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Clinical inertia among patients with type 2 diabetes mellitus treated with DPP-4i and/or SGLT-2i

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Abstract

Objectives: Failure to intensify treatment of patients with type 2 diabetes (T2D) in a timely manner is a common challenge. If newer oral anti-diabetic drugs (NOADs) such as dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium/glucose cotransporter 2 inhibitors (SGLT-2i) do not achieve metabolic control, injectable therapy like insulin or glucagon-like Peptide 1 (GLP-1) receptor agonists are required. We investigated the time in poor glycaemic control (PC, HbA1c>7%, >7.5%, >8%) in adults with T2D treated with DPP-4i/SGLT-2i until treatment intensification with insulin/GLP-1 or until the most recent documented visit.

Methods: T2D ≥18 years were identified from the diabetes patient follow-up registry (DPV), which captures data from diabetes specialist care. Patients with ≥2 documented visits with DPP-4i/SGLT-2i treatment and with the most recent treatment year ≥2015 were included.

Results: The study population consisted of 4,576 patients treated with DPP-4i/SGLT-2i. A subgroup of 1,416 patients were intensified with an injectable therapy. Mean time in PC until intensification with insulin/GLP-1 was 16.7 months (HbA1c>7%), 15.7 and 15.1 months (HbA1c>7.5%, HbA1c>8%) in this subgroup, respectively. Mean time in PC until most recent visit was 12.6, 9.9 and 8.4 months in the subgroup of patients without treatment intensification.

Conclusions: Even with NOADs, a substantial proportion of T2D do not achieve good metabolic control. These findings may be due to individualized target setting for HbA1c, or reluctance of patients and physicians towards injectable therapy. Effective diabetes management strategies are necessary to reduce the risk of adverse outcomes and to increase quality of life in T2D.

Introduction

Failure to intensify treatment of patients with type 2 diabetes (T2D) in a timely manner, defined as clinical or therapeutic inertia, is a common challenge in diabetes care (1). Despite evidence for a clear association between tight glycaemic control early in the disease progress and lower risk for micro- and macro-vascular complications in the long-term (2, 3), many patients with T2D do not achieve glycaemic control within an appropriate time period (4). Previous studies on clinical inertia used different thresholds for HbA1c to define poor glycaemic control, as target values of HbA1c vary between national and international guidelines (5-7). In order to reduce the risk of long-term complications, the International Diabetes Federation (IDF) recommend an HbA1c level $<7.0\%$ (53 mmol/mol) for adults with T2D (5). The German national guideline for diabetes management recommend an HbA1c value between 6.5% and 7.5% under consideration of individual treatment targets (6). If target values cannot be achieved by lifestyle intervention (such as diet and exercise), oral anti-diabetic drugs (OADs) or injectable therapy like insulin or glucagon-like Peptide 1 (GLP-1) receptor agonists (8, 9) are required.

Studies have reported clinical inertia for both intensification with OADs as well as injectable therapies with insulin (4, 10, 11). Khunti and colleagues (12) investigated the time to treatment intensification in adult patients with T2D initially treated with one to three OADs. The median time in poor glycaemic control ($\text{HbA1c} \geq 7\%$, $\geq 7.5\%$, $\geq 8\%$, respectively) until OAD treatment intensification ranged from around 2 to 7 years depending on the number of initial OADs (12). The median time in poor glycaemic control until insulin treatment intensification was around 7 years (12). However, newer OAD classes such as dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium/glucose cotransporter 2 inhibitors (SGLT-2i) have not been specifically studied in this context (4, 11). Insulin initiation was shown to be less likely in patients with newer OAD compared to sulphonylurea (13). Moreover, Montvida et al. emphasized the need for more studies on the differences in therapy initiation between drug classes (14). Recently, Mata-Cases et al. (15) investigated adult patients with T2D with initial non-insulin therapy in Catalonia, Spain. The authors reported a median time to first treatment intensification with an additional non-insulin drug or with insulin of 22.6 months and 17.1 months for poor glycaemic control thresholds of $\text{HbA1c} \geq 7.0\%$ and $\geq 8.0\%$, respectively. SGLT-2i was not considered in this study as it was not available during the study period (15). A recent literature review based on 53 studies reported that the median time to treatment intensification after an HbA1c measurement above a threshold ranged from 0.3 to >7.2 years (11).

