assigned a general target of <7.0 % [<53.0 mmol/mol]).
  - The majority of participants in both groups (57%) had HbA_{1c} targets of 7.0 % to 7.5 % (53.0 to 58.5 mmol/mol) (**Figure 1**).
- **Achievement of HbA_{1c} target at 12 weeks:**
  - Overall, 27.4% of participants achieved their individualized physician-determined HbA_{1c} target (**Figure 2**).
  - Only 23.5% of participants from the newly initiated group and 20.2% from the previously initiated group, achieved individualized targets or HbA_{1c} <7.0 % [<53 mmol/mol] without hypoglycaemia (**Figure 2**).

Table 1: Demographic and baseline characteristics

	Newly initiated (n=1716)	Previously initiated (n=1423)	All (N=3139)
Mean age, years (SD)	60 (11)	61 (10)	61 (11)
Gender, female, %	49	53	51
Mean BMI, kg/m² (SD)	30.6 (5.6)	30.4 (5.4)	30.5 (5.5)
Mean duration of diabetes, years (SD)	10 (7)	11 (7)	10 (7)
<1 year, %	6	5	6
1 to 5 years, %	22	20	21
5 to 10 years, %	33	29	31
>10 years, %	39	46	42
At least one diabetes medication[a], %	92	93	93
Microvascular complications[b], %	38	42	40
Diabetic, neuropathy %	28	29	28
Diabetic retinopathy, %	14	19	16

[a]Data included if >5% of participants are using diabetes medication. [b]At least one complication.
BMI, body mass index; SD, standard deviation

Figure 1: Individualized HbA_{1c} target set by physicians

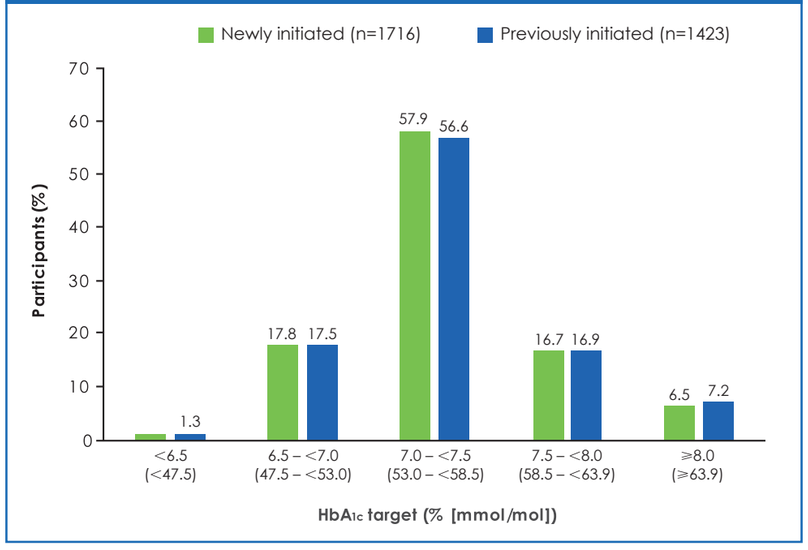
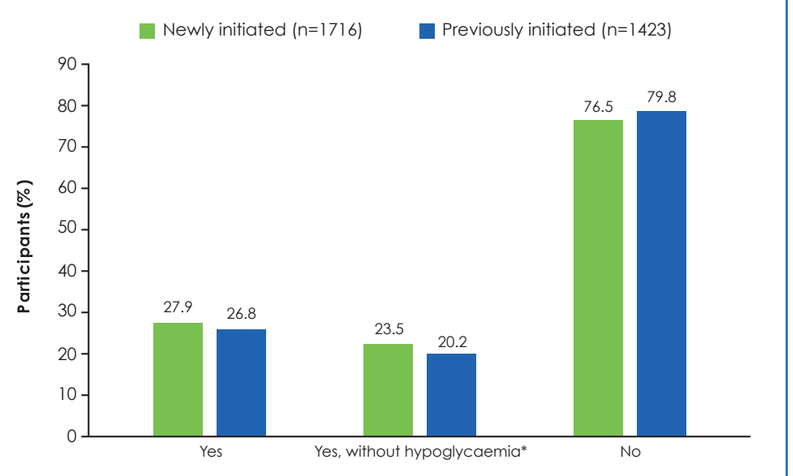


Figure 2: Individualized HbA_{1c} target achievement at week 12



*Symptomatic hypoglycaemia: any event associated with typical hypoglycaemic symptoms, regardless of blood glucose measurement.

