ABSTRACT

Introduction: CHOICE (CHanges to treatment and Outcomes in patients with type 2 diabetes initiating InjeCtablE therapy; NCT00635492) assessed, as its primary objective, the time to a ‘significant treatment change’ (defined within this paper) after patients with type 2 diabetes mellitus initiated their first injectable, glucose-lowering therapy [exenatide twice daily (BID) or insulin] in clinical practice in six European countries and evaluated outcomes during the study.

Methods: CHOICE was a 24-month, prospective, noninterventional observational study. Patients were invited to participate in CHOICE only after their treating physician had made the clinical decision to initiate first injectable therapy with either exenatide BID or insulin. Clinical data were collected at initiation of first injectable therapy and after approximately 3, 6, 12, 18, and 24 months.

ClinicalTrials.gov #NCT0635492.
Results: A total of 2,515 patients were recruited; 1,114 patients in the exenatide BID cohort and 1,274 patients in the insulin cohort were eligible for the 24-month analysis. During the study, 42.2% and 36.0% of patients from each cohort, respectively, had a significant treatment change. By 24 months, improved mean glycated hemoglobin ($p < 0.001$ for both cohorts) and reduced severity of several cardiovascular risk factors were observed in both cohorts; additionally, mean weight was reduced in the exenatide BID cohort ($p < 0.001$) and increased in the insulin cohort ($p < 0.001$). Hypoglycemia was reported by 18.4% of the exenatide BID cohort and 36.8% of the insulin cohort; 25.9% of the exenatide BID cohort and 10.0% of the insulin cohort had met the secondary endpoint of glycated hemoglobin $< 7.0\%$, no weight gain, and no hypoglycemia.

Conclusion: CHOICE provided data on exenatide BID and insulin usage patterns and 24-month outcomes in clinical practice. On average, improved glycemic control and reduced severity of cardiovascular risk factors were observed in both cohorts, and those in the exenatide BID cohort also had mean weight loss.

Keywords: Diabetes mellitus; Exenatide; Insulin; Injectable therapy; Type 2

INTRODUCTION

The management of type 2 diabetes mellitus (T2DM) requires a multifactorial treatment approach that addresses clinical and psychosocial aspects of this chronic illness. There are multiple therapeutic classes of oral and injectable treatments available for T2DM. Treatment should be selected and individualized based on specific patient requirements for glycemic control, and patient preferences, characteristics, and susceptibilities to side effects, including potential for weight gain and hypoglycemia [1].

Glucagon-like peptide (GLP)-1 receptor agonists are a relatively new class of medications for T2DM. Randomized clinical trials (RCTs) have shown that exenatide twice daily (BID), the first approved GLP-1 receptor agonist, provided glucose-lowering efficacy similar to that of insulin glargine and biphasic insulin aspart and that, in contrast with insulins, it was associated with weight loss [2–4]. Although RCTs provide the least biased estimates of efficacy, data derived from a trial setting have limited generalizability to routine clinical practice, where treatment may be initiated in patients dissimilar to those enrolled in the clinical trial program, or it may perform differently than in a controlled setting and where modification of therapy is more common [5, 6]. In addition, RCTs remove the most important factor affecting the way in which medical care is actually delivered: doctors and patients acting as individuals with differing beliefs, needs, and priorities. Well-designed prospective observational studies in clinical practice are therefore necessary to provide a holistic understanding of treatment [7, 8] and to enhance the evidence upon which the management of T2DM is based [1]. To date, limited information concerning the real-life use of GLP-1 receptor agonists in Europe is available and it is not clear how GLP-1 receptor agonists compare with initial insulin therapy in real life. For example, it has not been clear which patients are prescribed these agents or initial insulin treatment, how long GLP-1 receptor agonists are taken, how patients who eventually stop these agents or modify them by using different combinations of antidiabetes treatments are managed afterwards, and finally, why some patients stop or modify these therapies. Data are limited concerning
the effectiveness, safety, and associated resource use of both GLP-1 receptor agonists and insulin.

CHOICE (CHanges to treatment and Outcomes in patients with type 2 diabetes initiating InjeCtablE therapy; NCT00635492) was a 24-month prospective observational study conducted in multiple European countries. It was designed to assess the time to a significant treatment change after patients initiated their first injectable, glucose-lowering therapy in clinical practice and thereby evaluate patterns of initial injectable therapy usage and outcomes in clinical practice in patients with T2DM. Significant treatment change was defined as at least one of the following: discontinuation of any exenatide BID/insulin initiated at baseline; addition of a new medication (any route of administration) for the treatment of T2DM; a change in the number of times insulin is administered per day; or substitution of a human insulin for an analog insulin or vice versa (not including switching between brands of the same class/type of insulin). Details of the characteristics of patients initiating the two treatment strategies have been described [9]. This paper reports observed treatment changes and clinical outcomes during the study.

PATIENTS AND METHODS

Design and Patients

CHOICE is a prospective, multinational, noninterventional observational study that recruited patients from six European countries (Denmark, Belgium, France, Germany, Greece and Sweden) between January 2008 and October 2009. Eligible patients were aged ≥18 years and initiating their first injectable glucose-lowering therapy (with any type of insulin or exenatide BID) for the treatment of T2DM in routine clinical practice. Patients were recruited through 322 investigators (mainly secondary care sites). Patients were invited to participate in CHOICE only after their treating physician had made the clinical decision to initiate either exenatide BID or insulin. Therefore, treatment allocation was not randomized and patients were treated as determined by their physician and, at the time of injectable treatment initiation, were allocated to either the exenatide BID or insulin cohort for analysis purposes. Although exenatide once weekly and liraglutide have more recently been approved, these GLP-1 receptor agonists were not available for routine clinical use at the start of this study and hence were not included for study. At study entry, patients could be taking any oral antidiabetes drugs (OADs).

The primary endpoint was the time from starting the initial injectable regimen (exenatide BID or insulin) to significant treatment change. This endpoint was chosen to meet payer needs for data on duration of treatment with exenatide BID and to generate similar data on insulin treatment.

At baseline (initiation of injectable therapy), standard demographic and clinical data were collected from each patient. At subsequent visits (which occurred as part of routine clinical practice: approximately 3, 6, 12, 18 and 24 months after baseline), changes to injectable therapy, and the time of and reason for the change, were recorded. Follow-up clinical data collected during routine visits included: glycated hemoglobin (HbA1c; when available and taken from laboratory data obtained as part of routine clinical practice); body weight; waist circumference; body mass index (BMI); fasting lipids; hypoglycemia; gastrointestinal (GI) events (reported only from the 4 weeks preceding each visit); diabetes therapy and care; and concomitant
medications. Other adverse event data were not routinely collected as part of this study; investigators were instructed to report as they would in normal practice and as required by applicable laws, regulations and practice. Hypoglycemia was reported based on patient recall using no specific definition, except for severe hypoglycemia, which was defined as requiring third-party assistance or a hospital visit.

Patients gave written informed consent for the use of their data and appropriate ethical review board approval was obtained. For more detail on the design of the CHOICE study, see Matthaei et al. [9].

Analysis

Sample Size Justification
Monte Carlo simulation was used to calculate sample size, and assumed patient dropout rates of 10–15% per year and a median time to significant treatment change of 9.0 months for the exenatide BID cohort and 8.6 months for the insulin cohort [10; data on file]. Based on this, the study aimed to recruit a maximum of 800 patients per country/country group, with approximately 60% initiating insulin and 40% initiating exenatide BID. The insulin cohort was to be larger than the exenatide BID cohort because of the greater variability in the former cohort (linked to use of different insulin regimens).

