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A retrospective observational cohort study to investigate uncontrolled hyperglycaemia and delay in basal insulin intensification and non-intensification among individuals with type 2 diabetes in Denmark

Jan Håkon Rudolfsen[1]; Amoolya Gowda[2]; Kasper Løwe Røder[1]; Elisabeth de Laguiche[2]

Aim

To investigate the real-world patterns and behaviours around uncontrolled hyperglycaemia (UH) and treatment intensification (TI) in adults with type 2 diabetes (T2D) receiving basal insulin in Denmark.

Introduction

- In people living with T2D treated with basal insulin, failure to intensify treatment when clinically necessary (i.e. therapeutic inertia) can lead to extended periods of suboptimal glycaemic control, which are associated with increased risk of diabetes-related complications.[1,2]
- Prolonged duration of UH while receiving basal insulin before intensification of therapy can impede attainment of glycaemic targets.[3]
- Understanding and addressing the drivers of therapeutic inertia that prevent TI in people receiving basal insulin may lead to timely and appropriate treatment decisions, consequently improving overall outcomes for people living with T2D.[4] Therefore, investigation of real-world patterns in UH and basal insulin intensification practices in people living with T2D is warranted.

Methods

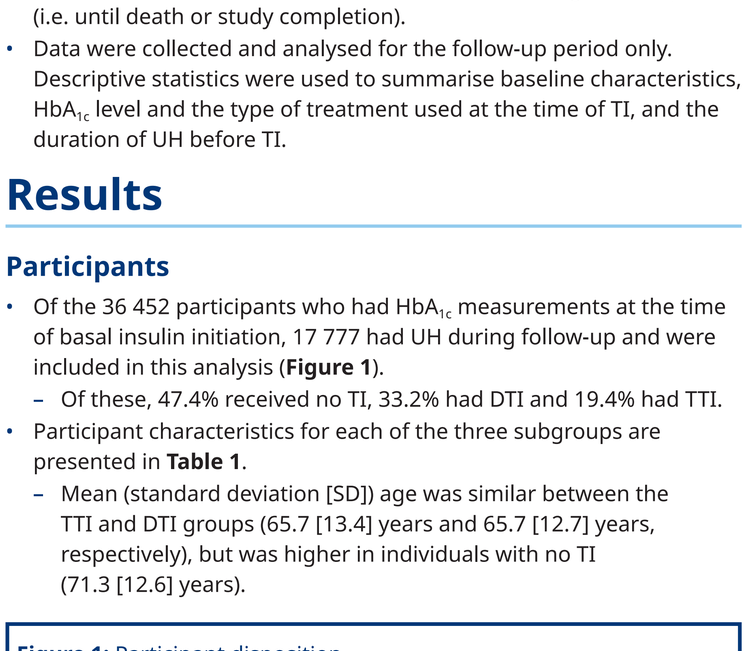
- This retrospective, observational cohort analysis used real-world data from Danish health and administrative registers from 1 January 2012 to 31 December 2022.
- Eligible participants were adults (aged ≥18 years) with T2D who were receiving basal insulin and had UH (defined as a glycated haemoglobin [HbA_{1c}] level >7.0% for ≥6 consecutive months) during the follow-up period.
- After basal insulin initiation and before the follow-up period, a 6-month period was applied to allow for insulin titration and attainment of glycaemic control.
- Participants were followed until TI, death or study completion.
- Timely treatment intensification (TTI) was defined as the initiation of bolus or premixed insulin, a fixed-ratio combination (FRC) of basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1 RA), or a non-insulin glucose-lowering agent within 6 months after the first HbA_{1c} level >7.0% measured at the beginning of the period of UH.
- Delayed treatment intensification (DTI) was defined as the absence of TI within 6 months after the first HbA_{1c} level >7.0% measured at the beginning of the period of UH.
- UH without TI was defined as the absence of TI during follow-up (i.e. until death or study completion).
- Data were collected and analysed for the follow-up period only. Descriptive statistics were used to summarise baseline characteristics, HbA_{1c} level and the type of treatment used at the time of TI, and the duration of UH before TI.

