BMJ Open

Characteristics of Patients with Type 2 Diabetes Mellitus Newly Treated with GLP-1 Receptor Agonists in Spain (CHADIG Study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010197
Article Type:	Research
Date Submitted by the Author:	13-Oct-2015
Complete List of Authors:	Mauricio, Didac; Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Department of Endocrinology & Nutrition Conget, Ignacio; Hospital Clinic, Endocrinology and Diabetes Unit Ortega-Basagoiti , Rafael; GSK, Medical Department Detournay, Bruno; CEMKA-EVAL
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Type 2 diabetes mellitus, GLP-1 receptor agonists, Patients' characteristics, Spain

Title

Characteristics of Patients with Type 2 Diabetes Mellitus Newly Treated with GLP-1 Receptor Agonists in Spain (CHADIG Study)

Corresponding Author

Dr. Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain

didacmauricio@gmail.com

Phone: +34. 627953473

Authors

Ignacio Conget

Diabetes Unit, ICMDM Hospital Clínic i Universitari, Barcelona, Spain

Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain

Rafael Ortega

Medical Director, CV & Metabolism

Medical Department, GlaxoSmithKline, Tres Cantos (Madrid), Spain.

Bruno Detournay

Director, CEMKA-EVAL, Bourg-la-Reine, France

On behalf of the CHADIG Study investigators

Key words:

Type 2 diabetes mellitus - GLP-1 receptor agonists – Patients' characteristics - Spain.

Word count: 2.574 words

ABSTRACT:

Objective

Several GLP-1 receptor agonists (GLP-1Ra) have been made recently available in Spain for type 2 diabetes mellitus (DM2) treatment. There are no published data on clinical and socio-demographic profile of patients initiating treatment with GLP-1Ra in Spain. Our objective was to understand these patients' characteristics in real world clinical practice.

Design

Cross-sectional, observational study.

Setting

Spanish specialist outpatient clinics.

Participants

403 adults with DM2 initiating GLP-1Ra treatment were included. **Primary and Secondary Outcome Measures**

Socio-demographic and DM2-related clinical data, including treatment at and after GLP-1Ra initiation and co-morbidities were collected.

Results

Evaluable patients (n=403; 50.9% female) were included (July 2013-March 2014) at 24 centres by 53 specialists (47 endocrinology, 6 internal medicine), with the following profile: (value±SD): age (58.3±10.4 years), diabetes duration (9.9±7 years), BMI (36.2±5.5) and HbA1c (8.4±1.4%); 14% had HbA1c ≤ 7%. Previous antidiabetic treatment: 53.8% only Oral Antidiabetic Drugs (OAD), 5.2% insulin and 40% insulin and OAD; of those receiving OAD, 35% single drug, 38.2% two drugs and 24% three drugs. Concomitant to GLP-1 Ra, 55.3% were only on OAD, 36.2% on both insulin and OAD and 7.2% only on insulin. Of

those receiving OAD, the GLP-1Ra was mainly associated to one drug (65%) or 2 drugs (31.8%). GLP-1Ra are frequently added to existing antidiabetic drugs, with DPP-4 inhibitors being the OAD most frequently switched (45% receiving one before starting GLP-1Ra, only 2.7% receiving it concomitantly).

Conclusions

In Spain, GLP-1Ra therapy is usually started in combination with OADs or OADs and insulin. These drugs are used in relatively young patients often not reaching therapeutic goals with other treatment combinations, roughly a decade after diagnosis and with a relatively high BMI. The latter could be explained by Spanish regional payers limiting reimbursed prescription to patients with a minimum BMI threshold (>30 in most regions, >35 in some).

Strenght and limitations of this study

- The study sample is fairly representative of the overall Spanish population of DM2 patients.
- The reason for treatment change was not recorded. Therefore, the reasons for prescribing GLP-1 Ra cannot be fully ascertained.
- Payers' restrictions to GLP-1 Ra in Spain resulted in first prescription mainly done by specialists, which may have resulted in some patient selection bias towards a more advanced, complex patient type.

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a chronic metabolic disorder with worldwide steadily increasing prevalence that is expected to grow in all age-groups worldwide from 2.8% in 2000 to 4.4% in 2030[1]. In Spain, the overall prevalence of diabetes mellitus adjusted for age and sex was estimated in a representative sample of the population to be 13.8%, of which about half (6.0%) had unknown diabetes[2] and, considering the Spanish population, the number of patients with diagnosed diabetes (treated or untreated with drugs) may be estimated to be over 3.6 million people. DM2 prevalence in Spain was estimated at 15.3% in men and 14.2% in women[3].

The short-term aim of therapy for hyperglycaemia is improved blood glucose control without significant tolerability or safety issues, and with the longer-term objective of reducing vascular damage. Although most initial pharmacological therapies include an oral glucose-lowering agent, a steady decline in islet beta-cell function results in progressive hyperglycemia, which requires a stepwise escalation of treatment. Eventually insulin is often required as the only therapy independent of the need for endogenous insulin production. Glucagon-like peptide-1 receptor agonists (GLP-1Ra) have recently become a therapeutic option. GLP-1Ra mimic, at supra-physiological levels, the action of endogenous glucagon-like peptide-1, in stimulating glucose-dependent insulin secretion and by suppressing glucagon secretion. Gastric emptying is delayed, especially in the early weeks of therapy. This, and perhaps a direct or indirect hypothalamic action, results in appetite/satiety changes and thus loss of body weight[4].

Despite being on the market since several years ago, little is known about the characteristics of patients treated with GLP-1Ra and about the place of these drugs in DM2 in the real life setting. Given that current available databases do not provide this information for Spanish

patients, the present observational study was conducted with the objective to describe demographic and clinical characteristics of patients with DM2 newly treated with GLP-1Ra in Spain.

PATIENTS AND METHODS

Study Design

This was a cross sectional, observational, non-interventional, multicenter study conducted in adult DM2 patients newly treated with GLP-1Ra in Spanish specialist outpatient clinics, since these drugs are mostly initiated in Spain by specialists. The study was approved by Research Ethics Committees from participating centres and was conducted according to the Declaration of Helsinki. All patients signed an informed consent.

Study Population

Patients were included in the study if they: a) were adults (≥ 18 years old) presenting with DM2 and visiting the investigator for any reason; b) were prescribed for the first time a GLP-1Ra the day of inclusion in the normal course of care, or who had initiated GLP-1Ra therapy within 3 months before the inclusion visit (as long as the study required information was available); and c) provided informed consent in writing to participate. Candidate patients were excluded if they were participating in a study with an investigational drug or procedure.

A sample size of 384 patients was required in order to estimate in the study population, with a confidence interval (95%) of ± 5%, a 50% proportion of one of the two main criteria of interest, body mass index (BMI) or HBA1c level at initiation of GLP-1Ra therapy. Assuming a 5% rate of non evaluable cases, 400 patients had to be enrolled. In order to prevent

selection bias, study subjects were invited to participate among consecutive patients visiting their respective physicians.

Patient inclusion took place during the period between July 2013 and March 2014. No interventional procedure or change in practice was required.

Measurements

Main variables of interest were BMI and blood glycated haemoglobin (HBA1c) level when initiating GLP-1Ra. Other study variables included demographic characteristics (age, gender), weight, height, arterial blood pressure, tobacco use, latest available clinical data (year of DM2 diagnosis, year of first anti-diabetic treatment, DM2-related complications and co-morbidities) prior to GLP-1Ra treatment, name, dosing schedule and date of first prescription of GLP-1Ra, HBA1c target at initiation, anti-diabetic treatments before initiating GLP-1Ra and simultaneously to the GLP-1Ra and latest available biological laboratory results (lipid and renal balance) before GLP-1Ra.

Statistical Analysis

Description of study results are shown as mean (standard deviation) values or as percentages with ranges and/or 95% confidence intervals, as applicable.

Relevant statistical tests were used to compare subgroups depending on type of data. For categorical data, group comparisons were performed by Chi-square provided that number of cases for each modality was >5, otherwise Fisher's exact tests were performed. For continuous data, Student's t test was used after having checked for required data assumptions.

RESULTS

In total, 403 evaluable patients were included by 53 investigators (47 endocrinologists and 6 internal medicine specialists) from 24 outpatient clinics; study sites were located at 10 out of 17 Spanish administrative regions (Autonomous Communities). Patients' characteristics are shown in Table 1. DM2 patients' mean (SD) age was 58.32 (10.4) years, 205 (50.9%) were female and most (96.3%) were born in Spain; all subjects had to be fluent in Spanish. DM2 diagnosis was done 9.92 (7.0) years before GLP-1Ra initiation, mean age at diagnosis was 48.35 (10.3) years and 66.7% used home glucose monitoring with an average of 8.78 (7.6) strips per week.

Table 1. Socio-demographic and clinical characteristics and treatments of patients before initiating GLP-1Ra treatment.

Age, years, mean (SD)		58.32 (10.4)
Sex, male, N (%)		198 (49.1)
Weight, kg. Mean (SD)		97.59 (17.9)
Height, cm. Mean (SD)		164.0 (10.0)
BMI, kg/m2. Mean (SD)		36.22 (5.5)
	Normal 18.5-25 kg/m2. N (%)	1 (0.2)
	Overweight 25-30 kg/m2. N (%)	24 (6.0)
	Obese ≥30 kg/m2. N (%)	378 (93.8)
Waist size, cm. Mean (SD)		114.28 (15.0)
Systolic/diastolic blood pressure, mmHg. Mean (SD)		140.55 (18.0)/80.35 (10.0)
Smoking habit, N (%)		
	Current	55 (13.6)
	Former	136 (33.7)
	Never smoked	212 (52.6)
Glycaemic control		