Table 2: Change in basal insulin dose and HbA_{1c} from baseline to week 12

	Newly initiated (n=1716)	Previously initiated (n=1423)	All (N=3139)
Daily insulin dose (U/kg), mean (SD)			
Baseline	0.17 (0.09)	0.29 (0.17)	0.22 (0.15)
12 weeks	0.27 (0.16)	0.34 (0.20)	0.31 (0.18)
Change	+0.10 (0.13)	+0.06 (0.10)	+0.08 (0.12)
HbA_{1c} (%), mean (SD)			
Baseline	9.1 (1.0)	8.6 (0.8)	8.9 (1.0)
12 weeks	7.8 (1.2)	7.7 (1.2)	7.7 (1.2)
Change	–1.4 (1.3)	–0.8 (1.1)	–1.1 (1.3)

SD, standard deviation

- **Change in basal insulin dose and HbA_{1c} from baseline to week 12:**
  - At week 12 both newly initiated and previously initiated participants showed a mean HbA_{1c} decrease from baseline with modest up-titration of insulin dose (**Table 2**).
- **Self-reported hypoglycaemia:**
  - Symptomatic hypoglycaemia was experienced by 18.3% and 14.2% of previously and newly initiated participants, respectively (**Table 3**).
  - The incidence of severe hypoglycaemia during the study was low (1.3% and 0.5% for previously and newly initiated, respectively) (**Table 3**).

Table 3: Self-reported hypoglycaemia

	Newly initiated (n=1716)	Previously initiated (n=1423)	All (N=3139)
Participants with at least one symptomatic event, %	14.2	18.3	16.0
Symptomatic events per participant, mean (SD), range	0.37 (1.36), 0–21	0.55 (1.96), 0–39	0.45 (1.66), 0–39
Frequency of symptomatic hypoglycaemia, % participants			
0 or 1 events	91.4	88.9	90.3
2 to 5 events	7.5	9.2	8.3
>5 events	1.1	1.9	1.5
Severity of symptomatic hypoglycaemia, % participants			
No symptomatic hypoglycaemia	85.8	81.7	84.0
Non-severe	13.7	17.0	15.2
Severe	0.5	1.3	0.8

SD, standard deviation

- **HbA_{1c} target achievement at 12 weeks:**
  - Univariate logistic regression analysis showed a positive association between the occurrence (p<0.001) and frequency (p=0.004) of symptomatic hypoglycaemia and HbA_{1c} target achievement.
  - Adjusting on baseline characteristics, the multivariate analysis demonstrated a significant positive association between the occurrence of symptomatic hypoglycaemia, and HbA_{1c} target achievement (**Table 4**).
  - Participants, who experienced ⩾2 symptomatic events were more likely to achieve their HbA_{1c} target compared to those who experienced 0–1 symptomatic hypoglycaemic events (**Table 4**).