Results

Participants

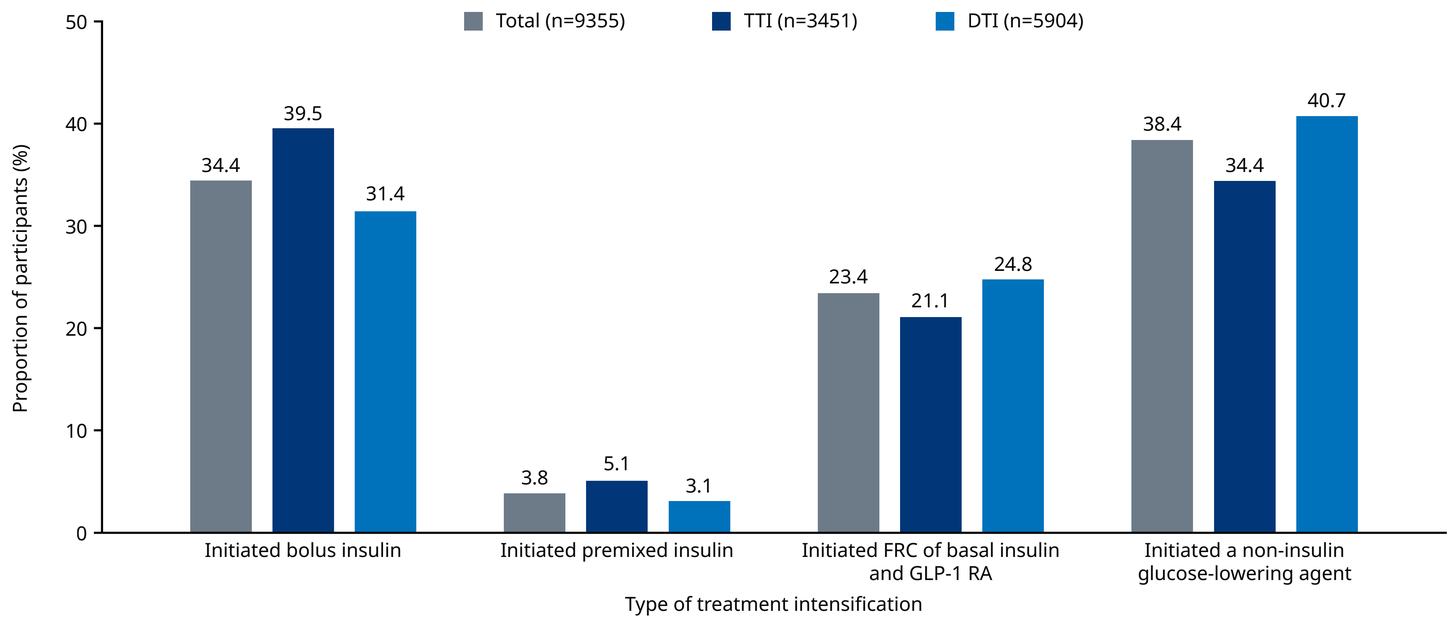
- Of the 36 452 participants who had HbA_{1c} measurements at the time of basal insulin initiation, 17 777 had UH during follow-up and were included in this analysis (**Figure 1**).
  - Of these, 47.4% received no TI, 33.2% had DTI and 19.4% had TTI.
- Participant characteristics for each of the three subgroups are presented in **Table 1**.
  - Mean (standard deviation [SD]) age was similar between the TTI and DTI groups (65.7 [13.4] years and 65.7 [12.7] years, respectively), but was higher in individuals with no TI (71.3 [12.6] years).

Figure 1: Participant disposition



UH was defined as an HbA_{1c} level of >7.0% for at least 6 consecutive months.
DTI, delayed treatment intensification; HbA_{1c}, glycated haemoglobin; TI, treatment intensification; TTI, timely treatment intensification; UH, uncontrolled hyperglycaemia.