Fasting blood glucose, g/l. Mean (SD)	1.77 (0.6)
HbA1c %. Mean (SD)	8.41 (1.4)
HbA1c <6.5%. N (%)	24 (6.0)
HbA1c 6.5-7%. N (%)	33 (8.2)
HbA1c 7-8%. N (%)	130 (32.3)
HbA1c >8%. N (%)	216 (53.6)
Lipid parameters. Mean (SD)	
Total cholesterol (g/l)	1.8 (0.4)
HDL cholesterol (g/l)	0.43 (0.1)
LDL cholesterol (g/l)	1.01 (0.3)
Triglycerides (g/l)	1.95 (1.4)
Creatinine clearance, ml/min. Mean (SD)	88.9 (24.1)
Normal ≥90 ml/min. N (%)	160 (46.8)
Mild renal impairment 60-90 ml/min. N (%)	145 (42.4)
Moderate renal impairment 45-60 ml/min. N (%)	30 (8.8)
Moderate renal impairment 30-45 ml/min. N (%)	7 (2.0)
DM2 history	
Time since diagnosis (years). Mean (SD)	9.91 (7.0)
Age at diagnosis (years). Mean (SD)	48.35 (10.3)
Time between DM2 diagnosis and first treatment, N (%)	
Concomitant	261 (81.1)
1 year	18 (5.6)
1-5 years	31 (9.6)
>5 years	12 (3.7)
Anti-diabetic treatment before/after initiation of GLP-1Ra	
OAD only. N (%)	217 (53.8)/223 (55.3)

OAD only, 1 drug. N (%)	76 (35.0)/0
OAD only, 2 drugs. N (%)	83 (38.2)/145 (65.0)
OAD only, 3 drugs. N (%)	52 (24.0) /71 (31.8)
OAD only, ≥4 drugs. N (%)	6 (2.8)/7 (3.1)
Insulin only. N (%)	21 (5.2)/29 (7.2)
OAD + insulin. N (%)	161 (40.0)/146 (36.2)
No anti-diabetic drugs. N (%)	4 (1.0)/5 (1.2)

Most (90.8%) patients presented with at least one current or past self-declared complication or co-morbidity and 47.3% were current or former smokers. Hypertension was present in 71.2% of patients (treated in 95.1% of them) and 70.2% had currently treated dyslipidaemia. Other most frequent complications or patient-declared co-morbidities included renal dysfunction (microalbuminuria in 18.4%, chronic renal insufficiency in 3.2%, proteinuria in 2.5%), ocular disease (diabetic retinopathy in 13.2%), macrovascular complications (myocardial infarction or ischemic heart disease in 13.2%, peripheral vascular disease in 4.5% or stroke in 3.5%), and peripheral neuropathy (5.7%).

At the time of the initiation of GLP-1Ra therapy, the mean (SD) body mass index (BMI) was 36.2 (5.5) kg/m2. As shown on Table 1, most patients (93.8%) were obese and showed a high mean waist size (114.28 cm).

Mean systolic and diastolic blood pressure values were 140.6 mmHg and 80.4 mmHg, respectively, with 43.6% of patients above the WHO-recommended[5] cut-off for hypertension diagnosis (>140 mmHg systolic or > 90 mmHg diastolic).

With regard to the drug prescribed, liraglutide was initiated in 48.6%, lixisenatide in 35.0%, weekly exanetide in 12.9% and daily exanetide in 3.5% of patients (Table 2).

Table 2. GLP-1Ra initiated and unit dose

GLP-1Ra	Dose	Number of patients (% for each drug)
Liraglutide	0.6 mg	29 (14.8)
	1.2 mg	126 (64.3)
	1.8 mg	41 (20.9)
Lixisenatide	10 µg	43 (30.5)
	20 µg	98 (69.5)
Weekly exenatide	2 mg	52 (100)
Exanetide	5 µg	1 (7.1)
	10 µg	13 (92.9)

Fasting blood glucose at GLP-1Ra initiation was available in 92.6% of patients with a mean value of 1.77 g/l (0.6). Mean HbA1c at GLP-1Ra initiation was 8.4 % (1.4) and in 53.6% of patients it was higher than 8%, while it was ≤ 7% in 14.2% of the subjects. Interestingly, patients with HbA1c ≤ 7%, as compared with the rest of the study population, had a higher mean BMI (38.7 vs. 35.8, p<0.001), were more often treated only with OAD before GLP1 analogue initiation (70.2% vs. 51.2%, p=0.0076), and more frequently receiving OAD treatment in monotherapy (50% vs. 31.6%, p=0.0279). Patients with HbA1 ≤ 7% before initiating GLP-1Ra, as compared with the rest of the study population, were more often prescribed weekly exanetide (29.8% vs 10.1%, p=0.0004) and, conversely, less lixisenatide (14.0% vs 38.4%, p=0.0003). Also, they mostly received GLP-1Ra in addition to OAD only (73.7% vs 53.8%, p=0.0049), and received less mixed treatment (OAD + insulin, 22.8% vs 38.4%, p=0.0229).

With respect to the lipids profile, mean values were 1.8 (0.4) g/l for total cholesterol, 0.43 (0.1) g/l for HDL cholesterol, 1.01 (0.3) g/l for LDL cholesterol, and 1.95 (1.4) g/l for triglycerides (Table 1).

Renal function tests showed a mean creatinine clearance of 88.9 (24.1) ml/min; 42.4% of patients presented mild (60-90 ml/min) and 10.8% moderate (30-60 ml/min) renal impairment (Table 1).

The first use of antidiabetic drugs was usually concomitant to diagnosis (81.1% of patients). At study visit, before GLP-1Ra initiation, 53.8% of patients were receiving only an oral antidiabetic (OAD) treatment and 40% had a mixed treatment with both insulin and OAD. 5.2% were only treated by insulin. Of patients only on OAD, most were treated with 2 drugs (38.2%) or a single drug (35%), and 24% received triple therapy (Table 1).

At GLP-1Ra initiation, the most frequent (90.7% of patients) individualized HbA1c target was 7%, however, this could only be recorded from 33% of study subjects.GLP-1Ra were mostly prescribed without any change in main classes of previous antidiabetic therapies (Table 1). In addition to the GLP-1Ra, more than half of patients (55.3%) received only an OAD, 36.2% had a mixed treatment with both insulin and OAD, and only 7.2% were treated with insulin without OAD. Mainly, types of antidiabetic treatments prescribed with the GLP-1Ra were similar to those used before its initiation (Table 3), but some patients already treated with 3 drugs stopped one of their OAD (most frequently DPP-4 inhibitors). Finally, the GLP-1Ra were most frequently prescribed with 2 OAD (65%) or with 3 OAD (31.8%); some patients (3.1%) received 4 different OAD or more.

Table 3. OAD used before and after GLP-1Ra treatment initiation

	n = 217	n = 223
Number of OAD	Before GLP-1Ra	With GLP-1Ra

1	76 (35.0%)	0
2	83 (38.2%)	145 (65.0%)
3	52 (24.0%)	71 (31.8%)
>3	6 (2.8%)	7 (3.1%)
Mean number of OAD (SD)	1.94 (0.8)	2.39 (0.6)
Biguanide		
Metformin	199 (91.7%)	214 (96.0%)
Sulphonylurea		
Gliclazide	47 (21.7%)	41 (18.4%)
Glimepiride	21 (9.7%)	18 (8.1%)
Glibenclamide	9 (4.1%)	-
Other	2 (1.0%)	2 (0.8%)
DPP-IV Inh		
Sitagliptin	57 (26.3%)	2 (0.9%)
Vildagliptin	33 (15.2%)	3 (1.3%)
Other	8 (3.7%)	1 (0.4%)
Metiglinide		
Repaglinide	30 (13.8%)	15 (6.7%)
Glitazone		
Pioglitazone	13 (6.0%)	11 (4.9%)
Alpha glucosidase Inh		
Acarbose	1 (0.5%)	-

DISCUSSION

This study provides demographic and clinical profiles of DM2 patients at the time of initiation of treatment with GLP-1Ra, as well as drug treatment for DM2 before and after initiation of GLP-1Ra in real life clinical practice in Spain. Study investigators were all

specialists (endocrinology and internal medicine) representing the usual setting where GLP-1Ra treatments are initiated in Spain, and participating centres were spread across the country covering 10 out of 17 administrative regions (autonomous communities). Thus, it seems reasonable to assume that the study sample is fairly representative of the overall country population of DM2 patients who were being prescribed GLP-1Ra for the first time during the study period.

Patients' characteristics differ somehow from the average DM2 Spanish population, as compared to recent epidemiological data[4,6-8] from Spain and elsewhere. Our patients were younger (58.3 years), with just slightly higher proportion of females (50.9%), more with obesity (93.8%) and high mean BMI (36.2 kg/m2), as well as mean arterial blood pressure (140.6/80.4 mmHg); more showed renal dysfunction (53.2%) and poor lipid balance (HDL cholesterol <0.5 g/l and LDL cholesterol ≥1 g/l); also, time since DM2 diagnosis was longer (9.9 years) and almost all subjects were on anti-diabetic pharmacological treatment before initiating GLP-1Ra. Glycaemic control was also poor with mean fasting glycaemia of 1.8 g/l and 85.9% of subjects showing HbA1c >7%. Since the reason for treatment change was not recorded (e.g., poor tolerability, compliance issues, patient's request, etc), the reasons for prescribing GLP-1 Ra to patients with HbA1c ≤7% (14.1%) cannot be fully ascertained. However, there are several intriguing findings (higher use of weekly exenatide, lower use of lixisenatide, higher BMI, higher use of OAD therapy in addition to the GLP-1 Ra) that could suggest an aim of weight loss as a primary driver for use, rather than pursuing more glycemic control with weight loss being an added benefit. In addition, with regional payers in Spain limiting reimbursed prescription of GLP-1Ra to patients with BMI above 30 (or 35 kg/m2 in some regions) and with so much emphasis put in the weight reduction potential of this class of drugs, the possibility that this has become a major factor for use in this subgroup cannot be ruled out.

With respect to anti-diabetic treatment prior to GLP-1Ra initiation, a proportion of study subjects was receiving insulin, either in combination with OAD or as single treatment. Compared to the average DM2 patient in Spain, this proportion (45%) is remarkably higher than recently published data (23%)[6], further reflecting that the patients' profiles from our study population represent a sub-set of DM2 individuals with a longer duration of the disease, who are less responsive to anti-diabetic treatment, with a more severe disease course and/or less compliant with disease management, among other possible explanations. All the above characteristics seem to describe a typical DM2 patient with a longer disease course, more risk factors (obesity and high BMI) and more diabetes-related co-morbidities (hypertension, renal dysfunction, hyperlipidemia) than in the average DM2 patient. In Spain, indications for use of GLP-1Ra, as described in the approved prescribing information[9-12], recommend its use when patients do not achieve glycaemic control with full doses of any, among various, OAD without mentioning other specific patient's characteristics or restrictions (except for moderate or severe renal dysfunction, hepatic impairment and use in children). However, these data show that Spanish physicians are initiating GLP1-Ra mostly in advanced DM2 cases, especially in overweight or obese individuals, reflecting current Spanish regional payers restrictions on GLP-1Ra reimbursed prescription only to patients with a BMI > 30 or >35 kg/m2.