Statistical Analysis
All patients who provided consent to release information, fulfilled the study entry criteria (‘eligible patients’), and had a case report form summary page signed by an investigator were included in the analysis. Analyses of the clinical endpoints were conducted on the eligible population in two ways: (1) according to the cohort (insulin or exenatide BID) that they were in at baseline (‘initiators analysis’); and (2) using the groups of patients with no significant treatment change (using the original study definitions) at study end or at the time of early discontinuation (this could be at any time) from the study (‘persisters analysis’). The persisters analysis was added post hoc due to the observed incidence of treatment changes. Early discontinuation occurred when a patient was lost to follow-up, withdrew from the study, or died at, or before, the 24-month visit.

The primary objective was analyzed using the initiators analysis group. Time to first significant treatment change was estimated using the Kaplan–Meier method for each treatment cohort. If multiple types of change occurred together, the changes were analyzed as occurring in the order presented above. Reasons for the change were summarized using descriptive statistics.

Treatment changes occurring in the insulin cohort were also categorized using an alternative set of definitions that described the intensity and efficacy of the new regimen relative to the starter regimen. This definition considered a significant treatment change to arise if at least one of the following occurred: switch (a change from one insulin regimen to another regimen of similar complexity and similar expected effectiveness); upgrade (a change from one insulin regimen to another of greater complexity or expected effectiveness); downgrade (a change from one insulin regimen to another of lesser complexity or expected effectiveness); discontinuation (the initial insulin regimen is stopped and no further insulin is started within 30 days); initiation of a GLP-1 receptor agonist; and ‘other’ (this category included changes that could be defined using the original criteria but which
did not fit within the new criteria); examples of these categories are summarized in Appendix Table 7.

Secondary objectives relating to clinical outcomes data, medication use, and incidence of GI events were reported for the initiators and persisters analysis groups using descriptive statistics for each visit as well as for the change from baseline. Changes in weight and HbA1c over time were explored using Mixed Models for Repeated Measures analyses, controlling for baseline weight/HbA1c, propensity score, treatment visit, and the treatment-by-visit interaction.

Propensity score analysis was used to estimate the probability that a patient would be assigned to a treatment group based on baseline characteristics [11]. Scores were derived from baseline data using logistic regression (0.10 threshold for between-cohort differences). Missing data were imputed with the overall mean or median for continuous variables, as well as the most frequent category for categorical variables. Patients were matched 1:1 by country based on the propensity score and optimal matching to identify matched subsets from the two cohorts.

Cox regression models were applied within each cohort to explore the association of baseline characteristics with time to significant treatment change and, post hoc, with the clinically relevant composite secondary endpoint of HbA1c <7.0%, no weight gain (≤1 kg), and no hypoglycemia [12]. Generalized estimating equation (GEE) models were developed post hoc to explore factors associated with switching treatment (from exenatide BID to insulin, or from any insulin to another insulin regimen of similar complexity and similar expected effectiveness). These models included baseline and time-dependent covariates. Baseline variables included microvascular and macrovascular diagnoses, age, gender, and duration of diabetes. Time-fluctuating variables included GI symptoms, hypoglycemic episodes, hospitalizations, and changes in BMI and HbA1c. Statistical comparisons of endpoints between the two cohorts were not conducted, as the two treatment cohorts comprised substantially different patient populations (see Matthaei et al. [9]). However, comparative data from a propensity score-derived matched subgroup of the initiators population (exenatide BID vs. insulin) are presented; paired t tests were used to compare changes in continuous variables and McNemar’s tests were used to compare categorical variables between the matched subgroups.

RESULTS

A total of 2,515 patients were recruited; 2,388 (95.0%) were eligible for the 24-month analysis; 1,114 in the exenatide BID cohort and 1,274 in the insulin cohort (these patients were included in the initiators analyses). Overall, 23.5% of the eligible patients discontinued the study at or before 24 months (reasons are shown in Fig. 1).

Demographic and Clinical Characteristics

Overall, patients in the exenatide BID cohort tended to be younger and more obese, but had better glycemic control and fewer diabetes complications compared with the insulin cohort (Table 1) [9].

Treatment Change

A total of 470 patients from the exenatide BID cohort (42.2%) and 459 patients from the insulin cohort (36.0%) had a significant treatment change during the study. Therefore,
644 patients from the exenatide BID cohort (57.8%) and 815 patients from the insulin cohort (64.0%) were included in the persisters analyses.

In the exenatide BID group, the proportion of enrolled patients experiencing treatment change was highest (20.8%) in the first 6 months post initiation, and lower thereafter (Fig. 2). Throughout the study, the proportions of patients who had not had a significant treatment change at 6, 12, 18 and 24 months were 79.2%, 67.8%, 59.3% and 53.9%, respectively. Almost three-fourths of the first significant treatment changes were discontinuations, with the remainder mainly comprising the addition of oral antidiabetes medications (Table 2).

In the insulin cohort, the proportions of enrolled patients who had a significant treatment change was also highest (22.1%) in the first 6 months post initiation, and then decreased during the remainder of the study (Fig. 2). Throughout the study, the proportions of patients who had not had significant treatment changes were 79.2%, 67.8%, 59.3% and 53.9%, respectively. Almost three-fourths of the first significant treatment changes were discontinuations, with the remainder mainly comprising the addition of oral antidiabetes medications (Table 2).

Fig. 1 Study disposition at 24 months. BID twice daily, DDP-IV dipeptidyl peptidase-IV, GLP-1 glucagon-like peptide-1, OAD oral antidiabetes drug

| Patients enrolled (N = 2515) | Evaluable patients (N = 2386) |
|-----------------------------|-------------------------------|
| Exenatide BID               | Insulin                       |
| (n = 1114)                  | (n = 1274)                    |
| Completed 24 months in the study: 873 (78.4%)/835 (75.0%)* | Completed 24 months in the study: 1025 (80.5%)/992 (77.9%)* |
| Discontinued at or before 24 months: 270 (25.0%) | Discontinued at or before 24 months: 282 (22.1%) |
| Death: 12 (1.1%) | Death: 40 (3.1%) |
| Lost to follow-up: 151 (13.6%) | Lost to follow-up: 172 (13.6%) |
| Physician decision: 32 (2.8%) | Physician decision: 23 (1.7%) |
| Sponsor decision: 2 (0.2%) | Sponsor decision: 3 (0.2%) |
| Subject decision: 62 (5.4%) | Subject decision: 46 (3.7%) |

At least 1 significant treatment change: 470 (42.2%) | No significant treatment change: 644 (57.8%)

Any significant treatment change: Discontinuation: 363 (35.3%) | Addition of OAD: 180 (16.2%) |
| Addition of injectable: 298 (29.8%) | Addition of injectable: 320 (30.5%) |

Antidiabetes medications started after discontinuation of initial treatment (n = 393) | Antidiabetes medications started after discontinuation of initial treatment (n = 116) |
| OADs (n = 86) | \(\text{OADs (n = 20)}\) |
| Metformin: 24 | Metformin: 14 |
| DPP-IV inhibitors: 46 | DPP-IV inhibitors: 7 |
| Sulfonylureas: 17 | Sulfonylureas: 3 |
| Thiazolidinediones: 29 | Thiazolidinediones: 4 |
| Injectables (n = 279) | Injectables (n = 117) |
| Analog GLP-1: 53 (liraglutide: 53) | Analog GLP-1: 11 (liraglutide: 11) |
| Insulins: Basal-bolus: 63 | Insulins: Basal-bolus: 17 |
| Long acting only: 96 | Long acting only: 27 |
| Mixture: 30 | Mixture: 42 |
| Short acting only: 16 | Short acting only: 7 |
| Other insulins: 21 | Other insulins: 13 |