Using data from the diabetes patients follow-up registry (DPV), which captures data from the diabetes specialist care setting, we investigated the time in poor glycaemic control in adult patients

with T2D treated with DPP-4i or SGLT-2i until treatment intensification with injectable glucose-lowering therapy (insulin or GLP-1 receptor agonists) or until most recent documented visit. The first objective of this study was to describe baseline characteristics of patients currently treated with DPP-4i and/or SGLT-2i from the DPV registry. The second objective was to examine the time from the first observation of HbA1c above the thresholds of 7%, 7.5% and 8%, respectively, until treatment intensification with insulin or GLP-1 receptor agonists or until most recent visit.

Methods

Study population and data source

Patients included in the analyses were identified from the multicentre, prospective DPV registry which obtains data primarily from diabetes specialist care (16). Within DPV, data for all types of diabetes are collected during routine examinations and anonymised data are sent to Ulm University regularly for data validation and analyses. In case of inconsistency, data are sent back to the respective centers for correction. The ethics committee of Ulm University as well as local review boards of the participating centers approved the data collection and analyses for quality control and research. Up to March 2017, 459 centers predominantly from Germany (416) and Austria (40) are involved in the DPV initiative.

Adult patients (≥ 18 years) with T2D, treated with DPP-4i and/or SGLT-2i were identified. Only patients that had at least 2 documented visits and who were treated with DPP-4i and/or SGLT-2i for at least 4 weeks, were included. To reflect recent clinical practice, patients were required to have a history of treatment with DPP-4i and/or SGLT-2i in 2015 or later.

Based on OAD therapy, patients with T2D were stratified into three groups: 1) DPP-4i only, 2) SGLT-2i only, 3) Combination of DPP-4i and SGLT-2i (DPP-4i + SGLT-2i). In case of switching between DPP-4i and SGLT-2i between the first and most recent documented visit, the patient was assigned to the combination group. Therefore, the combination group does not only include patients taking DPP-4i and SGLT-2i simultaneously. Treatment was irrespective of other OAD treatments (number of other OADs), for example if patients were treated with DPP-4i and any other OAD except SGLT-2i, patients were assigned to the DPP-4i only group. Patients starting insulin or GLP-1 receptor agonist treatment prior to or simultaneous to DPP-4i or SGLT-2i treatment were excluded because the aim was to study time to intensification with an injectable therapy after start of OAD treatment. Hence, the first documented visit on an injectable therapy had to be at a later time point than the first visit on DPP-4i and/or SGLT-2i therapy.

Time in poor glycaemic control was defined as the first HbA1c value $>7\%$ ($>7.5\%$, $>8\%$, respectively), not improving until initiation of an injectable therapy or until end of follow-up. Patients were followed from the first visit with DPP-4i and/or SGLT-2i therapy until initiation of an injectable therapy (insulin or GLP-1 receptor agonists) or until the most recent visit documented in DPV (data pool March 2017). In most instances initiation of an injectable therapy means an add on to the previous therapy in our study.

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128 Demographic and clinical data extracted from the DPV registry included sex, age, diabetes duration,
129 body mass index (BMI in kg/m²), HbA1c (in % or mmol/mol), systolic and diastolic blood pressure (in
130 mmHg), total cholesterol (in mg/dl), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)
131 cholesterol (in mg/dl), triglycerides (in mg/dl), diabetes treatment and year of therapy. The multiple
132 of the mean transformation method was used to standardize HbA1c values to the Diabetes Control
133 and Complications Trial (DCCT) reference range of 4.05–6.05% (20.7–42.6 mmol/mol) accounting for
134 different laboratory methods (17). Aggregated data (mean or median) during treatment with DPP-4i
135 and/or SGLT-2i (first to most recent visit with DPP-4i/SGLT-2i) was used for the analysis and was
136 defined as baseline.