With respect to the choice of GLP-1Ra among available drugs in Spain at the time this study was conducted, it should be noticed that two compounds from this class were launched while this study was recruiting patients, weekly exenetide, followed by lixisenatide some time later. Despite its apparent advantage with weekly dosing versus other GLP-1Ra, weekly exanetide was prescribed to 13% of study subjects while lixisenatide, which requires daily injections, was initiated in 35% of patients. Liraglutide, older in the market and also administered as daily injections, was also highly (49%) prescribed during this study. This, together with the

substantial number of individuals receiving insulin in combination with GLP-1Ra, could explain why GLP-1Ra compounds which are approved to be used in combination with insulin, such as lixisenatide and liraglutide, were prescribed more often in this cohort.

Real-life studies are deemed necessary to complement information retrieved with clinical trials. Both have limitations and should be seen as complementary. It is important to understand the strengths and weaknesses of both approaches. The choice of the investigators, the lack of a centralized laboratory, the lack of intensive monitoring among others, hamper the internal validity of real-life studies. The sites and investigators for this study were selected on the basis of being current users of GLP-1 Ra and able to achieve reasonably short start-up times. However, the number of sites and the fact that more than 50% of the Spanish Autonomous Communities (including those with larger populations) were included should provide a fair representativeness of the country's reality. Because of the existence of payers' restrictions to GLP-1 Ra use in Spain, first prescription of these compounds by the Primary Care Physicians was clearly minor at the time of conducting the study. Hence, the predominance of specialist sites may have resulted in some patient selection bias towards a more advanced, complex patient type. However, most guidelines and algorithms tend to place GLP-1 Ra late in the course of the disease, mainly for cost reasons, and most pivotal clinical trials of currently available studies have been conducted with patients with long duration of diabetes, so the bias may not have had as much impact as could be anticipated.

On the other hand, this study is the first effort to assess the clinical and sociodemographic profile of patients receiving an initial prescription of GLP-1 Ra in Spain, in a relevant number of patients and sites.

In conclusion, this study provides an updated description of DM2 patients initiating GLP-1Ra treatment in Spain. Their worse than the average DM2 patient clinical picture probably reflects clinicians behaviour towards limiting GLP-1Ra to more advanced disease, consistent

with payers' restrictions but potentially not totally aligned with the mechanistic background (which would call probably for use earlier in the course of the disease). Also, it may be worth reflecting further on whether emphasis being placed on the weight loss properties of this class of drugs is leading to somewhat forgetting that the primary aim of their use should be, in line with the approved indications, improving glycemic control, with weight loss as a highly desirable added benefit, rather than their major feature.

Acknowledgements

We are indebted to all investigators participating in the study for the collection of data and the provision and care for study patients:

Teresa Muros, Hospital Virgen de las Nieves, Granada

Carmen de la Cuesta, Nuevas Tecnologías en Diabetes y Endocrinología, Sevilla

Miguel Ángel Mangas, Hospital Virgen del Rocío, Sevilla

Cristina Hernández Herrero, Hospital Virgen de la Macarena, Sevilla

Paloma de Castro Hernandez, C.M.E. Ramon y Cajal, Zaragoza

Fernando Gómez Peralta, Hospital General de Segovia, Segovia

José Manuel Miralles García, Hospital Clínico de Salamanca, Salamanca

Encarna Martinez, CAP Centelles, Centelles

Guillem Cuatrecasas, Centro Médico Teknon, Barcelona

Eva Aguilera; Hospital German Trias i Pujol, Badalona

Marga Gimenez/Irene Vinagre, Hospital Clinic, Barcelona

Jordi Anglada, H Mutua de Terrasa, Terrassa

Manuel Pérez Maraver, Hospital de Bellvitge, Hospitalet de Llobregat

Jose Maria Manzanares, Hospital Sant Joan de Reus (Uni Rovira Virgili), Reus

Pablo Fernández Catalina, Hospital Montecelo, Pontevedra

Diego Bellido Guerrero, Hospital Arquitecto Marcide, Ferrol

Alfonso Soto González, Complejo Hospitalario Universitario A Coruña, A Coruña

Felipe Casanueva, Hospital Clínico de Santiago de Compostela,Santiago de Compostela

Lluis Masmiquel, Luis Alberto Gómez, Hospital Son Llatzer, Palma de Mallorca

Honorato García, Iñaqui Arguelles, Hospital Son Espases, Palma de Mallorca

Juan Garcia Puig, Hospital Universitario La Paz, Madrid

Miguel Angel Brito Sanfiel, Hospital Puerta del Hierro, Majadahonda

Francisco Javier Escalada, Clínica U. Navarra (CUN), Pamplona

Sonia Gaztambide, Hospital de Cruces, Barakaldo

Antonio Hernández Mijares, Hospital Dr. Peset, Valencia

Francisco Javier Ampudia-Blasco, Consulta Privada Clínica Alemania, Manises

Carlos Tréscoli, Hospital de la Ribera, Alzira

Francisco Merino Torres, Hospital La Fe, Valencia

Luis de Teresa Parreño, Clínica Mediterránea Neurociencias, Alicante

CEMKA-EVAL and IMS Health provided support in conducting the study. We gratefully acknowledge Dr. Manuel García-Losa of IMS Health for his contribution in medical writing of the manuscript.

Competing interests

All authors have read and understood BMJ policy on declaration of interests and have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf and declare financial support for the submitted work from GlaxoSmithKline and the following interests:

IC: reports receiving lecturing and consulting fees from Medtronic Inc., Bayer AG, GlaxoSmithKline, Eli Lilly & Co., NovoNordisk A/S, Sanofi-Aventis, Novartis, Astra Zeneca and MSD.

DM: speaking and/or consulting fees from Abbott, AstraZeneca, Bristol & MyersSquibb, GlaxoSmithKline, Medtronic, Merck Sharp Dohme, Eli Lilly, Novartis, NovoNordisk and Sanofi.

RO: employed by GlaxoSmithKline, a pharmaceutical company owner of a GLP-1 receptor agonist, which was not in the market at the time of this study.

BD: is employed by CEMKA-EVAL, a consultancy team working for numerous private companies and public national and international institutions in health care.

Funding

This study was funded by GlaxoSmithKline.

Authors contributions

Concept/design: DM, IC, RO, BD; Data analysis/interpretation: DM, IC, RO, BD; Drafting article: DM, IC, RO; Critical revision of article: DM, IC, RO, BD; Approval of article: DM, IC, RO, BD; Statistics: BD; Funding secured by: RO; Data collection: DM, IC.

References

[1] Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27(5):1047-53.

[2] Soriguer F, Goday A, Bosch-Comas A, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. *Diabetologia* 2012;55(1):88-93.

[3] Espelt A, Borrell C, Palència L,et al. Socioeconomic inequalities in the incidence and prevalence of type 2 diabetes mellitus in Europe. *Gac Sanit* 2013;27(6):494-501.

[4] Hall GC, McMahon AD, Dain MP, et al. Primary-care observational database study of the efficacy of GLP-1 receptor agonists and insulin in the UK. *Diabet Med* 2013;30(6):681-6.

[5] Chobanian AV, Bakris GL, Black HR, et al.The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 200321;289(19):2560-72. Epub 2003 May 14.

[6] Vinagre I, Mata-Cases M, Hermosilla E, et al. Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). *Diabetes Care* 2012;35(4):774-9.

[7] Mata-Cases M, Roura-Olmeda P, Berengué-Iglesias M, et al. Fifteen years of continuous improvement of quality care of type 2 diabetes mellitus in primary care in Catalonia, Spain. *Int J Clin Pract* 2012;66(3):289-98.

[8] Rodriguez-Poncelas A, Garre-Olmo J, Franch-Nadal J, et al. Prevalence of chronic kidney disease in patients with type 2 diabetes in Spain: PERCEDIME2 study. *BMC Nephrol* 2013;14:46.

[9] Victoza European Prescribing Information, available at http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf Last accessed 29 September 2014.

[10] Lyxumia European Prescribing Information, available at http://ec.europa.eu/health/documents/community-register/2013/20130201125120/anx_125120_es.pdf Last accessed 29 September 2014.

[11] Byetta European Prescribing Information, available at http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf Last accessed 29 September 2014.

[12] Bydureon European Prescribing Information, available at http://ec.europa.eu/health/documents/community-register/2011/20110617103730/anx_103730_es.pdf Last accessed 29 September 2014.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found OK
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported OK
Objectives	3	State specific objectives, including any prespecified hypotheses OK
Methods		
Study design	4	Present key elements of study design early in the paper OK
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection OK
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants OK
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable OK
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group OK
Bias	9	Describe any efforts to address potential sources of bias OK
Study size	10	Explain how the study size was arrived at OK
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why OK
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding OK
		(*b*) Describe any methods used to examine subgroups and interactions OK
		(*c*) Explain how missing data were addressed OK
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy OK
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed OK
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders OK
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures OK
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included OK
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives OK
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias OK
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence OK
Generalisability	21	Discuss the generalisability (external validity) of the study results OK
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based OK

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Characteristics of Patients with Type 2 Diabetes Mellitus Newly Treated with GLP-1 Receptor Agonists (CHADIG Study): a cross-sectional multicentre study in Spain

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010197.R1
Article Type:	Research
Date Submitted by the Author:	23-Feb-2016
Complete List of Authors:	Conget, Ignacio; Hospital Clinic, Endocrinology and Diabetes Unit Mauricio, Didac; Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Department of Endocrinology & Nutrition Ortega-Basagoiti , Rafael; GSK, Medical Department Detournay, Bruno; CEMKA-EVAL
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Type 2 diabetes mellitus, GLP-1 receptor agonists, Patients' characteristics, Spain

Title

Characteristics of Patients with Type 2 Diabetes Mellitus Newly Treated with GLP-1 Receptor Agonists (CHADIG Study): a cross-sectional multicentre study in Spain

Corresponding Author

Dr. Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain

didacmauricio@gmail.com

Phone: +34. 627953473

Authors

Ignacio Conget

Diabetes Unit, ICMDM Hospital Clínic i Universitari, Barcelona, Spain and CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM).

Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain and CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM).