*A total of 71 patients discontinued at the 24-month visit
treatment change at 6, 12, 18 and 24 months were 77.9%, 70.6%, 64.9% and 60.6%, respectively. The most common first significant treatment change for insulin patients was the addition of a new injectable antidiabetes medication (45.3% of first

| Variable                          | Initiators | Persistence |
|-----------------------------------|------------|-------------|
| Male [n (%)]                      | 598 (53.7) | 362 (56.2)  |
| Age (years)                       | 58.1 (10.1)| 58.0 (10.1) |
| Weight (kg)                       | 101.2 (21.7)| 101.1 (21.0)|
| BMI (kg/m²)                       | 35.3 (6.6) | 35.1 (6.6)  |
| Blood pressure (mmHg)             |            |             |
| Systolic                          | 137.7 (16.5)| 138.1 (16.6)|
| Diastolic                         | 81.7 (9.6) | 82.0 (10.0) |
| Time since diabetes diagnosis (years) | 8.2 (5.7) | 8.1 (5.2)  |
| HbA1c (%)                         | 8.4 (1.4)  | 8.4 (1.4)  |
| No. of OADs used [n (%)]          |            |             |
| 0                                 | 76 (6.8)   | 29 (4.5)    |
| 1                                 | 499 (44.8) | 220 (34.2)  |
| 2                                 | 491 (44.1) | 295 (45.8)  |
| ≥3                                | 48 (4.3)   | 100 (15.5)  |
| Insulin regimen [n (%)]           |            |             |
| Long-acting only                  | NA         | 627 (49.2)  |
| Short-acting only                 | NA         | 147 (11.5)  |
| Pre-mix                           | NA         | 312 (24.5)  |
| Basal-bolus                       | NA         | 174 (13.7)  |
| Other                             | NA         | 14 (1.1)    |
| Patients with ≥1 hypoglycemic event (in past 3 months) [n (%)] | 59 (5.3) | 56 (4.4) |
| Diabetes complications [n (%)]    |            |             |
| ≥1 macrovascular complication     | 200 (18.0) | 120 (18.6)  |
| ≥1 microvascular complication     | 164 (14.7) | 91 (14.1)   |

Continuous data are means (SD).
BID twice daily, BMI body mass index, HbA1c glycated hemoglobin, NA not applicable, OAD oral antidiabetes drug, SD standard deviation.

Incidence is based on patient recall of events occurring during the past 3 months.

Treatment change at 6, 12, 18 and 24 months were 77.9%, 70.6%, 64.9% and 60.6%, respectively. The most common first significant treatment change for insulin patients was the addition of a new injectable antidiabetes medication (45.3% of first
significant treatment changes; Table 2). When changes in the insulin cohort were considered using the alternative definition of treatment change (i.e., describing the intensity and efficacy of the new regimen relative to the starter regimen), 0.6% added a GLP-1 receptor agonist, 0.5% switched the type of insulin they were using, 16.5% upgraded therapy, 0.2% downgraded therapy, 7.7% discontinued therapy, and 10.5% had ‘other’ changes. The first significant treatment changes by insulin type are presented in Fig.3.

Throughout the 24-month observation period, 393 patients (35.3%) in the exenatide BID cohort and 155 patients (12.2%) in the insulin cohort discontinued at least one baseline injectable therapy. For 170 patients in the exenatide BID cohort (15.3%) and 87 patients in the insulin cohort (6.8%) this was because of inadequate response (Table 3). Other reasons for discontinuation are summarized in Table 3. Of the 393 patients from the exenatide BID cohort, 10 patients (2.5%) did not start anything else, 373 (94.9%) started an (additional) OAD, 53 (13.5%) started liraglutide, and 283 (72.0%) started insulin. Of

Table 2 First significant treatment change occurring during the 24 months following initiation of exenatide BID or insulin in patients with type 2 diabetes mellitus

| Variable                                                                 | Exenatide BID  
|-------------------------------------------------------------------------|----------------|
|                                                                         | (n = 1,114)    |
| At least one significant treatment change [n (%)]                       | 470 (42.2)     |
| First significant treatment change [n (%)]†                            | 459 (36.0)     |
| Discontinuation of any injectable medication initiated at baseline      | 349 (31.3)     |
| Addition of a new medication (any route of administration) for the treatment of type 2 diabetes  | 121 (10.9)     |
| Addition of a new oral medication                                      | 102 (9.2)      |
| Addition of a new injectable medication                                 | 19 (1.7)       |
| Change to the number of times insulin was administered per day          | NA             |
| Substitution of a human insulin for an analog insulin or vice versa    | NA             |

BID twice daily, NA not applicable

† Where two categories of significant treatment change occurred simultaneously, the categories were ordered: (1) discontinuation of any injectable medication initiated at baseline; (2) addition of new medication; (3) change to the number of times insulin was administered per day; (4) substitution of a human insulin for an analog insulin or vice versa
the 155 patients from the insulin cohort who discontinued their baseline insulin, 18 patients (11.6%) did not start anything else, 41 (26.5%) switched a human insulin for an analog insulin, or vice versa, 21 (13.5%) started an (additional) OAD, 11 (7.1%) started liraglutide, and 106 (68.4%) started a new insulin. In addition, 18.2% of the exenatide BID cohort and 13.1% of the insulin cohort discontinued their baseline OADs. All antidiabetes medications added or discontinued throughout the study are presented in Table 4.

Cox proportional hazards models, performed to investigate the impact of baseline medications and patient clinical characteristics on time to significant treatment changes, indicated that there was nothing of clinical relevance in either treatment cohort. In the exenatide BID cohort, the final Cox proportional hazards model identified the occurrence of GI symptoms in the last 4 weeks prior to initiation of injectable treatment to be statistically significantly associated with a higher risk of significant treatment change [hazard ratio (HR) 1.564; \( p = 0.007 \)]. In the insulin cohort, the final Cox proportional hazards model identified the following factors to be significantly associated with a higher risk of significant treatment change: higher baseline HbA1c (HR 1.121; \( p < 0.001 \)), the occurrence of GI symptoms in the last 4 weeks prior to initiation of injectable treatment (HR 2.040; \( p < 0.001 \)), and the type of insulin initiated. When compared with baseline initiation of long-acting insulin only, patients initiating basal-bolus insulin (HR 0.530; \( p < 0.001 \)) or mixtures (HR 0.762; \( p = 0.026 \)) were less likely, whereas those initiating short-acting insulin only were more likely (HR 2.373; \( p < 0.001 \)) to have a significant treatment change.

The post hoc GEE model showed that in the exenatide BID cohort, switching from exenatide BID to insulin therapy was more likely among patients who had an increase in BMI [no vs. yes, odds ratio (OR) 0.464; \( p < 0.001 \)] or HbA1c (no vs. yes, OR 0.731; \( p < 0.001 \)) over the duration of treatment. There was no evidence for an association between baseline characteristics and this switch. The observed incidence of changing the baseline insulin regimen (as per the primary endpoint) was higher in patients who had an increase in BMI (no vs. yes, OR 0.705; \( p < 0.001 \)), increase in HbA1c (no vs. yes, OR 0.645; \( p < 0.0001 \)), who experienced hypoglycemia (OR 0.691; \( p < 0.001 \)) or baseline microvascular diagnoses (≥1) were also associated with changes in insulin regimen (no vs. yes, OR 0.656; \( p < 0.01 \)).