137 *Statistical analysis*

138 Results of descriptive analyses are presented as median (interquartile range) or mean (standard
139 deviation) for continuous variables and proportions for categorical variables. Unadjusted
140 comparisons were conducted using Kruskal-Wallis or Chi-square test using false discovery rate to
141 adjust for multiple testing.

142 Time in poor glycaemic control was the primary outcome and was presented as mean time to event
143 (treatment intensification or most recent visit). Moreover, we estimated hazard ratios and
144 cumulative incidence functions of time to treatment intensification using Cox regression models as
145 described by Khunti et al. (12). Intensification with an injectable therapy was the event of interest
146 and patients without therapy intensification were censored at the time of the most recent visit. We
147 compared hazard ratios and cumulative incidence functions by prior treatment groups (DPP-4i only,
148 SGLT-2i only, DPP-4i + SGLT-2i) as well as by HbA1c threshold for poor glycaemic control (>7%, >7.5%,
149 >8%, respectively). Furthermore, we examined the progression of HbA1c during period of poor
150 glycaemic control in an additional analysis.

151 Statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary,NC). A p-value
152 <0.05 was considered as statistically significant. Moreover, SAS (SGPLOT procedure) was used to
153 graphically illustrate the progression of HbA1c values during the time period of poor glycaemic
154 control (defined as HbA1c >7%, >7.5% and >8%, respectively).

155 *Handling of missing HbA1c values*

156 To identify the time in poor glycaemic control, the first HbA1c measurement above the threshold
157 prior to intensification or most recent visit was used as the start value. Only periods with HbA1c

continuously above the defined threshold counted as time in poor control. In case of missing HbA1c values, information of the previous available measurement was used.

Results

By March 2017, the DPV registry comprised 483,421 diabetes patients. We identified 48,305 patients with T2D ≥ 18 years treated with DPP-4i and/or SGLT-2i (Figure 1). Of these, 7,517 patients had at least 2 documented visits, were treated for at least 4 weeks with DPP-4i and/or SGLT-2i and had the most recent visit on DPP-4i and/or SGLT-2i in 2015 or later. We excluded 2,941 patients who started with injectable therapy before or simultaneous to DPP-4i and/or SGLT-2i treatment. Hence, the overall study population for our first objective consisted of 4,576 patients treated with DPP-4i and/or SGLT-2i therapy who were either not intensified with injectable therapy or were intensified at a later time point. The included patients were treated with DPP-4i and/or SGLT-2i for a maximum of 159 months (13 years). A subgroup of 1,416 patients treated with DPP-4i and/or SGLT-2i were intensified with injectable therapy (insulin or GLP-1 receptor agonists), 83.8% of them were intensified with insulin.

Table 1 shows baseline characteristics of the overall study population (objective 1), the subgroup of patients with treatment intensification with injectable therapy and the subgroup of patients without treatment intensification with injectable therapy (objective 2). The median age of the study population was 66.4 years, the subgroup receiving treatment intensification was slightly older with a median age of 67.1 years, whereas the age of patients without treatment intensification was similar to the overall study population (66.2 years). Diabetes duration was significantly longer in patients with treatment intensification (median 9.0 years) compared to patients without (median 6.8 years). HbA1c was significantly higher in the subgroup with treatment intensification (median 7.3% vs. 6.7%) as were also BMI (30.8 vs 30.2 kg/m²), triglycerides (167 vs. 157 mg/dl). However, patients without treatment intensification showed higher HDL and LDL cholesterol levels (47.0 mg/dl vs 43.5 and 115.0 vs 110.0 mg/dl, respectively) in comparison to patients with treatment intensification. The mean treatment time with DPP-4i and/or SGLT-2i was 44.0 months in patients with therapy intensification vs 27.6 months in patients without. The majority of patients (75.5%) were treated with DPP-4i only, followed by a combined therapy of DPP-4i + SGLT-2i (19.2%) and a minority (5.4%) was treated with SGLT-2i only. The majority of the study population was treated with 2 OADs (50.9%) or at least 3 OADs (17.8%).