Rafael Ortega

Medical Director, CV & Metabolism

Medical Department, GlaxoSmithKline, Tres Cantos (Madrid), Spain.

Bruno Detournay

Director, CEMKA-EVAL, Bourg-la-Reine, France

On behalf of the CHADIG Study investigators

Key words:

Type 2 diabetes mellitus - GLP-1 receptor agonists – Patients' characteristics - Spain.

Word count: 3287 words (excluding abstract and front page)

ABSTRACT:

Objective

Several GLP-1 receptor agonists (GLP-1Ra) have been made recently available in Spain for type 2 diabetes mellitus (DM2) treatment. There are no published data on clinical and socio-demographic profile of patients initiating treatment with GLP-1Ra in Spain. Our objective was to understand these patients' characteristics in real world clinical practice.

Design

Cross-sectional, observational study.

Setting

Spanish specialist outpatient clinics.

Participants

403 adults with DM2 initiating GLP-1Ra treatment were included.

Primary and Secondary Outcome Measures

Socio-demographic and DM2-related clinical data, including treatment at and after GLP-1Ra initiation and co-morbidities were collected.

Results

Evaluable patients (n=403; 50.9% female) were included (July 2013-March 2014) at 24 centres by 53 specialists (47 endocrinology, 6 internal medicine), with the following profile:

(value±SD): age (58.3±10.4 years), diabetes duration (9.9±7 years), BMI (36.2±5.5) and HbA1c (8.4±1.4%); 14% had HbA1c ≤ 7%. Previous antidiabetic treatment: 53.8% only Oral Antidiabetic Drugs (OAD), 5.2% insulin and 40% insulin and OAD; of those receiving OAD, 35% single drug, 38.2% two drugs and 24% three drugs. Concomitant to GLP-1 Ra, 55.3% were only on OAD, 36.2% on both insulin and OAD and 7.2% only on insulin. Of those receiving OAD, the GLP-1Ra was mainly associated to one drug (65%) or 2 drugs (31.8%). GLP-1Ra are frequently added to existing antidiabetic drugs, with DPP-4 inhibitors being the OAD most frequently switched (45% receiving one before starting GLP-1Ra, only 2.7% receiving it concomitantly).

Conclusions

In Spain, GLP-1Ra therapy is usually started in combination with OADs or OADs and insulin. These drugs are used in relatively young patients often not reaching therapeutic goals with other treatment combinations, roughly a decade after diagnosis and with a relatively high BMI. The latter could be explained by Spanish regional payers limiting reimbursed prescription to patients with a minimum BMI threshold (>30 in most regions, >35 in some).

Strengths and limitations of this study

- To the best of our knowledge this is the first cross-sectional, non-retrospective effort study trying to find out the profiles of patients receiving initial prescriptions of GLP-1 Ra, since efforts so far have been largely limited to retrospective analyses or physician surveys.
- The study sample is fairly representative of the overall Spanish population of DM2 patients.
- The reason for treatment change was not recorded. Therefore, the reasons for prescribing GLP-1 Ra cannot be fully ascertained.

- Payers' restrictions to GLP-1 Ra in Spain resulted in first prescription mainly done by specialists, which may have resulted in some patient selection bias towards a more advanced, complex patient type.

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a chronic metabolic disorder with worldwide steadily increasing prevalence that is expected to grow in all age-groups worldwide from 2.8% in 2000 to 4.4% in 2030[1]. In Spain, the overall prevalence of diabetes mellitus adjusted for age and sex was estimated in a representative sample of the population to be 13.8%, of which about half (6.0%) had unknown diabetes[2] and, considering the Spanish population, the number of patients with diagnosed diabetes (treated or untreated with drugs) may be estimated to be over 3.6 million people. DM2 prevalence in Spain was estimated at 15.3% in men and 14.2% in women[3].

The short-term aim of therapy for hyperglycemia is improved blood glucose control without significant tolerability or safety issues, and with the longer-term objective of reducing vascular damage. Although most initial pharmacological therapies include an oral glucose-lowering agent, a steady decline in islet beta-cell function results in progressive hyperglycemia, which requires a stepwise escalation of treatment. Eventually insulin is often required as the only therapy independent of the need for endogenous insulin production. Glucagon-like peptide-1 receptor agonists (GLP-1Ra) have recently become a therapeutic option. GLP-1Ra mimic, at supra-physiological levels, the action of endogenous glucagon-like peptide-1, in stimulating glucose-dependent insulin secretion and by suppressing glucagon secretion. Gastric emptying is delayed, especially in the early weeks of therapy. This, and perhaps a direct or indirect hypothalamic action, results in appetite/satiety changes and thus loss of body weight[4].

Despite being on the market since several years ago, little is known about the characteristics of patients treated with GLP-1Ra and about the place of these drugs in DM2 in the real life setting. In fact, we could not find any prospective study aiming at finding out these aspects,

which may be quite relevant. The published literature includes several efforts using retrospective analyses of existing databases[4-7] or physician surveys[8]. Furthermore, current available databases do not provide this information for patients in Spain and in most other countries. Hence, the present the present cross-sectional study was conducted in a real practice environment with the objective of finding and describing the demographic and clinical characteristics of patients with DM2 who receive initial prescriptions of a GLP-1Ra in Spain for the treatment of DM2 and, as such, constitutes a novel approach which may be valuable in learning about the patient profiles and the decision drivers of treating physicians to initiate therapy with a GLP-1 Ra, something which indeed may vary depending on the countries and circumstances.

PATIENTS AND METHODS

Study Design

This was a cross sectional, observational, non-interventional, multicenter study conducted in adult DM2 patients newly treated with GLP-1Ra in Spanish specialist outpatient clinics, since these drugs are mostly initiated in Spain by specialists. The study was approved by Research Ethics Committees from participating centers and was conducted according to the Declaration of Helsinki. All patients signed an informed consent.

Study Population

Participating physicians were invited to record characteristics of consecutive patients attending outpatient specialist clinics since in Spain initial prescriptions of GLP-1 Ra are mostly made by specialists across the country. Patients were included in the study if they: a) were adults (≥ 18 years old) presenting with DM2 and visiting the investigator for any reason; b) were prescribed for the first time a GLP-1Ra the day of inclusion in the normal

course of care, or who had initiated GLP-1Ra therapy within 3 months before the inclusion visit (as long as the study required information was available); and c) provided informed consent in writing to participate. Candidate patients were excluded if they were participating in a study with an investigational drug or procedure.

A sample size of 384 patients was required in order to estimate in the study population, with a confidence interval (95%) of ± 5%, a 50% proportion of one of the two main criteria of interest, body mass index (BMI) or HbA1c level at initiation of GLP-1Ra therapy. Assuming a 5% rate of non evaluable cases, 400 patients had to be enrolled. Patient inclusion took place during the period between July 2013 and March 2014. No interventional procedure or change in practice was required.

Measurements

Main variables of interest were BMI and blood glycated hemoglobin (HBA1c) level when initiating GLP-1Ra. Other study variables included demographic characteristics (age, gender), weight, height, arterial blood pressure, tobacco use, latest available clinical data (year of DM2 diagnosis, year of first anti-diabetic treatment, DM2-related complications and co-morbidities) prior to GLP-1Ra treatment, name, dosing schedule and date of first prescription of GLP-1Ra, HbA1c target at initiation, anti-diabetic treatments before initiating GLP-1Ra and simultaneously to the GLP-1Ra and latest available biological laboratory results (lipid and renal balance) before GLP-1Ra.

Statistical Analysis

Description of study results is shown as mean (standard deviation) values or as percentages with ranges and/or 95% confidence intervals, as applicable.

Relevant statistical tests were used to compare subgroups depending on type of data. For categorical data, group comparisons were performed by Chi-square provided that number of cases for each modality was >5, otherwise Fisher's exact tests were performed. For continuous data, Student's t test was used after having checked for required data assumptions.

RESULTS

In total, 403 evaluable patients were included by 53 investigators (47 endocrinologists and 6 internal medicine specialists) from 24 outpatient clinics; study sites were located at 10 out of 17 Spanish administrative regions (Autonomous Communities). Patients' characteristics are shown in Table 1. DM2 patients' mean (SD) age was 58.32 (10.4) years, 205 (50.9%) were female and most (96.3%) were born in Spain; all subjects had to be fluent in Spanish. DM2 diagnosis was done 9.92 (7.0) years before GLP-1Ra initiation, mean age at diagnosis was 48.35 (10.3) years and 66.7% used home glucose monitoring with an average of 8.78 (7.6) strips per week.

Table 1. Socio-demographic and clinical characteristics and treatments of patients before initiating GLP-1Ra treatment.

Age, years, mean (SD)	58.32 (10.4)
Sex, male, N (%)	198 (49.1)
Weight, kg. Mean (SD)	97.59 (17.9)

Height, cm. Mean (SD)		164.0 (10.0)
BMI, kg/m2. Mean (SD)		36.22 (5.5)
	Normal 18.5-25 kg/m2. N (%)	1 (0.2)
	Overweight 25-30 kg/m2. N (%)	24 (6.0)
	Obese ≥30 kg/m2. N (%)	378 (93.8)
Waist size, cm. Mean (SD)		114.28 (15.0)
Systolic/diastolic blood pressure, mmHg. Mean (SD)		140.55 (18.0)/80.35 (10.0)
Smoking habit, N (%)		
	Current	55 (13.6)
	Former	136 (33.7)
	Never smoked	212 (52.6)
Glycemic control		
	Fasting blood glucose, g/l. Mean (SD)	1.77 (0.6)
	HbA1c %. Mean (SD)	8.41 (1.4)
	HbA1c <6.5%. N (%)	24 (6.0)
	HbA1c 6.5-7%. N (%)	33 (8.2)
	HbA1c 7-8%. N (%)	130 (32.3)
	HbA1c >8%. N (%)	216 (53.6)
Lipid parameters. Mean (SD)		
	Total cholesterol (g/l)	1.8 (0.4)
	HDL cholesterol (g/l)	0.43 (0.1)
	LDL cholesterol (g/l)	1.01 (0.3)
	Triglycerides (g/l)	1.95 (1.4)
Creatinine clearance, ml/min. Mean (SD)		88.9 (24.1)
	Normal ≥90 ml/min. N (%)	160 (46.8)
	Mild renal impairment 60-90 ml/min. N (%)	145 (42.4)