Clinical Outcomes and Adverse Events

**Exenatide BID**

Improvements were observed in HbA1c in the exenatide BID cohort (Table 5). When
| Variable | Exenatide BID (n = 1,114) | Insulin (n = 1,274) |
|----------|--------------------------|---------------------|
| Time (months) | 0–3 | 3–6 | 6–12 | 12–18 | 18–24 | 0–24 | 0–3 | 3–6 | 6–12 | 12–18 | 18–24 | 0–24 |
| **Discontinued** [n (%)] | 98 (8.8) | 75 (6.7) | 97 (8.7) | 73 (6.6) | 44 (3.9) | 393 a (35.3) | 36 (2.8) | 30 (2.4) | 31 (2.4) | 32 (2.5) | 21 (1.6) | 155 a (12.2) |

**Reason for discontinuation**

- **Adverse event**
  - 21 (1.9) | 30 (2.3) | 37 (3.3) | 26 (2.3) | 35 (3.1) | 170 (15.3) | 20 (1.6) | 14 (1.1) | 20 (1.6) | 21 (1.6) | 9 (0.7) | 87 (6.8)
  - 47 (4.2) | 26 (2.3) | 7 (0.6) | 5 (0.4) | 5 (0.4) | 91 (8.2) | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.1) |

- **Noncompliance**
  - 1 (0.1) | 3 (0.3) | 1 (0.1) | 2 (0.2) | 1 (0.1) | 9 (0.8) | 0 (0) | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 (0) | 3 (0.2) |

- **Subject decision**
  - 21 (1.9) | 9 (0.8) | 19 (1.7) | 16 (1.4) | 4 (0.4) | 69 (6.2) | 4 (0.3) | 4 (0.3) | 2 (0.2) | 2 (0.2) | 3 (0.2) | 15 (1.2) |

- **Cannot afford medication**
  - 1 (0.1) | 2 (0.2) | 1 (0.1) | 0 (0) | 0 (0) | 4 (0.4) | 0 (0) | 1 (0.1) | 0 (0) | 0 (0) | 0 (0) | 1 (0.1) |

- **Other**
  - 7 (0.6) | 9 (0.8) | 12 (1.1) | 13 (1.2) | 8 (0.7) | 50 (4.5) | 11 (0.9) | 7 (0.5) | 7 (0.5) | 6 (0.5) | 5 (0.4) | 38 (3.0) |

* an additional 6 patients in the exenatide cohort and 5 patients in the insulin cohort discontinued after 24 months

**BID** twice daily

Only one reason could be selected by health care professionals

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Table 3 Discontinuation of baseline treatment during the 24 months following initiation of exenatide BID or insulin in patients with type 2 diabetes mellitus

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Table 4  Antidiabetes medications added or discontinued during the 24 months following initiation of exenatide BID or insulin in patients with type 2 diabetes mellitus

| Variable | Exenatide BID ($n = 1,114$) | Insulin ($n = 1,274$) |
|----------|-----------------------------|-----------------------|
|          | Between baseline and 24 months | Added within 6 weeks of first significant treatment change | Between baseline and 24 months | Added within 6 weeks of first significant treatment change |
| Injectable antidiabetes therapy added [$n$ (%)] | 298 (26.8) 257 (23.1) | 325 (25.5) 298 (23.4) |
| Insulin | | | |
| Long-acting | 159 (14.3) 126 (11.3) | 82 (6.4) 63 (4.9) |
| Intermediate-acting | 61 (5.5) 45 (4.0) | 62 (4.9) 55 (4.3) |
| Fast/short-acting | 92 (8.3) 54 (4.8) | 148 (11.6) 117 (9.2) |
| Mixtures | 60 (5.4) 41 (3.7) | 88 (6.9) 76 (6.0) |
| Exenatide | 0 (0) 0 (0) | 2 (0.2) 0 (0) |
| Liraglutide | 53 (4.8) 34 (3.1) | 15 (1.2) 8 (0.6) |
| Injectable antidiabetes therapy discontinued [$n$ (%)] | 396 (35.5) NA | 170 (13.3) NA |
| Insulin | | | |
| Long-acting | 18 (1.6) NA | 67 (5.3) NA |
| Intermediate-acting | 13 (1.2) NA | 50 (3.9) NA |
| Fast-acting | 6 (0.5) NA | 40 (3.1) NA |
| Mixtures | 7 (0.6) NA | 51 (4.0) NA |
| Exenatide | 393 (35.3) NA | 0 (0) NA |
| Liraglutide | 8 (0.7) NA | 1 (0.1) NA |
| OADs added [$n$ (%)] | 180 (16.2) 158 (14.2) | 88 (6.9) 65 (5.1) |
| Insulin | | | |
| Alpha-glucosidase inhibitors | 4 (0.4) 4 (0.4) | 3 (0.2) 1 (0.1) |
| DPP-IV inhibitor | 41 (3.7) 28 (2.5) | 18 (1.4) 10 (0.8) |
| Metformin | 32 (2.9) 30 (2.7) | 23 (1.8) 18 (1.4) |
| SU | 63 (5.7) 53 (4.8) | 21 (1.6) 15 (1.2) |
| Meglitinide | 21 (1.9) 14 (1.3) | 17 (1.3) 15 (1.2) |
| TZD | 29 (2.6) 24 (2.2) | 9 (0.7) 5 (0.4) |
| Metformin and DPP-IV inhibitor | 5 (0.4) 3 (0.2) | 5 (0.4) 1 (0.1) |
| Metformin and SU | 5 (0.4) 4 (0.4) | 0 (0) 0 (0) |
| Metformin and TZD | 10 (0.9) 6 (0.5) | 2 (0.2) 2 (0.2) |
| Other | 0 (0) 0 (0) | 2 (0.2) 1 (0.1) |
controlling for baseline HbA1c, treatment and visit, statistically significant improvements in glycemic control were observed over the course of the study in the exenatide BID initiator population \( (p < 0.001) \). Mean (standard deviation, SD) HbA1c was 8.4 (1.4)% units at baseline, 7.5 (1.2)% units at 3 months, and remained between 7.3 (1.2)% units and 7.4 (1.2)% units at each further visit.

Improvements were also seen in mean values of variables for a number of other cardiovascular risk factors, including blood pressure and lipid parameters (Table 5). In addition, mean weight was significantly reduced in the exenatide BID cohort by 24 months (Table 5; \( p < 0.001 \)). Weight loss (>1.0 kg) was achieved by 62.2% of initiators and 72.5% of persisters in the exenatide BID cohort. In the initiators group, mean (SD) baseline weight was 101.2 (21.8) kg; at 3 months, this was 98.7 (21.7) kg and at each further visit, mean weight remained between 97.7 (20.8) kg and 98.3 (21.3) kg. In the exenatide BID persisters group, mean weight decreased until month 18 and remained below baseline levels for the remainder of the study.