Of the 4,576 patients, 41.1% were in poor glycaemic control with HbA1c $> 7\%$ prior to most recent visit. The proportion of patients in poor glycaemic control was significantly higher in the group that was intensified with injectable therapy. Of the 1,416 patients with injectable therapy intensification,

191 645 (45.6%) were in poor glycaemic control with HbA1c >7% prior to start of an injectable therapy.
192 Moreover, 433 (30.6%) and 288 (20.3%) patients were in poor glycaemic control with HbA1c >7.5%
193 and >8% prior to therapy intensification, respectively. Of the 3,160 patients without intensification
194 1,083 (34.3%), 685 (21.7%) and 434 (13.7%) were in poor glycaemic control with HbA1c >7%, >7.5%
195 and >8% prior to most recent visit. Baseline characteristic of patients in poor glycaemic control with
196 HbA1c >7% prior to start of injectable therapy or prior to most recent visit are reported in
197 supplemental table 1. During treatment with DPP-4i and/or SGLT-2i 23.4% of the patients in poor
198 glycaemic control were intensified with an additional OAD. Whereas, in the overall study population
199 around 20% were intensified with an additional OAD (Table 1). Supplemental table 1 also shows that
200 25.5% of the patients in poor control without *injectable* treatment intensification were intensified
201 with an additional OAD.

202 Time in poor glycaemic control to treatment intensification or most recent visit separated by HbA1c
203 threshold and by OAD treatment group is shown in Table 2. Depending on the HbA1c threshold, time
204 in poor glycaemic control was 14.1 months (HbA1c >7%), 12.1 months (HbA1c >7.5%) and 11.1
205 months (HbA1c >8%) in the overall study population. The subgroup of patients with treatment
206 intensification were on average 16.7 months (HbA1c >7%), 15.7 months (HbA1c >7.5%) and 15.1
207 months (HbA1c >8%) in poor glycaemic control. Moreover, the average time in poor glycaemic
208 control until most recent visit was 12.6 months (HbA1c >7%), 9.9 and 8.4 months (HbA1c >7.5%, >8%,
209 respectively) in patients without treatment intensification.

210 Overall, results stratified by prior treatment showed shorter time in poor glycaemic control (HbA1c
211 >7%, >7.5% and >8%) for patients treated with SGLT-2i therapy only compared to DPP-4i only or a
212 combination of DPP-4i + SGLT-2i. However, it has to be noted that SGLT-2i have recently been
213 approved and therefore the treatment time with SGLT-2i was also shorter. The proportion of time in
214 poor glycaemic control was highest for patients treated with SGLT-2i only (68% of time) compared to
215 DPP-4i only (43% of time) or a combination of DPP-4i + SGLT-2i (40% of time) for HbA1c threshold of
216 >7% and also for all other thresholds (Table 2). Moreover, the group of patients taking only SGLT-2i
217 was smaller than the other treatment groups.

218 As we estimated the probability of being intensified with an injectable therapy while being in poor
219 control, Cox regression was conducted for 1,728 patients (1,083 in poor control but not intensified,
220 645 in poor control and intensified with an injectable therapy). Cumulative incidence functions for
221 treatment groups by time in poor glycaemic control for HbA1c >7% are presented in Figure 2 A. A
222 higher probability for therapy intensification in patients with SGLT-2i only compared to the other
223 treatment groups at any given time after first HbA1c >7% was observed (Figure 2 A). However,
224 pairwise hazard ratios showed no statistically significant differences between the treatment groups

(SGLT-2i only vs. DPP-4i only: 1.27 [95%-confidence interval: 0.87; 1.86], SGLT-2i only vs. DPP-4i+SGLT-2i: 1.22 [0.82; 1.83]).

The probability of being intensified with an injectable therapy was lowest for glycaemic control with an HbA1c threshold >7% (Figure 2 B). We observed a statistically significant lower probability of being intensified with an HbA1c threshold of >7% compared to >8% (hazard ratio 0.81 [0.68; 0.98]). No statistically significant difference was found between the thresholds >7% and >7.5% (0.97 [0.78; 1.20]).