Figure 2: Glucose-lowering agents used for basal insulin intensification in participants receiving timely and delayed treatment intensification



DTI, delayed treatment intensification; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist; n, number of participants; TTI, timely treatment intensification.

  - In the TTI and DTI groups, participants had a similar age distribution, whereas the no TI group included a higher proportion of individuals aged at least 65 years.
- Comorbidity burden (mean [SD] Charlson Comorbidity Index) was highest for individuals with no TI (2.6 [3.2] points) in the 5 years before study completion, followed by the TTI (1.4 [2.2] points) and DTI (1.2 [2.1] points) groups (**Table 1**).

HbA_{1c} level at time of basal insulin intensification

- The observed mean HbA_{1c} at the time of TI was 0.2%-points higher for the DTI group than the TTI group (**Table 2**).
- Overall, 60.8% of participants had an HbA_{1c} >8.0% at the time of basal insulin intensification; this proportion was higher in the DTI group (74.4%) than the TTI group (62.8%).

Duration of uncontrolled hyperglycaemia

- For individuals in the DTI group, the mean duration of UH before intensifying basal insulin treatment was approximately 2 years (**Table 3**); 25.0% of these individuals spent over 2.6 years with UH before TI.
- Individuals in the TTI group spent approximately 2 months with UH before TI.

Table 1: Participant characteristics at time of event[a]

	Total (n=17 777)	TTI (n=3451)	DTI (n=5904)	UH without TI (n=8422)
Age, mean (SD), years	68.4 (13.1)	65.7 (13.4)	65.7 (12.7)	71.3 (12.6)
Age group, n (%)				
18–34 years	189 (1.1)	76 (2.2)	78 (1.3)	35 (0.4)
35–44 years	563 (3.2)	169 (4.9)	241 (4.1)	153 (1.8)
45–54 years	2086 (11.7)	473 (13.7)	891 (15.1)	722 (8.6)
55–64 years	3965 (22.3)	811 (23.5)	1506 (25.5)	1648 (19.6)
≥65 years	10 974 (61.7)	1922 (55.7)	3188 (54.0)	5864 (69.6)
Sex, male, n (%)	10 990 (61.8)	2141 (62.0)	3700 (62.7)	5149 (61.1)
Duration of T2D, mean (SD), years	12.8 (6.3)	10.1 (6.4)	11.9 (5.8)	14.4 (6.1)
Duration of UH before event, mean (SD), months	19.4 (19.7)	2.0 (1.7)	23.1 (16.8)	23.9 (21.6)
Event, n (%)				
Study completion	6865 (38.6)	–	–	6865 (81.5)
Died	1557 (8.8)	–	–	1557 (18.5)
Insulin intensification	9355 (52.6)	3451 (100.0)	5904 (100.0)	–
CCI score, mean (SD),[b] points	1.9 (2.8)	1.4 (2.2)	1.2 (2.1)	2.6 (3.2)
Diabetes-related comorbidities observed in the 5 years before the event,[a] n (%)				
Hypertension[c]	5250 (29.5)	1115 (32.3)	1815 (30.7)	2320 (27.5)
Dyslipidaemia[d]	337 (1.9)	81 (2.3)	139 (2.4)	117 (1.4)
Cardiovascular disease[e]	5329 (30.0)	980 (28.4)	1586 (26.9)	2763 (32.8)
Nephropathy	1909 (10.7)	377 (10.9)	613 (10.4)	919 (10.9)
Retinopathy	1638 (9.2)	302 (8.8)	570 (9.7)	766 (9.1)

UH was defined as an HbA_{1c} level of >7.0% for at least 6 consecutive months.
[a]Event refers to either insulin intensification (TTI and DTI subgroups), death or study completion (UH without TI subgroup). [b]CCI scores include comorbidities reported in the 5 years before time of basal insulin intensification, death or study completion. [c]Hypertension was identified using ICD-10 code I10. [d]Dyslipidaemia was identified using ICD-10 code E78.5. [e]Cardiovascular disease was identified using the ICD-10 codes I10.1, I13.0, I13.2, I20–I25, I45, I50, I60–I72 and I173.0.
%, percentage of participants; CCI, Charlson Comorbidity Index; DTI, delayed treatment intensification; HbA_{1c}, glycated haemoglobin; ICD-10, International Classification of Diseases, Tenth Revision; n, number of participants; SD, standard deviation; T2D, type 2 diabetes; TI, treatment intensification; TTI, timely treatment intensification; UH, uncontrolled hyperglycaemia.