Overall, 18.4% of patients who initiated exenatide BID (15.7% of persisters) experienced at least one episode of hypoglycemia. The majority of episodes occurred in patients receiving concomitant sulfonylureas (Fig. 4). Severe hypoglycemia (requiring third-party assistance or a hospital visit) was experienced by 1.6% of initiators and 1.1% of persisters.
Table 5  Clinical findings 24 months after initiation of exenatide BID or insulin in patients with type 2 diabetes mellitus

| Variable                              | Exenatide BID                | Insulin                  |
|---------------------------------------|------------------------------|--------------------------|
|                                       | Initiators population       | Persisters population    | Initiators population | Persisters population |
| Proportion of patients at 24 months   | (n = 705)                   | (n = 396)                | (n = 871)             | (n = 530)             |
| HbA1c <7.0% [n (%)]a                  | 258 (36.6)                  | 166 (41.9)               | 333 (38.2)            | 217 (40.9)            |
|                                       | (n = 744)                   | (n = 418)                | (n = 899)             | (n = 548)             |
|                                       | 127 (17.1)                  | 86 (20.6)                | 129 (14.3)            | 87 (15.9)             |
| Patients with ≥1 hypoglycemic event [n (%)]c | (n = 1,061)            | (n = 607)                | (n = 1,221)           | (n = 766)             |
|                                       | 195 (18.4)                  | 95 (15.7)                | 449 (36.8)            | 254 (33.2)            |
| Patients with ≥1 GI symptoms [n (%)]d | (n = 1,060)                | (n = 606)                | (n = 1,219)           | (n = 765)             |
|                                       | 327 (30.8)                  | 142 (23.4)               | 64 (5.3)              | 23 (3.0)              |
| Mean change from baseline to 24 months|                             |                          |                        |                        |
| HbA1c [% (SD; 95% CI)]                | (n = 795)                   | (n = 453)                | (n = 924)             | (n = 568)             |
|                                       | −1.0 (1.5; −1.1 to −0.9)    | −1.2 (1.5; −1.3 to −1.0) | −1.7 (1.8; −1.8 to −1.6) | −1.8 (1.9; −2.0 to −1.6) |
| Body weight [kg (SD; 95% CI)]         | (n = 810)                   | (n = 462)                | (n = 945)             | (n = 588)             |
|                                       | −3.2 (7.9; −3.8 to −2.7)    | −4.8 (7.2; −5.5 to −4.2) | 2.2 (6.2; 1.8 to 2.6) | 2.0 (6.2; 1.5 to 2.5) |
| Body weight according to insulin type [kg (SD; 95% CI)] | NA                          | NA                       | (n = 131)             | (n = 103)             |
| Basal-bolus                           | NA                          | NA                       | 3.0 (7.0; 1.8 to 4.3)  | 3.4 (6.6; 2.1 to 4.6)  |
| Long-acting only                      | NA                          | NA                       | (n = 452)             | (n = 274)             |
|                                       | 1.7 (5.2; 1.2 to 2.2)       | 1.4 (4.6; 0.8 to 1.9)    | (n = 247)             | (n = 169)             |
| Mixtures only                         | NA                          | NA                       | 2.2 (7.6; 1.3 to 3.2)  | 2.0 (8.3; 0.7 to 3.2)  |
| Short-acting only                     | NA                          | NA                       | (n = 105)             | (n = 35)              |
|                                       | 2.7 (5.5; 1.7 to 3.8)       | 3.1 (4.5; 1.5 to 4.6)    | (n = 10)              | (n = 7)               |
| Other                                 | NA                          | NA                       | 2.2 (4.6; −1.1 to 5.6) | 3.0 (4.0; −0.7 to 6.7) |
| BMI [kg/m² (SD; 95% CI)]              | (n = 805)                   | (n = 458)                | (n = 942)             | (n = 586)             |
|                                       | −1.1 (2.8; −1.3 to −0.9)    | −1.7 (2.5; −1.9 to −1.5) | 0.8 (2.2; 0.6 to 0.9)  | 0.7 (2.2; 0.6 to 0.9)  |
| Waist circumference [cm (SD; 95% CI)] | (n = 578)                   | (n = 363)                | (n = 693)             | (n = 434)             |
|                                       | −3.3 (8.1; −4.0 to −2.6)    | −4.6 (7.9; −5.4 to −3.8) | 1.4 (8.6; 0.8 to 2.1)  | 1.8 (9.4; 0.9 to 2.7)  |
| Blood pressure [mmHg (SD; 95% CI)]    | (n = 764)                   | (n = 436)                | (n = 883)             | (n = 556)             |
### Table 5 continued

| Variable                  | Exenatide BID | Insulin |
|---------------------------|---------------|---------|
|                           | Initiators population | Persisters population | Initiators population | Persisters population |
|                           |                |          |                |          |
| **Systolic**              |                |          |                |          |
|                           | $-3.1$ (17.9; $-4.4$ to $-1.9$) | $-4.2$ (17.9; $-5.9$ to $-2.5$) | $-3.5$ (18.2; $-4.7$ to $-2.3$) | $-3.2$ (17.8; $-4.7$ to $-1.8$) |
| **Diastolic**             |                |          |                |          |
|                           | $-3.2$ (11.2; $-4.0$ to $-2.4$) | $-3.4$ (11.1; $-4.5$ to $-2.4$) | $-2.0$ (11.1; $-2.8$ to $-1.3$) | $-2.1$ (11.0; $-3.0$ to $-1.2$) |
| **Plasma lipids [mmol/L (SD; 95% CI)]** |          |          |                |          |
| Total cholesterol         | $(n = 641)$   | $(n = 385)$ | $(n = 731)$ | $(n = 455)$ |
|                           | $-0.3$ (1.1; $-0.4$ to $-0.2$) | $-0.3$ (1.1; $-0.4$ to $-0.2$) | $-0.4$ (1.2; $-0.4$ to $-0.3$) | $-0.4$ (1.2; $-0.5$ to $-0.3$) |
| LDL cholesterol           | $(n = 590)$   | $(n = 360)$ | $(n = 670)$ | $(n = 424)$ |
|                           | $-0.2$ (0.9; $-0.2$ to $-0.1$) | $-0.2$ (0.8; $-0.3$ to $-0.1$) | $-0.3$ (1.0; $-0.3$ to $-0.2$) | $-0.3$ (1.0; $-0.4$ to $-0.2$) |
| HDL cholesterol           | $(n = 611)$   | $(n = 374)$ | $(n = 686)$ | $(n = 434)$ |
|                           | $0.0$ (0.2; 0.0 to 0.1) | $0.0$ (0.2; 0.0 to 0.1) | $0.1$ (0.3; 0.0 to 0.1) | $0.1$ (0.4; 0.0 to 0.1) |
| Triglycerides             | $(n = 626)$   | $(n = 379)$ | $(n = 711)$ | $(n = 442)$ |
|                           | $-0.4$ (1.3; $-0.5$ to $-0.3$) | $-0.4$ (1.3; $-0.5$ to $-0.2$) | $-0.4$ (1.5; $-0.5$ to $-0.3$) | $-0.3$ (1.4; $-0.5$ to $-0.2$) |

Continuous data are means (SD; 95% CI)

**BID** twice daily, **BMI** body mass index, **CI** confidence interval, **GI** gastrointestinal, **HbA1c** glycated hemoglobin, **HDL** high-density lipoprotein, **LDL** low-density lipoprotein, **NA** not applicable, **SD** standard deviation

a Data from the subgroup of 959 patients in the exenatide BID initiators group and 1,170 patients in the insulin initiators group with baseline HbA1c ≥ 7.0% at baseline (254 and 299 patients, respectively, had missing data), and the 551 patients in the exenatide BID persisters group and 779 patients in the insulin persisters group with baseline HbA1c ≥ 7.0% at baseline (155 and 209 patients, respectively, had missing data)

b Data from the subgroup of 1,019 patients in the exenatide BID initiators group and 1,208 patients in the insulin initiators group with baseline HbA1c ≥ 6.5% at baseline (275 and 309 patients, respectively, had missing data), and the 583 patients in the exenatide BID persisters group and 765 patients in the insulin persisters group with baseline HbA1c ≥ 6.5% at baseline (165 and 217 patients, respectively, had missing data)

c Incidence is based on patient recall of events occurring during the past 24 months

d Patients experiencing GI symptoms between baseline and 24 months
visit) was experienced by 1.2% of exenatide BID initiators (11 patients) and 1.1% of persisters (6 patients). During the 3 months before the baseline visit, the exenatide BID cohort had experienced a mean (SD) of 0.4 (5.7) hypoglycemic events. During the study, patients in this cohort experienced a mean (SD) of 1.3 (5.4) hypoglycemic events.