Supplemental Figure 1 shows the progression of HbA1c values during the period of poor glycaemic control. HbA1c increases with increasing time in poor glycaemic control. We observed the steepest increment in HbA1c when poor glycaemic control was defined with a threshold >7.5% (Supplemental Figure 1 B).

Discussion

We investigated the time in poor glycaemic control (HbA1c >7%, >7.5%, >8%) in adult patients with T2D treated with DPP-4i or SGLT-2i until treatment intensification with an injectable glucose-lowering therapy (insulin or GLP-1 receptor agonists) or until most recent documented visit in the multicentre, prospective DPV registry. We identified 4,576 patients treated with DPP-4i and/or SGLT-2i and a subgroup of 1,416 patients who were intensified with an injectable therapy. Our results indicated that patients with treatment intensification with injectable therapy have a more progressive disease compared to patients without treatment intensification with injectable therapy. Patients with injectable therapy showed significantly higher HbA1c levels, higher BMI and a longer diabetes duration. Almost half of the patients (45.6%) with injectable therapy intensification were in poor glycaemic control with HbA1c >7% prior to start of injectable therapy. Mean time in poor glycaemic control until intensification with insulin or GLP-1 receptor agonists was 16.7 months with HbA1c >7%, 15.7 months with HbA1c >7.5% and 15.1 months with HbA1c >8%. Moreover, 34.3% of the subgroup of patients without therapy intensification were in poor glycaemic control (HbA1c >7%) prior to the most recent visit. Time in poor glycaemic control in patients without treatment intensification was 12.6 months (HbA1c >7%), 9.9 months (HbA1c >7.5%) or 8.4 months (HbA1c >8%).

Results of our analysis are comparable with a recently conducted study on adult T2D patients in Catalonia, Spain (15). Mata-Cases and co-authors examined the time in poor glycaemic control from a non-insulin treatment to intensification with an additional non-insulin drug or insulin in 23,678 patients with T2D. The authors observed a median time in poor glycaemic control of 22.6 months and 17.1 months for HbA1c $\geq$ 7% and $\geq$ 8%. Hence, time in poor glycaemic control was longer compared to our analyses. However, we only investigated intensification with an injectable therapy,

and in contrast to our study SGLT-2i treatment was not considered in the study of Mata-Cases et al. (15).

Khunti et al. (12) investigated the time in poor glycaemic control from treatment with one, two or three OADs to intensification with insulin in the U.K. Median time to treatment intensification with insulin was around 7 years with HbA1c thresholds of $\geq 7\%$ or $\geq 7.5\%$. Median time to intensification with insulin was also 7 years when HbA1c was $\geq 8\%$ and with initial treatment with one or two OADs. Patients with prior treatment with three OADs were in poor control for a median of 6 years until intensification with insulin. Due to the fact that we investigated newer OAD substances (DPP-4i and SGLT-2i) our observation period was shorter compared to the study of Khunti and colleagues (12). Moreover, in contrast to our study Khunti and colleagues (12) used prescriptions to identify treatment, whereas we used health care provider documented therapy only. In contrast to the Clinical Practice Research Datalink database used by Khunti et al. (12), DPV is not a primary care database, but DPV obtains data primarily from diabetes specialist care. Therefore, using primary care data might show longer time periods in poor glycaemic control compared to patients from specialist care, as there might be differences in disease management by specialists and primary care physicians (18). Nevertheless, results of our analyses showed that even in specialist care and with newer OADs a substantial proportion of patients with T2D do not achieve treatment targets for good metabolic control. Similar results were reported in a retrospective cohort study by Paul et al. (19) where the median time to treatment intensification with insulin was 16 months for HbA1c $\geq 7\%$ and 14 months for HbA1c $\geq 7.5\%$ in newly diagnosed adult patients with T2D. A recent review on clinical inertia emphasized that delays in treatment intensification are common in primary as well as specialist care and delay in intensification increased with the number of OADs (11).

Our results indicated differences in time in poor glycaemic control between different prior OAD treatment groups. Patients with prior SGLT-2i treatment only showed a shorter time in poor glycaemic control, however a higher proportion of time in poor control when taking full treatment time into consideration, and a higher probability of being intensified with an injectable therapy compared to patients with DPP-4i treatment only or a combination of DPP-4i+SGLT-2i. The differences were not statistically significant and might be explained by the fact that the number of patients with SGLT-2i treatment only was small as SGLT-2i have recently been approved by the European Medicines Agency. Further studies are needed to investigate newer OAD substances in order to consolidate these findings.