Moderate renal impairment 45-60 ml/min. N (%)	30 (8.8)
Moderate renal impairment 30-45 ml/min. N (%)	7 (2.0)
DM2 history	
Time since diagnosis (years). Mean (SD)	9.91 (7.0)
Age at diagnosis (years). Mean (SD)	48.35 (10.3)
Time between DM2 diagnosis and first treatment, N (%)	
Concomitant	261 (81.1)
1 year	18 (5.6)
1-5 years	31 (9.6)
>5 years	12 (3.7)
Anti-diabetic treatment before/after initiation of GLP-1Ra	
OAD only. N (%)	217 (53.8)/223 (55.3)
OAD only, 1 drug. N (%)	76 (35.0)/0
OAD only, 2 drugs. N (%)	83 (38.2)/145 (65.0)
OAD only, 3 drugs. N (%)	52 (24.0) /71 (31.8)
OAD only, ≥4 drugs. N (%)	6 (2.8)/7 (3.1)
Insulin only. N (%)	21 (5.2)/29 (7.2)
OAD + insulin. N (%)	161 (40.0)/146 (36.2)
No anti-diabetic drugs. N (%)	4 (1.0)/5 (1.2)

Most (90.8%) patients presented with at least one current or past self-declared complication or co-morbidity and 47.3% were current or former smokers. Hypertension was present in 71.2% of patients (treated in 95.1% of them) and 70.2% had currently treated dyslipidaemia. Other most frequent complications or patient-declared co-morbidities included renal dysfunction (microalbuminuria in 18.4%, chronic renal insufficiency in 3.2%, proteinuria in

2.5%), ocular disease (diabetic retinopathy in 13.2%), macrovascular complications (myocardial infarction or ischemic heart disease in 13.2%, peripheral vascular disease in 4.5% or stroke in 3.5%), and peripheral neuropathy (5.7%).

At the time of the initiation of GLP-1Ra therapy, the mean (SD) body mass index (BMI) was 36.2 (5.5) kg/m2. As shown on Table 1, most patients (93.8%) were obese and showed a high mean waist size (114.28 cm).

Mean systolic and diastolic blood pressure values were 140.6 mmHg and 80.4 mmHg, respectively, with 43.6% of patients above the WHO-recommended[9] cut-off for hypertension diagnosis (>140 mmHg systolic or > 90 mmHg diastolic).

With regard to the drug prescribed, liraglutide was initiated in 48.6%, lixisenatide in 35.0%, weekly exenatide in 12.9% and daily exenatide in 3.5% of patients (Table 2).

Table 2. GLP-1Ra initiated and unit dose

GLP-1Ra	Dose	Number of patients (% for each drug)
Liraglutide	0.6 mg	29 (14.8)
	1.2 mg	126 (64.3)
	1.8 mg	41 (20.9)
Lixisenatide	10 µg	43 (30.5)
	20 µg	98 (69.5)
Weekly exenatide	2 mg	52 (100)
Exenatide	5 µg	1 (7.1)
	10 µg	13 (92.9)

Fasting blood glucose at GLP-1Ra initiation was available in 92.6% of patients with a mean value of 1.77 g/l (0.6). Mean HbA1c at GLP-1Ra initiation was 8.4 % (1.4) and in 53.6% of patients it was higher than 8%, while it was ≤ 7% in 14.2% of the subjects. Interestingly,

patients with HbA1c ≤ 7%, as compared with the rest of the study population, had a higher mean BMI (38.7 vs. 35.8, p<0.001), were more often treated only with OAD before GLP1 analogue initiation (70.2% vs. 51.2%, p=0.0076), and more frequently receiving OAD treatment in monotherapy (50% vs. 31.6%, p=0.0279). Patients with HbA1 ≤ 7% before initiating GLP-1Ra, as compared with the rest of the study population, were more often prescribed weekly exenatide (29.8% vs. 10.1%, p=0.0004) and, conversely, less lixisenatide (14.0% vs. 38.4%, p=0.0003). Also, they mostly received GLP-1Ra in addition to OAD only (73.7% vs. 53.8%, p=0.0049), and received less mixed treatment (OAD + insulin, 22.8% vs. 38.4%, p=0.0229).

With respect to the lipids profile, mean values were 1.8 (0.4) g/l for total cholesterol, 0.43 (0.1) g/l for HDL cholesterol, 1.01 (0.3) g/l for LDL cholesterol, and 1.95 (1.4) g/l for triglycerides (Table 1).

Renal function tests showed a mean creatinine clearance of 88.9 (24.1) ml/min; 42.4% of patients presented mild (60-90 ml/min) and 10.8% moderate (30-60 ml/min) renal impairment (Table 1).

The first use of antidiabetic drugs was usually concomitant to diagnosis (81.1% of patients). At study visit, before GLP-1Ra initiation, 53.8% of patients were receiving only an oral antidiabetic (OAD) treatment and 40% had a mixed treatment with both insulin and OAD. 5.2% were only treated by insulin. Of patients only on OAD, most were treated with 2 drugs (38.2%) or a single drug (35%), and 24% received triple therapy (Table 1).

At GLP-1Ra initiation, the most frequent (90.7% of patients) individualized HbA1c target was 7%, however, this could only be recorded from 33% of study subjects.GLP-1Ra were mostly prescribed without any change in main classes of previous antidiabetic therapies (Table 1). In addition to the GLP-1Ra, more than half of patients (55.3%) received only an

OAD, 36.2% had a mixed treatment with both insulin and OAD, and only 7.2% were treated with insulin without OAD. Mainly, types of antidiabetic treatments prescribed with the GLP-1Ra were similar to those used before its initiation (Table 3), but some patients already treated with 3 drugs stopped one of their OAD (most frequently DPP-4 inhibitors). Finally, the GLP-1Ra were most frequently prescribed with 2 OAD (65%) or with 3 OAD (31.8%); some patients (3.1%) received 4 different OAD or more.

Table 3. OAD used before and after GLP-1Ra treatment initiation

	n = 217	n = 223
Number of OAD	Before GLP-1Ra	With GLP-1Ra
1	76 (35.0%)	0
2	83 (38.2%)	145 (65.0%)
3	52 (24.0%)	71 (31.8%)
>3	6 (2.8%)	7 (3.1%)
Mean number of OAD (SD)	1.94 (0.8)	2.39 (0.6)
Biguanide		
Metformin	199 (91.7%)	214 (96.0%)
Sulphonylurea		
Gliclazide	47 (21.7%)	41 (18.4%)
Glimepiride	21 (9.7%)	18 (8.1%)
Glibenclamide	9 (4.1%)	-
Other	2 (1.0%)	2 (0.8%)
DPP-IV Inh		
Sitagliptin	57 (26.3%)	2 (0.9%)
Vildagliptin	33 (15.2%)	3 (1.3%)
Other	8 (3.7%)	1 (0.4%)
Metiglinide		

Repaglinide	30 (13.8%)	15 (6.7%)
	Glitazone	
Pioglitazone	13 (6.0%)	11 (4.9%)
	Alpha glucosidase Inh	
Acarbose	1 (0.5%)	-

DISCUSSION

This study provides demographic and clinical profiles of DM2 patients at the time of initiation of treatment with GLP-1Ra, as well as drug treatment for DM2 before and after initiation of GLP-1Ra in real life clinical practice in Spain. Study investigators were all specialists (endocrinology and internal medicine) representing the usual setting where GLP-1Ra treatments are initiated in Spain, and participating centres were spread across the country covering 10 out of 17 administrative regions (autonomous communities). Thus, it seems reasonable to assume that the study sample is fairly representative of the overall country population of DM2 patients who were being prescribed GLP-1Ra for the first time during the study period.

Patients' characteristics differ somehow from the average DM2 Spanish population, as compared to recent epidemiological data[10-12]. Our patients were younger (58.3 years), with just slightly higher proportion of females (50.9%), more with obesity (93.8%) and high mean BMI (36.2 kg/m2), as well as mean arterial blood pressure (140.6/80.4 mmHg); more showed renal dysfunction (53.2%) and poor lipid balance (HDL cholesterol <0.5 g/l and LDL cholesterol ≥1 g/l); also, time since DM2 diagnosis was longer (9.9 years) and almost all subjects were on anti-diabetic pharmacological treatment before initiating GLP-1Ra. Glycemic control was also poor with mean fasting glycemia of 1.8 g/l and 85.9% of subjects showing HbA1c >7%. Since the reason for treatment change was not recorded (e.g., poor

tolerability, compliance issues, patient's request, etc), the reasons for prescribing GLP-1 Ra to patients with HbA1c ≤7% (14.1%) cannot be fully ascertained. However, there are several intriguing findings (higher use of weekly exenatide, lower use of lixisenatide, higher BMI, higher use of OAD therapy in addition to the GLP-1 Ra) that could suggest an aim of weight loss as a primary driver for use, rather than pursuing more glycemic control with weight loss being an added benefit. In addition, with regional payers in Spain limiting reimbursed prescription of GLP-1Ra to patients with BMI above 30 (or 35 kg/m2 in some regions) and with so much emphasis put in the weight reduction potential of this class of drugs, the possibility that this has become a major factor for use in this subgroup cannot be ruled out.

With respect to anti-diabetic treatment prior to GLP-1Ra initiation, a proportion of study subjects was receiving insulin, either in combination with OAD or as single treatment. Compared to the average DM2 patient in Spain, this proportion (45%) is remarkably higher than recently published data (23%)[10], further reflecting that the patients' profiles from our study population represent a sub-set of DM2 individuals with a longer duration of the disease, who are less responsive to anti-diabetic treatment, with a more severe disease course and/or less compliant with disease management, among other possible explanations. All the above characteristics seem to describe a typical DM2 patient with a longer disease course, more risk factors (obesity and high BMI) and more diabetes-related co-morbidities (hypertension, renal dysfunction, hyperlipidemia) than in the average DM2 patient. In Spain, indications for use of GLP-1Ra, as described in the approved prescribing information[13-16], recommend its use when patients do not achieve glycemic control with full doses of any, among various, OAD without mentioning other specific patient's characteristics or restrictions (except for moderate or severe renal dysfunction, hepatic impairment and use in children). However, these data show that Spanish physicians are initiating GLP1-Ra mostly in advanced DM2 cases, especially in overweight or obese individuals, reflecting current Spanish regional payers restrictions on

GLP-1Ra reimbursed prescription only to patients with a BMI > 30 or >35 kg/m2. In terms of duration of diabetes, this would appear to be in contrast with some recent physician survey in the UK[8], where it would appear that GLP-1RA are used in patients with shorter duration of diabetes. The importance of the need for further glycemic control and weight loss is, in that survey, in line with the findings of the present study.