At 24 months, the proportion of patients who met the composite endpoint of HbA₁c <7.0%, no weight gain (≤1 kg change), and no hypoglycemia was 25.9% and 32.2% in the exenatide BID initiator and persister populations, respectively. A shorter duration of diabetes (p = 0.002) and lower HbA₁c (p < 0.001) were associated with achievement of this outcome in the exenatide BID cohort.

Overall, 30.8% of the exenatide BID cohort experienced GI events; most commonly, nausea (16.8% of patients). The number of patients with GI events was higher in the first 6 months (26.2% of patients with data) than in all subsequent 6-month periods (<8% of patients with data; events were reported from the 4 weeks prior to each visit only).

### Insulin

Improvements were observed in HbA₁c in the insulin cohort (Table 5). When controlling for baseline HbA₁c, treatment and visit, statistically significant improvements in glycemic control were observed over the course of the study in the insulin initiator population (p < 0.001). Mean (SD) HbA₁c values were 9.2 (1.9)% units at baseline, 7.5 (1.4)% units at 3 months, and between 7.3 (1.0)% units and 7.3 (1.1)% units for the remainder of the study period.

Improvements were also seen in mean values of variables for a number of other cardiovascular risk factors, including blood pressure and lipid parameters (Table 5). However, mean weight was significantly increased in the insulin cohort (Table 5; p < 0.001). Overall, 58.7% of insulin initiators and 57.3% of persisters gained weight (>1.0 kg), with mean weight tending to increase throughout the entire study for both initiators and persisters. In the initiators group, mean (SD) baseline weight was 84.2 (17.6) kg; at 3 months, mean weight was 84.9 (17.3) kg and at each further visit, mean weight was between 85.6 (17.4) kg and 86.7 (17.8) kg.

Overall, 36.8% of patients who initiated insulin (33.3% of persisters) experienced at least one episode of hypoglycemia (Fig. 4). Severe hypoglycemia (requiring third-party assistance or a hospital visit) was experienced by 8.4% of insulin initiators (76 patients) and 5.7% of persisters (34 patients). During the 3 months before the baseline visit, patients in
the insulin cohort had experienced a mean (SD) of 0.2 (2.3) hypoglycemic events. During the study, patients in this cohort experienced a mean (SD) of 3.7 (14.2) hypoglycemic events.

At 24 months, the proportion of patients who met the clinically relevant composite endpoint of HbA₁c <7.0%, no weight gain (<1 kg change), and no hypoglycemia was 10.0% and 11.8% in the insulin initiator and persister populations, respectively. A shorter duration of diabetes (p < 0.001), lower HbA₁c (p < 0.001), lower diastolic blood pressure (p = 0.050), higher BMI (p = 0.002), the absence of GI symptoms (p = 0.005), and initial insulin regimen (mixtures versus basal only; p = 0.004) were associated with achievement of the composite endpoint.

Overall, 5.3% of patients in the insulin cohort experienced GI events (most commonly abdominal pain in 2.5% of patients).

**Propensity-Matched Subgroup**

Propensity matching of baseline patient and disease characteristics identified 619 pairs of patients who could be compared (51.8% of the total sample). These patients had a mean (SD) duration of diabetes of 9.1 (6.3) years [9.0 (6.0) years for the exenatide BID group and 9.2 (6.6) years for the insulin group]; other baseline characteristics are summarized in Table 6. In this propensity-matched subgroup, patients in the exenatide BID group had significantly greater mean (SD) weight loss (p < 0.0001) and a lower incidence of patient-recalled hypoglycemia (p < 0.0001) than the insulin group during the study (Table 6). However, there was no significant difference between treatment groups regarding mean (SD) change in HbA₁c or in the percentages of patients at 24 months with HbA₁c <7.0% or <6.5%. At 24 months, the proportion of patients who met the composite endpoint of HbA₁c <7.0%, no weight gain (<1 kg change), and no hypoglycemia was 26.9% in the exenatide BID group and 11.0% in the insulin group (p < 0.0001, McNemar’s test) (post hoc analysis).

**DISCUSSION**

CHOICE was a prospective observational study designed to evaluate patterns of exenatide BID and insulin usage and outcomes in clinical practice in multiple European countries. In this study, 42.2% of patients who initiated exenatide BID and 36.0% who initiated insulin had a significant treatment change during the 24 months after these treatments were started. In another European study of insulin initiation [13], rates of treatment change in the 24-month period following insulin initiation were 2.9–19.4% (depending on insulin regimen). It is unclear why the results of that study differed from our findings. In CHOICE, patients in the two treatment cohorts were substantially different, with the exenatide BID cohort tending to have a younger age, higher body weight, BMI, waist circumference and diastolic blood pressure, lower total and low-density lipoprotein (LDL)-cholesterol levels, a shorter time since diabetes diagnosis, and better glycemic control at baseline than patients in the insulin cohort [9]. Therefore, we were unable to compare the clinical findings for the total exenatide BID and insulin cohorts.

Time to significant treatment change was chosen as the primary outcome of this study, because it was anticipated that patients prescribed exenatide BID would continue to move through the available treatment algorithms until insulin was initiated. A combination of factors, including glycemic control and tolerability, were believed to influence treatment changes or
Table 6 Baseline and 24-month clinical data for patients initiated on exenatide BID or insulin therapy: a propensity score subpopulation analysis