We observed a consistent increase in HbA1c during the period of poor glycaemic control. The change in HbA1c over time from initial OAD therapy to initiation of an insulin therapy was studied in more detail by Evans and co-authors (20) using medical records of UK primary care practices. The authors

found an average increase in HbA1c of 0.7% prior to insulin therapy. Moreover, the authors emphasized that delays in treatment intensification might be associated with an increased risk of subsequent micro-vascular and macro-vascular diseases (20).

Results of the UK Prospective Diabetes Study (UKPDS) showed beneficial effects of an intensive strategy to control blood glucose levels in patients with T2D on long-term diabetes complications and mortality. These findings were recently supported by a study on the impact of clinical inertia on cardiovascular risk (19). A one year delayed treatment intensification was associated with a significantly increased risk of macrovascular events (hazard ratio 1.62 [1.46; 1.80]) in patients with an HbA1c $\geq 7\%$. Similar results were found for HbA1c values of $\geq 7.5\%$ (19).

Several factors might have an impact on treatment intensification in type 2 diabetes patients. Adherence to treatment might be one important factor. Grant et al. (21) reported an association between medication adherence and clinical inertia in patients with T2D. The probability of a treatment intensification was higher in patients with an adherence rate of $>90\%$ compared to patients with a lower adherence rate (21). Moreover, good medication adherence was also linked to a reduced risk of all-cause mortality and hospital admission in T2D (22). The international Diabetes Attitudes, Wishes and Needs (DAWN) study involved 13 countries in Asia, Australia, Europe and North America and examined attitudes towards insulin therapy among patients with T2D and health care providers (23). Differences between countries were observed, but in general patients suffering from complications and diabetes-related distress are more receptive to insulin therapy than patients without these conditions (23). Moreover, delay of insulin therapy was less likely in diabetes specialists than in primary care physicians (18, 23).

It has to be noticed that target values are not absolutely fixed in the context of personalized medicine. Therefore, if a patient is just above the target one would rather decide for not intensifying treatment with insulin. National and international guidelines also emphasize the importance of individual treatment targets. Depending on individualized treatment targets which are based on factors such as comorbidity, age and patient preference, the German national guidelines for diabetes management recommend HbA1c values between 6.5% and 7.5% for patients with type 2 diabetes (6). Therapy intensification is recommended if individual target values for HbA1c cannot be achieved after 3 to 6 months. IDF-Guidelines as well as the American Diabetes Association define an HbA1c treatment target $<7\%$ and suggest to evaluate the response to each newly initiated therapy initiation or dose increase after 3 months (5). Hence, our results show that the time in poor glycaemic control is longer than the time period recommended by national and international guidelines.

Strengths and Limitations

The strengths of this study are that real world data from the DPV registry was used, which is a large-

scaled, nationwide cohort of adult patients with T2D. The analyses were conducted on data from a real-world setting which is representative for the routine specialist care of diabetes patients in Germany and Austria. This study also shows that clinical inertia is not only present in a primary care setting, but also is present in specialist care. However, some limitations should be considered. We did not have information on other factors that might also have an impact on treatment intensification such as life style, nutrition and social-economic factors. Patients documented in DPV are primarily seen by a diabetes specialist, which is not representative for primary care and therefore not comparable to previous studies using primary care data. However, it is important to note that the distribution between primary and secondary care differs between health care systems. Moreover, due to the recent market approval of SGLT-2i the number of patients treated with SGLT-2i only was small and follow-up period short.

Conclusions

Our analyses supported previous findings on delayed treatment intensification with insulin or GLP-1 receptor agonists in patients with T2D. Even with newer OAD (DPP-4i or SGLT-2i), a substantial number of patients do not achieve targets for good metabolic control. In real-life care, time interval until treatment intensification with injectable therapy seems long. This may be due to individualized target setting for HbA1c, or reluctance of patients and physicians towards injectable therapy. Long time periods in poor glycaemic control may increase the risks of diabetes related diseases. An effective diabetes management is necessary in order to reduce the risk of adverse outcomes and to increase the quality of life in adult patients with T2D.