Treatment intensification behaviour

- A relatively higher proportion of individuals in the TTI group than the DTI group initiated bolus insulin (39.5% versus 31.4%) or premixed insulin (5.1% versus 3.1%) (**Figure 2**).
- Conversely, more individuals in the DTI group than the TTI group intensified treatment with a non-insulin glucose-lowering agent (40.7% versus 34.4%) or an FRC of basal insulin and GLP-1 RA (24.8% versus 21.1%).

Table 2: HbA_{1c} level at time of event[a]

	HbA_{1c} level at time of event[a]			
	Total (n=17 777)	TTI (n=3451)	DTI (n=5904)	UH without TI (n=8422)
Mean (SD), %-points	8.9 (2.3)	9.0 (4.0)	9.2 (3.8)	8.6 (3.9)
HbA_{1c} ≤8.0%, n (%)	6965 (39.2)	1285 (37.2)	1514 (25.6)	4166 (49.5)
HbA_{1c} >8.0%, n (%)	10 812 (60.8)	2166 (62.8)	4390 (74.4)	4256 (50.5)

UH was defined as an HbA_{1c} level of >7.0% for at least 6 consecutive months.
[a]Event refers to either insulin intensification (TTI and DTI subgroups), death or study completion (UH without TI subgroup).
%, percentage of participants; DTI, delayed treatment intensification; HbA_{1c}, glycated haemoglobin; n, number of participants; SD, standard deviation; TI, treatment intensification; TTI, timely treatment intensification; UH, uncontrolled hyperglycaemia.

Table 3: Duration of uncontrolled hyperglycaemia before event[a]

	Duration of UH before event[a]		
	TTI (n=3451)	DTI (n=5904)	UH without TI (n=8422)
Mean (SD), days	61.8 (52.4)	701.6 (511.0)	728.7 (657.8)
Median (25th quartile, 75th quartile), days	61 (0, 91)	548 (304, 944)	487 (274, 1035)

UH was defined as an HbA_{1c} level of >7.0% for at least 6 consecutive months.
[a]Event refers to either insulin intensification (TTI and DTI subgroups), death or study completion (UH without TI subgroup).
DTI, delayed treatment intensification; HbA_{1c}, glycated haemoglobin; SD, standard deviation; TI, treatment intensification; TTI, timely treatment intensification; UH, uncontrolled hyperglycaemia.

Conclusion

- Timely intensification of treatment in people living with T2D with uncontrolled hyperglycaemia while receiving basal insulin therapy was uncommon in Denmark.
- Almost half of the individuals included in this analysis did not receive any treatment intensification during the study period, despite having uncontrolled hyperglycaemia for at least 6 months; only 19.4% of individuals received timely basal insulin intensification.
- One-third of individuals experienced delays in treatment intensification, spending on average approximately 2 years with uncontrolled hyperglycaemia before treatment intensification.
- At the time of basal insulin intensification, observed mean HbA_{1c} levels were 0.2%-points higher in those with delayed treatment intensification than those with timely treatment intensification, although a higher proportion of individuals in the delayed treatment intensification group had an HbA_{1c} >8.0%.
- Individuals who did not intensify basal insulin treatment tended to be older (aged ≥65 years), with a higher comorbidity burden than those who received timely or delayed treatment intensification.
- Further investigation into individuals with uncontrolled hypoglycaemia who do not intensify basal insulin treatment could be beneficial.

[1]EY Denmark, Frederiksberg, Denmark; [2]Novo Nordisk, Søborg, Denmark.

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Disclosures:
JHR and KLR are employees of EY Denmark.
AG and EdL are employees of Novo Nordisk and hold stock in Novo Nordisk.

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