With respect to the choice of GLP-1Ra among available drugs in Spain at the time this study was conducted, it should be noticed that two compounds from this class were launched while this study was recruiting patients, weekly exenatide, followed by lixisenatide some time later. Despite its apparent advantage with weekly dosing versus other GLP-1Ra, weekly exenatide was prescribed to 13% of study subjects while lixisenatide, which requires daily injections, was initiated in 35% of patients. Liraglutide, older in the market and also administered as daily injections, was also highly (49%) prescribed during this study. This, together with the substantial number of individuals receiving insulin in combination with GLP-1Ra, could explain why GLP-1Ra compounds which are approved to be used in combination with insulin, such as lixisenatide and liraglutide, were prescribed more often in this cohort.

Real-life studies are deemed necessary to complement information retrieved with clinical trials. Both have limitations and should be seen as complementary. It is important to understand the strengths and weaknesses of both approaches. The choice of the investigators, the lack of a centralized laboratory, the lack of intensive monitoring among others, hamper the internal validity of real-life studies. The sites and investigators for this study were selected on the basis of being current users of GLP-1 Ra and able to achieve reasonably short start-up times. However, the number of sites and the fact that more than 50% of the Spanish Autonomous Communities (including those with larger populations) were included should provide a fair representativeness of the country's reality. Because of the existence of payers' restrictions to GLP-1 Ra use in Spain, first prescription of these compounds by the Primary

Care Physicians was clearly minor at the time of conducting the study. Hence, the predominance of specialist sites may have resulted in some patient selection bias towards a more advanced, complex patient type. However, most guidelines and algorithms tend to place GLP-1 Ra late in the course of the disease, mainly for cost reasons, and most pivotal clinical trials of currently available studies have been conducted with patients with long duration of diabetes, so the bias may not have had as much impact as could be anticipated.

On the other hand, this study is the first effort to assess the clinical and sociodemographic profile of patients receiving an initial prescription of GLP-1 Ra in Spain, in a relevant number of patients and sites. Moreover, its , its cross-sectional, non-retrospective nature brings a new and different perspective since the published data so far come from retrospective analyses of databases mostly aiming at assessing comparative efficacy, or to physician surveys providing perceptions of what is behind the decision to prescribe or not a GLP-1 Ra. As such, it should provide valuable insight in learning about such treatment patterns.

In conclusion, this study provides an updated description of DM2 patients initiating GLP-1Ra treatment in Spain. Their worse than the average DM2 patient clinical picture probably reflects clinicians behavior towards limiting GLP-1Ra to more advanced disease, consistent with payers' restrictions but potentially not totally aligned with the mechanistic background (which would call probably for use earlier in the course of the disease). Also, it may be worth reflecting further on whether emphasis being placed on the weight loss properties of this class of drugs is leading to somewhat forgetting that the primary aim of their use should be, in line with the approved indications, improving glycemic control, with weight loss as a highly desirable added benefit, rather than their major feature.

Acknowledgements

We are indebted to all investigators participating in the study. CEMKA-EVAL and IMS Health provided support in conducting the study. CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM) is an initiative from Instituto de Salud Carlos III. We gratefully acknowledge Dr. Manuel García-Losa of IMS Health for his contribution in medical writing of the manuscript; as an employee of IMS Health, Dr. Garcia's editorial assistance was funded by GlaxoSmithKline.

Competing interests

All authors have read and understood BMJ policy on declaration of interests and have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf and declare financial support for the submitted work from GlaxoSmithKline and the following interests:

IC: reports receiving lecturing and consulting fees from Medtronic Inc., Bayer AG, GlaxoSmithKline, Eli Lilly & Co., NovoNordisk A/S, Sanofi-Aventis, Novartis, Astra Zeneca and MSD.

DM: speaking and/or consulting fees from Abbott, AstraZeneca, Bristol & Myers Squibb, GlaxoSmithKline, Medtronic, Merck Sharp Dohme, Eli Lilly, Novartis, NovoNordisk and Sanofi.

RO: employed by GlaxoSmithKline, a pharmaceutical company owner of a GLP-1 receptor agonist, which was not in the market at the time of this study.

BD: is employed by CEMKA-EVAL, a consultancy team working for numerous private companies and public national and international institutions in health care.

Funding

This study was funded by GlaxoSmithKline.

Author's contributions

Concept/design: DM, IC, RO, BD; Data analysis/interpretation: DM, IC, RO, BD; Drafting article: DM, IC, RO; Critical revision of article: DM, IC, RO, BD; Approval of article: DM, IC, RO, BD; Statistics: BD; Funding secured by: RO; Data collection: DM, IC.

Data sharing

No additional data available.

References

[1] Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5):1047-53.

[2] Soriguer F, Goday A, Bosch-Comas A, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. *Diabetologia* 2012; 55(1):88-93.

[3] Espelt A, Borrell C, Palència L, et al. Socioeconomic inequalities in the incidence and prevalence of type 2 diabetes mellitus in Europe. *Gac Sanit* 2013; 27 (6):494-501.

[4] Hall GC, McMahon AD, Dain MP, et al. Primary-care observational database study of the efficacy of GLP-1 receptor agonists and insulin in the UK. *Diabet Med* 2013; 30 (6):681-6.

[5] Pawaskar M, Bonafede M, Johnson B et al. Medication utilization patterns among type 2 diabetes patients initiating Exenatide BID or insulin glargine: a retrospective database study. *BMC Endocrine Disorders* 2013, 13:20.

[6] Evans M, McEwan P, O'Shea R et al. A Retrospective, Case-Note Survey of Type 2 Diabetes Patients Prescribed Incretin-Based Therapies in Clinical Practice. Diabetes Ther (2013) 4:27–40.

[7] Nyeland ME, Ploug UJ, Richards A et al. Evaluation of the effectiveness of liraglutide and sitagliptin in type 2 diabetes: a retrospective study in UK primary care. Int J Clin Pract, March 2015, 69, 3, 281–91.

[8] Matza LS, Curtis S, Jordan J et al. Physician Perceptions of GLP-1 Receptor Agonists in the UK. Curr Med Res Opin. 2016 Jan 25:1-33. [Epub ahead of print]

[9] Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289 (19): 2560-72. Epub 2003 May 14.

[10] Vinagre I, Mata-Cases M, Hermosilla E, et al. Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). Diabetes Care 2012; 35 (4): 774-9.

[11] Mata-Cases M, Roura-Olmeda P, Berengué-Iglesias M, et al. Fifteen years of continuous improvement of quality care of type 2 diabetes mellitus in primary care in Catalonia, Spain. *Int J Clin Pract* 2012; 66 (3): 289-98.

[12] Rodriguez-Poncelas A, Garre-Olmo J, Franch-Nadal J, et al. Prevalence of chronic kidney disease in patients with type 2 diabetes in Spain: PERCEDIME2 study. *BMC Nephrol* 2013; 14:46.

[13] Victoza European Prescribing Information, available at http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf Last accessed 29 September 2014.

[14] Lyxumia European Prescribing Information, available at http://ec.europa.eu/health/documents/community-register/2013/20130201125120/anx_125120_es.pdf Last accessed 29 September 2014.

[15] Byetta European Prescribing Information, available at http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf Last accessed 29 September 2014.

[16] Bydureon European Prescribing Information, available at http://ec.europa.eu/health/documents/community-register/2011/20110617103730/anx_103730_es.pdf Last accessed 29 September 2014.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N / A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	N /A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	N / A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N / A
		(c) Consider use of a flow diagram	N / A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	N / A
Outcome data	15*	Report numbers of outcome events or summary measures	N / A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N / A
		(*b*) Report category boundaries when continuous variables were categorized	N / A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N / A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Characteristics of Patients with Type 2 Diabetes Mellitus Newly Treated with GLP-1 Receptor Agonists (CHADIG Study): a cross-sectional multicentre study in Spain

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010197.R2
Article Type:	Research
Date Submitted by the Author:	15-Apr-2016
Complete List of Authors:	Conget, Ignacio; Hospital Clinic, Endocrinology and Diabetes Unit Mauricio, Didac; Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Department of Endocrinology & Nutrition Ortega-Basagoiti , Rafael; GSK, Medical Department Detournay, Bruno; CEMKA-EVAL
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Type 2 diabetes mellitus, GLP-1 receptor agonists, Patients' characteristics, Spain

Title

Characteristics of Patients with Type 2 Diabetes Mellitus Newly Treated with GLP-1 Receptor Agonists (CHADIG Study): a cross-sectional multicentre study in Spain

Corresponding Author

Dr. Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain

didacmauricio@gmail.com

Phone: +34. 627953473

Authors

Ignacio Conget

Diabetes Unit, ICMDM Hospital Clínic i Universitari, Barcelona, Spain and CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM).

Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute and Hospital Universitari Germans Trias i Pujol, Badalona (Barcelona), Spain and CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM).

Rafael Ortega

Medical Director, CV & Metabolism

Medical Department, GlaxoSmithKline, Tres Cantos (Madrid), Spain.

Bruno Detournay

Director, CEMKA-EVAL, Bourg-la-Reine, France

On behalf of the CHADIG Study investigators

Key words:

Type 2 diabetes mellitus - GLP-1 receptor agonists – Patients' characteristics - Spain.

Word count: 3287 words (excluding abstract, front page and references)

ABSTRACT:

Objective

Several GLP-1 receptor agonists (GLP-1Ra) have been made recently available in Spain for type 2 diabetes mellitus (DM2) treatment. There are no published data on clinical and socio-demographic profile of patients initiating treatment with GLP-1Ra in Spain. Our objective was to understand these patients' characteristics in real world clinical practice.

Design

Cross-sectional, observational study.

Setting

Spanish specialist outpatient clinics.

Participants

403 adults with DM2 initiating GLP-1Ra treatment were included.

Primary and Secondary Outcome Measures

Socio-demographic and DM2-related clinical data, including treatment at and after GLP-1Ra initiation and co-morbidities were collected.