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Tables

Table 1. Baseline (aggregated data from first to most recent visit with DPP-4i/SGLT-2i) characteristics of type 2 diabetes patients with DPP-4i and/or SGLT-2i treatment (overall study population, n = 4,576), subgroup of patients with treatment intensification with injectable therapy (n = 1,416) and subgroup of patients without treatment intensification with injectable therapy (n = 3,160).

Patient characteristics	Overall study population (n = 4,576)		Patients with treatment intensification (n = 1,416)		Patients without treatment intensification (n = 3,160)		p-value*
	N	Median (Q1; Q3 [†]) or Percent	N	Median (Q1; Q3 [†]) or Percent	N	Median (Q1; Q3 [†]) or Percent	
Age (years)	4,576	66.4 (56.9; 75.0)	1,416	67.1 (57.4; 75.1)	3,160	66.2 (56.7; 74.9)	0.236
Male sex	4,576	56.5	1,416	57.7	3,160	55.9	0.270
Diabetes duration (years)	4,576	7.5 (3.6; 12.7)	1,416	9.0 (5.1; 14.1)	3,160	6.8 (2.9; 12.1)	<0.01
BMI (kg/m ²)	4,441	30.4 (26.9; 34.8)	1,385	30.8 (27.0; 35.3)	3,056	30.2 (26.8; 34.5)	0.019
HbA1c (%)	4,413	6.8 (6.3; 7.6)	1,395	7.3 (6.6; 8.1)	3,018	6.7 (6.2; 7.4)	<0.01
HbA1c (mmol/mol)	4,413	51.2 (45.2; 59.8)	1,395	55.8 (49.0; 65.2)	3,018	49.4 (44.0; 57.1)	<0.01
Systolic BP (mmHg)	4,444	135.0 (127.5; 142.5)	1,405	134.0 (127.0; 142.0)	3,039	135.0 (127.5; 143.0)	0.048
Diastolic BP (mmHg)	4,440	80.0 (74.0; 84.0)	1,404	80.0 (73.0; 82.5)	3,036	80.0 (75.0; 84.5)	<0.01
Total cholesterol (mg/dl)	3,618	186.0 (161.0; 215.0)	1,200	184.0 (158.0; 212.5)	2,418	187.0 (162.5; 217.0)	0.013

HDL cholesterol (mg/dl)	3,367	45.5 (38.0; 55.0)	1,119	43.5 (37.0; 52.0)	2,248	47.0 (38.7; 56.5)	<0.01
LDL cholesterol (mg/dl)	3,430	113.5 (90.0; 137.0)	1,146	110.0 (88.0; 135.0)	2,284	115.0 (91.4; 139.0)	0.002
Triglycerides (mg/dl)	3,570	159.8 (117.0; 228.0)	1,193	166.5 (122.0; 237.0)	2,377	157.0 (115.0; 223.0)	<0.01
Proportion 1 OAD	4,576	31.3	1,416	29.0	3,160	32.3	0.039
Proportion 2 OAD	4,576	50.9	1,416	51.4	3,160	50.7	0.701
Proportion ≥3 OAD	4,576	17.8	1,416	19.6	3,160	17.0	0.041
Treatment time on DPP-4i/SGLT-2i (months) [‡]	4,576	32.7 (28.4)	1,416	44.0 (30.6)	3,160	27.6 (25.8)	<0.01
Proportion SGLT-2i only	4,576	5.4	1,416	3.1	3,160	6.4	<0.01
Proportion DPP-4i only	4,576	75.5	1,416	72.1	3,160	77	<0.02
Proportion combination DPP-4i + SGLT-2i	4,576	19.2	1,416	24.8	3,160	16.6	<0.01
Proportion intensified with additional OAD	4,576	20.7	1,416	20.0	3,160	21.0	0.442
Proportion in PC [§] (HbA1c >7%)	4,576	41.1	1,416	45.6	3,160	34.3	<0.01
Proportion in PC [§] (HbA1c >7.5%)	4,576	27.8	1,416	30.6	3,160	21.7	<0.01
Proportion in PC [§] (HbA1c >8.%)	4,576	18.8	1,416	20.3	3,160	13.7	<0.01