Table 4: Multivariate logistic regression model of HbA_{1c} target achievement at 12 weeks

Multivariate model		OR (95% CI)	p-value*
Symptomatic hypoglycaemia	Yes	Reference	**<0.001**
	No	0.645 (0.513 to 0.810)	<0.001
Frequency of symptomatic hypoglycaemia	0 or 1	Reference	**0.001**
	2 to 5	1.463 (1.080 to 1.981)	0.014
	>5	2.690 (1.385 to 5.224)	0.003
Number of symptomatic hypoglycaemic events	n	1.088 (1.030 to 1.149)	**0.002**
Symptomatic hypoglycaemia severity	No	Reference	**<0.001**
	Non-severe	1.526 (1.208 to 1.926)	<0.001
	Severe	2.148 (0.886 to 5.207)	0.091

* Global p-values are presented in bold.
Multivariate analysis adjusted on baseline characteristics of region, age, duration of diabetes, HbA_{1c}, use of sulphonylureas and/or glinides, use of glucagon-like peptide-1 receptor agonists. Other factors were selected by stepwise analysis.
CI, confidence interval; OR, odds ratio

DISCUSSION

- DUNE benefitted from a large, real-world population, with a comprehensive collection of patient characteristics.
- Most participants did not achieve individualized HbA_{1c} targets set by physicians.[14]
- The short study duration may have contributed to a lower than expected rate of hypoglycaemia (16% overall), and impacted on the associations with target achievement. Nevertheless, participants reporting symptomatic hypoglycaemia were significantly more likely to achieve HbA_{1c} target than those who did not report an event.
- While it has previously been suggested that hypoglycaemia may negatively impact the achievement of HbA_{1c} targets, this was not observed in the DUNE study.
- The modest dose increase observed suggests that there is an opportunity for people with T2DM and their physicians to titrate insulin more effectively. Further studies are required to better understand the reasons behind the lack of insulin titration and why many individuals with T2DM do not achieve HbA_{1c} targets in the real-world setting.

CONCLUSIONS

- **Results from this real-world study showed that while HbA_{1c} levels fell substantially, most participants did not achieve individualized HbA_{1c} targets (mostly 7.0–7.5 %).**
- **Participants who reached HbA_{1c} target were more likely to experience symptomatic hypoglycaemia.**

DISCLOSURES: Luigi Meneghini — **Advisory panel**: Novo Nordisk, Sanofi; **Consultant**: Novo Nordisk, Sanofi. Didac Mauricio — **Advisory panel**: Sanofi, Praxis Pharmaceutical, AstraZeneca, Novo Nordisk, MSD; **Speaker's bureau**: Menarini, GlaxoSmithKline, Eli Lilly, Sanofi, Novartis, Novo Nordisk, MSD. Emanuela Orsi — **Advisory panel**: Boehringer Ingelheim, Eli Lilly; Speaker's bureau: Takeda, Johnson & Johnson, Novo Nordisk, AstraZeneca. Anna Cali — **Employee**: Sanofi; **Stock/shareholder**: Sanofi. Jukka Westerbacka — **Employee**: Sanofi. Peter Stella — **Employee**: Sanofi. Christophe Candelas — **Employee**: Sanofi. Valerie Pilorget — **Employee**: Sanofi; Stock/shareholder: Sanofi. Riccardo Perfetti — **Employee**: Sanofi; **Stock/shareholder**: Sanofi. Kamlesh Khunti — **Advisory panel**: Novartis, Novo Nordisk, Sanofi, Eli Lilly, Servier, MSD; **Board member**: Novartis, Novo Nordisk, Sanofi, Eli Lilly, Servier, MSD; **Consultant**: Novartis, Novo Nordisk, Sanofi, Eli Lilly, Servier, MSD, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Lilly, Roche; **Speaker's bureau**: Novartis, Novo Nordisk, Sanofi, Eli Lilly, Servier, MSD, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly; **Research support**: Novartis, Novo Nordisk, Sanofi, Eli Lilly, Pfizer, Boehringer Ingelheim, MSD, AstraZeneca, Lilly, Janssen and Roche.

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FUNDING: This poster was presented previously at the 77th Scientific Sessions of the American Diabetes Association (ADA); 9–13 June 2017; San Diego, CA, USA, 990-P. This study was funded by SANOFI. The authors received editorial/writing support in the preparation of this poster provided by Arthur Holland (PhD) of Fishawack Communications Ltd, funded by SANOFI.