Results

Evaluable patients (n=403; 50.9% female) were included (July 2013-March 2014) at 24 centres by 53 specialists (47 endocrinology, 6 internal medicine), with the following profile:

(value±SD): age (58.3±10.4 years), diabetes duration (9.9±7 years), BMI (36.2±5.5) and HbA1c (8.4±1.4%); 14% had HbA1c ≤ 7%. Previous antidiabetic treatment: 53.8% only Oral Antidiabetic Drugs (OAD), 5.2% insulin and 40% insulin and OAD; of those receiving OAD, 35% single drug, 38.2% two drugs and 24% three drugs. Concomitant to GLP-1 Ra, 55.3% were only on OAD, 36.2% on both insulin and OAD and 7.2% only on insulin. Of those receiving OAD, the GLP-1Ra was mainly associated to one drug (65%) or 2 drugs (31.8%). GLP-1Ra are frequently added to existing antidiabetic drugs, with DPP-4 inhibitors being the OAD most frequently switched (45% receiving one before starting GLP-1Ra, only 2.7% receiving it concomitantly).

Conclusions

In Spain, GLP-1Ra therapy is usually started in combination with OADs or OADs and insulin. These drugs are used in relatively young patients often not reaching therapeutic goals with other treatment combinations, roughly a decade after diagnosis and with a relatively high BMI. The latter could be explained by Spanish regional payers limiting reimbursed prescription to patients with a minimum BMI threshold (>30 in most regions, >35 in some).

Strengths and limitations of this study

- To the best of our knowledge this is the first cross-sectional effort trying to find out the profiles of patients receiving initial prescriptions of GLP-1 Ra, since efforts so far have been largely limited to retrospective analyses or physician surveys.
- The study sample is fairly representative of the overall Spanish population of DM2 patients.
- The reason for treatment change was not recorded. Therefore, the reasons for prescribing GLP-1 Ra cannot be fully ascertained.

- Payers' restrictions to GLP-1 Ra in Spain resulted in first prescription mainly done by specialists, which may have resulted in some patient selection bias towards a more advanced, complex patient type.

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a chronic metabolic disorder with worldwide steadily increasing prevalence that is expected to grow in all age-groups worldwide from 2.8% in 2000 to 4.4% in 2030[1]. In Spain, the overall prevalence of diabetes mellitus in adults adjusted for age and sex was estimated in a representative sample of the population to be 13.8%, of which about half (6.0%) had unknown diabetes[2] and, considering the Spanish population, the number of patients with diagnosed diabetes (treated or untreated with drugs) may be estimated to be over 3.6 million people. Total (known and unknown) DM2 prevalence in Spain was estimated at 15.3% in men and 14.2% in women[3].

The short-term aim of therapy for hyperglycemia is improved blood glucose control without significant tolerability or safety issues, and with the longer-term objective of reducing vascular damage. Although most initial pharmacological therapies include an oral glucose-lowering agent, a steady decline in islet beta-cell function results in progressive hyperglycemia, which requires a stepwise escalation of treatment. Eventually insulin is often required as the only therapy independent of the need for endogenous insulin production. Glucagon-like peptide-1 receptor agonists (GLP-1Ra) have recently become a therapeutic option. GLP-1Ra mimic, at supra-physiological levels, the action of endogenous glucagon-like peptide-1, in stimulating glucose-dependent insulin secretion and by suppressing glucagon secretion. Gastric emptying is delayed, especially in the early weeks of therapy. This, and perhaps a direct or indirect hypothalamic action, results in appetite/satiety changes and thus loss of body weight[4].

Despite being on the market since several years ago, little is known about the characteristics of patients treated with GLP-1Ra and about the place of these drugs in DM2 in the real life setting. In fact, we could not find any prospective study aiming at finding out these aspects,

which may be quite relevant. The published literature includes several efforts using retrospective analyses of existing databases[4-7] or physician surveys[8]. Furthermore, current available databases do not provide this information for patients in Spain and in most other countries. Hence, the present the present cross-sectional study was conducted in a real practice environment with the objective of finding and describing the demographic and clinical characteristics of patients with DM2 who receive initial prescriptions of a GLP-1Ra in Spain for the treatment of DM2 and, as such, constitutes a novel approach which may be valuable in learning about the patient profiles and the decision drivers of treating physicians to initiate therapy with a GLP-1 Ra, something which indeed may vary depending on the countries and circumstances.

PATIENTS AND METHODS

Study Design

This was a cross sectional, observational, non-interventional, multicenter study conducted in adult DM2 patients newly treated with GLP-1Ra in Spanish specialist outpatient clinics, since these drugs are mostly initiated in Spain by specialists. The study was approved by Research Ethics Committees from participating centers and was conducted according to the Declaration of Helsinki. All patients signed an informed consent.

Study Population

Participating physicians were invited to record characteristics of consecutive patients attending outpatient specialist clinics since in Spain initial prescriptions of GLP-1 Ra are mostly made by specialists across the country. Patients were included in the study if they: a) were adults (≥ 18 years old) presenting with DM2 and visiting the investigator for any reason; b) were prescribed for the first time a GLP-1Ra the day of inclusion in the normal

course of care, or who had initiated GLP-1Ra therapy within 3 months before the inclusion visit (as long as the study required information was available); and c) provided informed consent in writing to participate. Candidate patients were excluded if they were participating in a study with an investigational drug or procedure.

A sample size of 384 patients was required in order to estimate in the study population, with a confidence interval (95%) of ± 5%, a 50% proportion of one of the two main criteria of interest, body mass index (BMI) or HbA1c level at initiation of GLP-1Ra therapy. Assuming a 5% rate of non evaluable cases, 400 patients had to be enrolled. Patient inclusion took place during the period between July 2013 and March 2014. No interventional procedure or change in practice was required.

Measurements

Main variables of interest were BMI and blood glycated hemoglobin (HBA1c) level when initiating GLP-1Ra. Other study variables included demographic characteristics (age, gender), weight, height, arterial blood pressure, tobacco use, latest available clinical data (year of DM2 diagnosis, year of first anti-diabetic treatment, DM2-related complications and co-morbidities) prior to GLP-1Ra treatment, name, dosing schedule and date of first prescription of GLP-1Ra, HbA1c target at initiation, anti-diabetic treatments before initiating GLP-1Ra and simultaneously to the GLP-1Ra and latest available biological laboratory results (lipid and renal balance) before GLP-1Ra.

Statistical Analysis

Description of study results is shown as mean (standard deviation) values or as percentages with ranges and/or 95% confidence intervals, as applicable.

Relevant statistical tests were used to compare subgroups depending on type of data. For categorical data, group comparisons were performed by Chi-square provided that number of cases for each modality was >5, otherwise Fisher's exact tests were performed. For continuous data, Student's t test was used after having checked for required data assumptions.

RESULTS

In total, 403 evaluable patients were included by 53 investigators (47 endocrinologists and 6 internal medicine specialists) from 24 outpatient clinics; study sites were located at 10 out of 17 Spanish administrative regions (Autonomous Communities). Patients' characteristics are shown in Table 1. DM2 patients' mean (SD) age was 58.32 (10.4) years, 205 (50.9%) were female and most (96.3%) were born in Spain; all subjects had to be fluent in Spanish. DM2 diagnosis was done 9.92 (7.0) years before GLP-1Ra initiation, mean age at diagnosis was 48.35 (10.3) years and 66.7% used home glucose monitoring with an average of 8.78 (7.6) strips per week.

Table 1. Socio-demographic and clinical characteristics and treatments of patients before initiating GLP-1Ra treatment.

Age, years, mean (SD)	58.32 (10.4)
Sex, male, N (%)	198 (49.1)
Weight, kg. Mean (SD)	97.59 (17.9)

Height, cm. Mean (SD)		164.0 (10.0)
BMI, kg/m2. Mean (SD)		36.22 (5.5)
	Normal 18.5-25 kg/m2. N (%)	1 (0.2)
	Overweight 25-30 kg/m2. N (%)	24 (6.0)
	Obese ≥30 kg/m2. N (%)	378 (93.8)
Waist size, cm. Mean (SD)		114.28 (15.0)
Systolic/diastolic blood pressure, mmHg. Mean (SD)		140.55 (18.0)/80.35 (10.0)
Smoking habit, N (%)		
	Current	55 (13.6)
	Former	136 (33.7)
	Never smoked	212 (52.6)
Glycemic control		
	Fasting blood glucose, g/l. Mean (SD)	1.77 (0.6)
	HbA1c %. Mean (SD)	8.41 (1.4)
	HbA1c <6.5%. N (%)	24 (6.0)
	HbA1c 6.5-7%. N (%)	33 (8.2)
	HbA1c 7-8%. N (%)	130 (32.3)
	HbA1c >8%. N (%)	216 (53.6)
Lipid parameters. Mean (SD)		
	Total cholesterol (g/l)	1.8 (0.4)
	HDL cholesterol (g/l)	0.43 (0.1)
	LDL cholesterol (g/l)	1.01 (0.3)
	Triglycerides (g/l)	1.95 (1.4)
Creatinine clearance, ml/min. Mean (SD)		88.9 (24.1)
	Normal ≥90 ml/min. N (%)	160 (46.8)
	Mild renal impairment 60-90 ml/min. N (%)	145 (42.4)

Moderate renal impairment 45-60 ml/min. N (%)	30 (8.8)
Moderate renal impairment 30-45 ml/min. N (%)	7 (2.0)
DM2 history	
Time since diagnosis (years). Mean (SD)	9.91 (7.0)
Age at diagnosis (years). Mean (SD)	48.35 (10.3)
Time between DM2 diagnosis and first treatment, N (%)	
Concomitant	261 (81.1)
1 year	18 (5.6)
1-5 years	31 (9.6)
>5 years	12 (3.7)
Anti-diabetic treatment before/after initiation of GLP-1Ra	
OAD only. N (%)	217 (53.8)/223 (55.3)
OAD only, 1 drug. N (%)	76 (35.0)/0
OAD only, 2 drugs. N (%)	83 (38.2)/145 (65.0)
OAD only, 3 drugs. N (%)	52 (24.0) /71 (31.8)
OAD only, ≥4 drugs. N (%)	6 (2.8)/7 (3.1)
Insulin only. N (%)	21 (5.2)/29 (7.2)
OAD + insulin. N (%)	161 (40.0)/146 (36.2)
No anti-diabetic drugs. N (%)	4 (1.0)/5 (1.2)

Most (90.8%) patients presented with at least one current or past self-declared complication or co-morbidity and 47.3% were current or former smokers. Hypertension was present in 71.2% of patients (treated in 95.1% of them) and 70.2% had currently treated dyslipidaemia. Other most frequent complications or patient-declared co-morbidities included renal dysfunction (microalbuminuria in 18.4%, chronic renal insufficiency in 3.2%, proteinuria in

2.5%), ocular disease (diabetic retinopathy in 13.2%), macrovascular complications (myocardial infarction or ischemic heart disease in 13.2%, peripheral vascular disease in 4.5% or stroke in 3.5%), and peripheral neuropathy (5.7%).