*patients with vs without treatment intensification

[†]25th-quartile; 75th-quartile

[‡]mean (standard deviation)

[§]poor glycaemic control prior to treatment intensification or most recent visit

Table 2. Time in poor glycaemic control until treatment intensification with injectable therapy or most recent visit separated by HbA1c threshold and by OAD treatment group.

	Overall patients in poor glycaemic control				Patients with treatment intensification				Patients without treatment intensification			
	N	Treatment time [†]	Time [†] in PC [‡]	% of time in PC [‡]	N	Treatment time [†]	Time [†] in PC [‡]	% of time in PC [‡]	N	Treatment time [†]	Time [†] in PC [‡]	% of time in PC [‡]
HbA1c >7%	1,728	33.1 (28.2)	14.1 (17.3)	42.6	645	44.4 (30.5)	16.7 (17.7)	37.6	1,083	26.3 (24.5)	12.6 (16.9)	47.9
DPP-4i only	1,223	33.8 (28.0)	14.5 (17.9)	42.9	460	44.7 (29.9)	17.6 (18.4)	39.4	763	27.2 (24.6)	12.7 (17.3)	46.7
SGLT-2i only	95	10.3 (9.7)	7.0 (8.3)	68.0	26	14.5 (13.4)	8.6 (11.4)	59.3	69	8.8 (7.5)	6.4 (6.7)	72.7
Combination DPP-4i+SGLT-2i	410	36.2 (29.4)	14.5 (16.7)	40.1	159	48.3 (31.5)	15.6 (16.2)	32.3	251	28.6 (25.2)	13.8 (17.0)	48.3
HbA1c >7.5%	1,118	31.8 (27.7)	12.1 (16.6)	38.1	433	43.0 (29.6)	15.7 (17.8)	36.5	685	24.8 (23.9)	9.9 (15.3)	39.9
DPP-4i only	776	32.7 (27.7)	16.6 (19.0)	50.8	303	43.8 (28.9)	19.2 (19.6)	43.8	473	25.6 (24.3)	14.9 (18.5)	58.2
SGLT-2i only	59	10.7 (11.1)	8.2 (9.6)	76.7	16	15.3 (16.3)	10.5 (14.2)	68.6	43	9.0 (8.0)	7.3 (7.2)	81.1
Combination DPP-4i+SGLT-2i	283	33.9 (28.5)	16.0 (17.6)	47.2	114	44.8 (30.9)	16.3 (16.1)	36.4	169	26.5 (24.1)	15.9 (18.5)	60.0

HbA1c >8%	722	30.6 (27.3)	11.1 (16.3)	36.3	288	40.9 (29.4)	15.1 (18.3)	36.9	434	23.8 (23.5)	8.4 (14.2)	35.3
DPP-4i only	501	32.3 (27.5)	17.4 (19.9)	53.9	201	42.5 (29.2)	18.9 (20.2)	44.5	300	25.4 (24.0)	16.3 (19.6)	64.2
SGLT-2i only	42	10.7 (11.9)	9.3 (10.8)	86.9	15	14.1 (16.1)	11.0 (14.5)	78.0	27	8.7 (8.6)	8.3 (8.1)	95.4
Combination DPP-4i+SGLT-2i	179	30.7 (27.6)	16.1 (18.2)	52.4	72	42.0 (29.8)	17.3 (17.5)	41.2	107	23.1 (23.3)	15.3 (18.8)	66.2

[†]Mean time in months (standard deviation)

[‡]poor glycaemic control

Figure Legends

Figure 1. Selection of study population for objective 1 and 2.

Figure 2. Cumulative incidence of treatment intensification with insulin or GLP-1 receptor agonists by
A) prior OAD treatment B) HbA1c threshold for poor glycaemic control.

Figures

Figure 1

Figure 2