| Variable                        | Exenatide BID (n = 619) | Insulin (n = 619) | p value (change) |
|---------------------------------|--------------------------|-------------------|-----------------|
|                                 | Baseline                 | 24 months         | Baseline        | 24 months   |         |
| Weight (kg)                     | (n = 618)                | (n = 448)         | (n = 615)       | (n = 474)   |         |
|                                 | 93.2 (18.1)              | 90.8 (18.7)       | 91.8 (18.1)     | 93.8 (18.4) | <0.0001 |
| Change in weight (kg)           | (n = 448)                |                   | (n = 472)       |             |         |
|                                 | −2.8 (6.6)               |                   | 1.5 (6.6)       |             |         |
| Blood pressure (mmHg)           |                          |                   |                 |             |         |
| Systolic                        | (n = 615)                | (n = 425)         | (n = 612)       | (n = 442)   |         |
|                                 | 137.2 (16.7)             | 133.7 (14.5)      | 137.5 (16.5)    | 134.0 (15.0)|         |
| Change in systolic              | (n = 422)                |                   | (n = 437)       |             | 0.3783  |
|                                 | −3.6 (17.5)              |                   | −3.1 (16.4)     |             |         |
| Diastolic                       | (n = 615)                | (n = 425)         | (n = 612)       | (n = 442)   |         |
|                                 | 81.1 (9.3)               | 77.5 (9.6)        | 80.9 (10.0)     | 79.1 (8.8)  |         |
| Change in diastolic             | (n = 422)                |                   | (n = 437)       |             | 0.0017  |
|                                 | −3.7 (11.2)              |                   | −1.5 (10.6)     |             |         |
| HbA1c (%)                       | (n = 600)                | (n = 452)         | (n = 604)       | (n = 473)   |         |
|                                 | 8.7 (1.5)                | 7.3 (1.1)         | 8.6 (1.5)       | 7.3 (1.1)   |         |
| Change in HbA1c (%)             | (n = 443)                |                   | (n = 463)       |             | 0.8473  |
|                                 | −1.3 (1.5)               |                   | −1.2 (1.5)      |             |         |
| HbA1c <7.0% [n (%)]             | (n = 600)                | (n = 411)         | (n = 604)       | (n = 420)   |         |
|                                 | 45 (7.5)                 | 165 (40.1)        | 56 (9.3)        | 154 (36.7)  |         |
| HbA1c <6.5% [n (%)]             | (n = 600)                | (n = 421)         | (n = 604)       | (n = 441)   |         |
|                                 | 30 (5.0)                 | 69 (16.4)         | 28 (4.6)        | 67 (15.2)   |         |
| Patients with ≥1 hypoglycemic event [n (%)]<sup>c</sup> | (n = 619)                | (n = 590)         | (n = 619)       | (n = 597)   |         |
|                                 | 35 (5.7)                 | 120 (20.3)*       | 30 (4.8)        | 199 (33.3)  |         |
| Patients with ≥1 GI symptoms, [n (%)]<sup>d</sup> | (n = 618)                | (n = 590)         | (n = 619)       | (n = 597)   |         |
|                                 | 30 (4.9)                 | 182 (30.8)*       | 30 (4.8)        | 35 (5.9)    |         |
| Lipids (mmol/L)                 |                          |                   |                 |             |         |
| Total cholesterol               | (n = 561)                | (n = 336)         | (n = 551)       | (n = 381)   |         |
|                                 | 5.0 (1.0)                | 4.7 (1.0)         | 5.0 (1.1)       | 4.8 (1.0)   |         |
| Change in total cholesterol     | (n = 354)                |                   | (n = 362)       |             | 0.2066  |
|                                 | −0.2 (1.0)               |                   | −0.3 (1.1)      |             |         |
Clinicians and reimbursement authorities in the European Union are therefore interested in how long patients remain on exenatide BID before intensifying or discontinuing their therapy, and what treatment changes are made. In addition, guidelines recommend that patients maintain glycemic control [1] because a lack of glycemic control is associated with increased morbidity [14], so the time taken to modify treatment in response to poor control or unwanted adverse effects for patients initiated on exenatide BID or insulin is of interest. We found that the proportion of enrolled patients with treatment change in the exenatide BID group was highest in the first 6 months of the study and then decreased throughout the remainder of the study. The majority of the first significant treatment changes in this cohort were discontinuations, with the remainder mainly comprising the addition of oral antidiabetes medications. The most frequent reasons for treatment change were inadequate response and adverse events. This is consistent with the results of a recently published clinical trial [15]. Post hoc analyses of CHOICE identified

| Variable          | Exenatide BID (n = 619) | Insulin (n = 619) | p value (change) |
|-------------------|-------------------------|-------------------|------------------|
|                   | Baseline | 24 months | Baseline | 24 months |         |
| HDL cholesterol   | (n = 542) | (n = 358) | (n = 527) | (n = 361) |         |
|                   | 1.2 (0.3) | 1.2 (0.3) | 1.2 (0.4) | 1.2 (0.4) | –       |
| Change in HDL     | (n = 339) | (n = 338) |         |         | 0.6591  |
| LDL cholesterol   | (n = 531) | (n = 346) | (n = 514) | (n = 357) |         |
|                   | 2.8 (0.9) | 2.7 (0.9) | 3.0 (1.0) | 2.8 (0.9) | –       |
| Change in LDL     | (n = 327) | (n = 330) |         |         | 0.4268  |
| Triglycerides     | (n = 551) | (n = 360) | (n = 547) | (n = 372) |         |
|                   | 2.4 (1.6) | 1.9 (1.2) | 2.4 (2.0) | 1.9 (1.1) | –       |
| Change in triglycerides | (n = 344) | (n = 353) |         |         | 0.2045  |
|                   | –0.4 (1.4) | –0.3 (1.5) |         |         |         |

Continuous data are means (SD); changes were compared between the 2 matched subgroups using paired t tests. BID twice daily, GI gastrointestinal, HbA1c glycated hemoglobin, HDL high-density lipoprotein, LDL low-density lipoprotein, SD standard deviation

* p < 0.0001 versus insulin, McNemar’s test

a Data from the subgroup of 555 patients in the exenatide BID group and 548 patients in the insulin group with HbA1c ≥7.0% at baseline (144 and 128 patients, respectively, had missing data at 24 months)
b Data from the subgroup of 570 patients in the exenatide BID group and 576 patients in the insulin group with HbA1c ≥6.5% at baseline (149 and 135 patients, respectively, had missing data at 24 months)
c Incidence is based on patient recall of events occurring: baseline = past 3 months; 24 months = past 24 months
d Patients with GI symptoms at baseline and those experiencing GI symptoms between baseline and 24 months
increased BMI or HbA1c as factors associated with a switch from exenatide BID to insulin therapy.

In the insulin cohort, the proportions of patients with significant treatment change were also highest in the first 6 months of the study and then decreased throughout the remainder of the study. The most common first significant treatment change for patients on insulin was the addition of a new injectable antidiabetes medication, with most patients requiring upgraded therapy to a more intensive regimen. When compared with baseline initiation of long-acting insulin only, patients initiating basal-bolus insulin or mixtures were less likely to have significant treatment change, and those initiating short-acting insulin only were more likely to have significant treatment change (Fig. 3). These observations are in line with results of the 4T trial, which indicated that, after 1 year, patients initially treated only with long-acting insulin were more likely to require a change in treatment (additional dose or addition of a second insulin) than patients initially receiving basal-bolus insulin [16] and, after 3 years, patients initiated only on short-acting or long-acting insulin required higher insulin doses than those initiated on basal-bolus insulin [17]. However, patients initiating only short-acting insulin in the 4T trial were less likely to require addition of another type of insulin than patients initiated on long-acting insulin after 1 year [16]. A switch from the initial insulin regimen to another of similar complexity and efficacy was more likely in patients with at least one microvascular diagnosis at baseline, and in patients with an increase in BMI or HbA1c or who experienced hypoglycemia during treatment with their baseline regimen. However, for both the exenatide BID and insulin cohorts, treatment change could not be directly linked with HbA1c levels reported in this study as treatment changes could have occurred between study time-points, whereas HbA1c measurements were recorded at study visits (i.e., not necessarily at the time of treatment change).

Clinical findings from CHOICE appear consistent when comparing findings from the initiators population (which included patients who had changed treatment), persisters population (which comprised only patients who remained on their initial injectable therapy at study end or study discontinuation) and on-drug population (which comprised all patients from the initiators population up to the time of any switch of treatment or discontinuation of the initial injectable therapy; data not shown). They are also in line with findings from RCTs [18–20] and other observational studies [21–24], although comparability of the primary analyses (the ‘initiators’ analyses) with findings from other studies is limited by the fact that patients could be started on an alternative treatment while remaining in CHOICE. The demographics and characteristics of the patients from CHOICE who were initiated on exenatide BID were consistent with those of patients from the Exenatide BID Observational Study (ExOS) conducted in the United States [21, 22]. The Association of British Clinical Diabetologists’ nationwide exenatide audit, which was performed in the United Kingdom, included patients who were broadly similar to our population, except that their mean baseline HbA1c was higher (9.47%) than in our study, and 33.9% of patients in their study were also receiving insulin at the time exenatide was initiated [24]. In the US study, which was single-arm and included patients initiated on exenatide BID, irrespective of previous insulin use, significant improvements were observed after 12 months in HbA1c (−0.80%), weight
(-2.4 kg), and BMI (-0.83 kg/m²; p ≤ 0.0001 for all) [21, 22]. The UK audit of patients recently started on exenatide also revealed clinical improvements after a median of 6 months of exenatide therapy (the regimen was not described), with reported decreases of 0.73% for HbA1c, 5.9 kg for weight, and 2.2 kg/m² for BMI (p < 0.001 for all) [24]. Another study that used a real-world setting to evaluate the effectiveness of exenatide BID was the retrospective claims database audit of Brixner et al. [23]. Patients who were included in this latter analysis were selected according to the exenatide BID label [25] and had data for the first 6 months after initiation of exenatide BID. Clinical improvements in this study were again consistent with our findings and those reported in the other studies discussed here. However, these studies have certain limitations in that all were of relatively short duration (6 or 12 months) and were either single-arm or retrospective in design. When compared with prospective observational studies evaluating initial use of insulin, 24-month results of the INSTIGATE study showed that in three European countries, 23.9% of patients changed their insulin regimen (which was initiated at the discretion of the treating physician) and patients achieved similar reductions in HbA1c as are reported in our study [26]. In CHOICE, HbA1c was reduced by 1.0% units in the exenatide BID cohort and 1.7% units in the insulin cohort, although the change is likely confounded by the higher baseline HbA1c in the insulin cohort.

There has recently been a move toward comparative effectiveness research and the desire to compare therapies in clinical practice [1, 27]. Although CHOICE was not designed to do this, a matched subgroup of patients, including approximately half the study population, was identified using propensity score data. Analyses conducted in these patients did not demonstrate a difference between the exenatide BID group and the insulin group in mean changes in HbA1c, and percentages of patients at 24 months with HbA1c <7.0% or <6.5%. However, patients in the exenatide BID-matched group had significantly greater mean weight loss (p < 0.0001) and a lower incidence of patient-recalled hypoglycemia (p < 0.0001) than the insulin-matched group during the study. These findings are consistent with the results of RCTs comparing GLP-1 receptor agonists and insulin therapy [2–4, 28–30]. Although the incidence of hypoglycemia relied on patient recall and was not measured objectively in CHOICE, these episodes may better reflect patient-relevant hypoglycemia (i.e., those episodes that may have caused anxiety or concern, or had an impact on behavior or the self-management of diabetes). In our study, 26.9% of patients in the exenatide BID-matched subgroup achieved the clinically relevant composite endpoint of HbA1c <7.0%, no weight gain (≤1 kg change), and no hypoglycemia at 24 months. This compares with 40% of liraglutide 1.8 mg and 32% of liraglutide 1.2 mg recipients achieving this endpoint according to the meta-analysis of Zinman et al. [12]. However, these results for liraglutide were achieved at 26 weeks in RCTs, whereas our findings were obtained after a considerably longer duration of treatment and in a prospective, observational manner. These findings, along with the requirement for glucose monitoring and limited flexibility in lifestyle to avoid hypoglycemia with insulin, support the preferential use of GLP-1 receptor agonists over insulin in selected patients, such as those requiring weight loss or who are at risk of hypoglycemia, as is recommended [1].

Prospective observational studies have certain limitations, including the unknown
magnitude of observer effects, the potential for investigators to be influenced by the scrutiny that occurs during a prospective study, and the potential for selection bias. The inclusion of two treatment cohorts is anticipated to have helped reduce prescribing bias, as is the fact that patients were invited to participate in our study only after the clinical decision had been made to initiate exenatide BID or insulin. This inclusion criterion also avoided several additional problems identified with some observational studies, such as their propensity to change the prescribing habits of the participating physicians [31, 32].

Although the sample was designed to be representative, recruitment targets were prespecified, sample sizes were small in some countries, the ratio of exenatide BID to insulin patients varied between countries, and patients were mostly recruited in secondary care centers. The CHOICE study has provided the first available data on the use of exenatide BID in routine clinical practice across Europe. It is likely that treatment patterns have changed since this study was conducted. Additional GLP-1 receptor agonist therapies are now available (exenatide once weekly and liraglutide, for instance) and in March 2012, exenatide BID received EU approval as adjunctive therapy in adult patients with T2DM who have not achieved adequate glycemic control with basal insulin, with or without metformin and/or pioglitazone [33]. The latter was not an approved indication for exenatide BID for the duration of CHOICE, and only two patients from the insulin cohort were initiated on this agent during the study. However, we expect that this new indication for exenatide BID may have a substantial impact on prescribing trends for patients with T2DM, as UK-based audits have shown that between 30% and 40% of the patients initiated on GLP-1 receptor agonists before this indication was approved were also receiving basal insulin concomitantly [24, 34].

CONCLUSION

In addition to estimating the time to first significant treatment change and evaluating reasons for the treatment change following initiation of injectable therapy, CHOICE provided data on exenatide BID usage patterns and 24-month outcomes in clinical practice. Results show that 42.2% of patients initiated on exenatide BID and 36.0% of those initiated on insulin as their first injectable glucose-lowering therapy had a significant treatment change during the first 24 months of therapy. Nevertheless, patients in both treatment cohorts achieved improved glycemic control and a reduced severity of cardiovascular risk factors, and those in the exenatide BID cohort also achieved mean weight loss. These findings for exenatide BID were consistent with results reported from RCTs.

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Conflict of interest. Chantal Mathieu is an advisory board member for Lilly Belgium. Thure Krarup is an advisory board member
for Lilly Denmark. Stephan Matthaei and Bruno Guerci have received honoraria from Eli Lilly for lectures and consultancy. Claes-Göran Östenson has received honoraria from Eli Lilly for consultancy. Matthew Reaney and Hélène Sapin are employees of Eli Lilly but are not shareholders. Jacek Kiljański and Carole Salaun-Martin are employees of Eli Lilly and holders of Eli Lilly shares and share options. Michael Theodorakis declares no conflict of interest.

**Compliance with ethics guidelines.** Patients gave written informed consent for the use of their data and appropriate ethical review board approval was obtained.

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**APPENDIX**

See Table 7.

**Table 7** Examples of switch, upgrade, downgrade and discontinuation of insulin therapy according to the alternative definition of treatment change

| Baseline regimen | New regimen                        | Treatment change     |
|------------------|------------------------------------|----------------------|
| Basal analog insulin | NPH                               | Switch               |
| Basal analog insulin | Prandial only, pre-mix             | Upgrade              |
| NPH               | Basal analog insulin               | Switch               |
| NPH               | Prandial only, pre-mix             | Upgrade              |
| Pre-mix           | Basal/NPH only, prandial only,     | Downgrade            |
| Pre-mix           | Basal-bolus                        | Upgrade              |
| Prandial analog insulin | Basal/NPH only                  | Downgrade            |
| Prandial analog insulin | Prandial human insulin          | Switch               |
| Prandial human insulin | Basal/NPH only                   | Downgrade            |
| Prandial human insulin | Pre-mix                           | Upgrade              |
| Prandial analog insulin | Pre-mix                           | Upgrade              |
| Prandial human insulin | Prandial analog insulin          | Switch               |
| Basal-bolus       | Basal/NPH only, prandial only, pre-mix | Downgrade        |
| Basal-bolus (human and/or analog) | Basal-bolus (analog and/or human) | Switch               |
| Any regimen       | No regimen started within 30 days  | Discontinuation      |
| Any regimen       | Same insulin regimen, oral antidiabetes drug | Other              |

*NPH* neutral protamine hagedorn
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