At the time of the initiation of GLP-1Ra therapy, the mean (SD) body mass index (BMI) was 36.2 (5.5) kg/m2. As shown on Table 1, most patients (93.8%) were obese and showed a high mean waist size (114.28 cm).

Mean systolic and diastolic blood pressure values were 140.6 mmHg and 80.4 mmHg, respectively, with 43.6% of patients above the WHO-recommended[9] cut-off for hypertension diagnosis (>140 mmHg systolic or > 90 mmHg diastolic).

With regard to the drug prescribed, liraglutide was initiated in 48.6%, lixisenatide in 35.0%, weekly exenatide in 12.9% and daily exenatide in 3.5% of patients (Table 2).

Table 2. GLP-1Ra initiated and unit dose

GLP-1Ra	Dose	Number of patients (% for each drug)
Liraglutide	0.6 mg	29 (14.8)
	1.2 mg	126 (64.3)
	1.8 mg	41 (20.9)
Lixisenatide	10 µg	43 (30.5)
	20 µg	98 (69.5)
Weekly exenatide	2 mg	52 (100)
Exenatide	5 µg	1 (7.1)
	10 µg	13 (92.9)

Fasting blood glucose at GLP-1Ra initiation was available in 92.6% of patients with a mean value of 1.77 g/l (0.6). Mean HbA1c at GLP-1Ra initiation was 8.4 % (1.4) and in 53.6% of patients it was higher than 8%, while it was ≤ 7% in 14.2% of the subjects. Interestingly,

patients with HbA1c ≤ 7%, as compared with the rest of the study population, had a higher mean BMI (38.7 vs. 35.8, p<0.001), were more often treated only with OAD before GLP1 analogue initiation (70.2% vs. 51.2%, p=0.0076), and more frequently receiving OAD treatment in monotherapy (50% vs. 31.6%, p=0.0279). Patients with HbA1 ≤ 7% before initiating GLP-1Ra, as compared with the rest of the study population, were more often prescribed weekly exenatide (29.8% vs. 10.1%, p=0.0004) and, conversely, less lixisenatide (14.0% vs. 38.4%, p=0.0003). Also, they mostly received GLP-1Ra in addition to OAD only (73.7% vs. 53.8%, p=0.0049), and received less mixed treatment (OAD + insulin, 22.8% vs. 38.4%, p=0.0229).

With respect to the lipids profile, mean values were 1.8 (0.4) g/l for total cholesterol, 0.43 (0.1) g/l for HDL cholesterol, 1.01 (0.3) g/l for LDL cholesterol, and 1.95 (1.4) g/l for triglycerides (Table 1).

Renal function tests showed a mean creatinine clearance of 88.9 (24.1) ml/min; 42.4% of patients presented mild (60-90 ml/min) and 10.8% moderate (30-60 ml/min) renal impairment (Table 1).

The first use of antidiabetic drugs was usually concomitant to diagnosis (81.1% of patients). At study visit, before GLP-1Ra initiation, 53.8% of patients were receiving only an oral antidiabetic (OAD) treatment and 40% had a mixed treatment with both insulin and OAD. 5.2% were only treated by insulin. Of patients only on OAD, most were treated with 2 drugs (38.2%) or a single drug (35%), and 24% received triple therapy (Table 1).

At GLP-1Ra initiation, the most frequent (90.7% of patients) individualized HbA1c target was 7%, however, this could only be recorded from 33% of study subjects.GLP-1Ra were mostly prescribed without any change in main classes of previous antidiabetic therapies (Table 1). In addition to the GLP-1Ra, more than half of patients (55.3%) received only an

OAD, 36.2% had a mixed treatment with both insulin and OAD, and only 7.2% were treated with insulin without OAD. Mainly, types of antidiabetic treatments prescribed with the GLP-1Ra were similar to those used before its initiation (Table 3), but some patients already treated with 3 drugs stopped one of their OAD (most frequently DPP-4 inhibitors). Finally, the GLP-1Ra were most frequently prescribed with 2 OAD (65%) or with 3 OAD (31.8%); some patients (3.1%) received 4 different OAD or more.

Table 3. OAD used before and after GLP-1Ra treatment initiation

	n = 217	n = 223
Number of OAD	Before GLP-1Ra	With GLP-1Ra
1	76 (35.0%)	0
2	83 (38.2%)	145 (65.0%)
3	52 (24.0%)	71 (31.8%)
>3	6 (2.8%)	7 (3.1%)
Mean number of OAD (SD)	1.94 (0.8)	2.39 (0.6)
Biguanide		
Metformin	199 (91.7%)	214 (96.0%)
Sulphonylurea		
Gliclazide	47 (21.7%)	41 (18.4%)
Glimepiride	21 (9.7%)	18 (8.1%)
Glibenclamide	9 (4.1%)	-
Other	2 (1.0%)	2 (0.8%)
DPP-IV Inh		
Sitagliptin	57 (26.3%)	2 (0.9%)
Vildagliptin	33 (15.2%)	3 (1.3%)
Other	8 (3.7%)	1 (0.4%)
Metiglinide		

Repaglinide	30 (13.8%)	15 (6.7%)
	Glitazone	
Pioglitazone	13 (6.0%)	11 (4.9%)
	Alpha glucosidase Inh	
Acarbose	1 (0.5%)	-

DISCUSSION

This study provides demographic and clinical profiles of DM2 patients at the time of initiation of treatment with GLP-1Ra, as well as drug treatment for DM2 before and after initiation of GLP-1Ra in real life clinical practice in Spain. Study investigators were all specialists (endocrinology and internal medicine) representing the usual setting where GLP-1Ra treatments are initiated in Spain, and participating centres were spread across the country covering 10 out of 17 administrative regions (autonomous communities). Thus, it seems reasonable to assume that the study sample is fairly representative of the overall country population of DM2 patients who were being prescribed GLP-1Ra for the first time during the study period.

Patients' characteristics differ somehow from the average DM2 Spanish population, as compared to recent epidemiological data[10-12]. Our patients were younger (58.3 years), with just slightly higher proportion of females (50.9%), more with obesity (93.8%) and high mean BMI (36.2 kg/m2), as well as mean arterial blood pressure (140.6/80.4 mmHg); more showed renal dysfunction (53.2%) and poor lipid balance (HDL cholesterol <0.5 g/l and LDL cholesterol ≥1 g/l); also, time since DM2 diagnosis was longer (9.9 years) and almost all subjects were on anti-diabetic pharmacological treatment before initiating GLP-1Ra. Glycemic control was also poor with mean fasting glycemia of 1.8 g/l and 85.9% of subjects showing HbA1c >7%. Since the reason for treatment change was not recorded (e.g., poor

tolerability, compliance issues, patient's request, etc), the reasons for prescribing GLP-1 Ra to patients with HbA1c ≤7% (14.1%) cannot be fully ascertained. However, there are several intriguing findings (higher use of weekly exenatide, lower use of lixisenatide, higher BMI, higher use of OAD therapy in addition to the GLP-1 Ra) that could suggest an aim of weight loss as a primary driver for use, rather than pursuing more glycemic control with weight loss being an added benefit. In addition, with regional payers in Spain limiting reimbursed prescription of GLP-1Ra to patients with BMI above 30 (or 35 kg/m2 in some regions) and with so much emphasis put in the weight reduction potential of this class of drugs, the possibility that this has become a major factor for use in this subgroup cannot be ruled out.

With respect to anti-diabetic treatment prior to GLP-1Ra initiation, a proportion of study subjects was receiving insulin, either in combination with OAD or as single treatment. Compared to the average DM2 patient in Spain, this proportion (45%) is remarkably higher than recently published data (23%)[10], further reflecting that the patients' profiles from our study population represent a sub-set of DM2 individuals with a longer duration of the disease, who are less responsive to anti-diabetic treatment, with a more severe disease course and/or less compliant with disease management, among other possible explanations. All the above characteristics seem to describe a typical DM2 patient with a longer disease course, more risk factors (obesity and high BMI) and more diabetes-related co-morbidities (hypertension, renal dysfunction, hyperlipidemia) than in the average DM2 patient. In Spain, indications for use of GLP-1Ra, as described in the approved prescribing information[13-16], recommend its use when patients do not achieve glycemic control with full doses of any, among various, OAD without mentioning other specific patient's characteristics or restrictions (except for moderate or severe renal dysfunction, hepatic impairment and use in children). However, these data show that Spanish physicians are initiating GLP1-Ra mostly in advanced DM2 cases, especially in overweight or obese individuals, reflecting current Spanish regional payers restrictions on

GLP-1Ra reimbursed prescription only to patients with a BMI > 30 or >35 kg/m2. In terms of duration of diabetes, this would appear to be in contrast with some recent physician survey in the UK[8], where it would appear that GLP-1RA are used in patients with shorter duration of diabetes. The importance of the need for further glycemic control and weight loss is, in that survey, in line with the findings of the present study.

With respect to the choice of GLP-1Ra among available drugs in Spain at the time this study was conducted, it should be noticed that two compounds from this class were launched while this study was recruiting patients, weekly exenatide, followed by lixisenatide some time later. Despite its apparent advantage with weekly dosing versus other GLP-1Ra, weekly exenatide was prescribed to 13% of study subjects while lixisenatide, which requires daily injections, was initiated in 35% of patients. Liraglutide, older in the market and also administered as daily injections, was also highly (49%) prescribed during this study. This, together with the substantial number of individuals receiving insulin in combination with GLP-1Ra, could explain why GLP-1Ra compounds which are approved to be used in combination with insulin, such as lixisenatide and liraglutide, were prescribed more often in this cohort.

Real-life studies are deemed necessary to complement information retrieved with clinical trials. Both have limitations and should be seen as complementary. It is important to understand the strengths and weaknesses of both approaches. The choice of the investigators, the lack of a centralized laboratory, the lack of intensive monitoring among others, hamper the internal validity of real-life studies. The sites and investigators for this study were selected on the basis of being current users of GLP-1 Ra and able to achieve reasonably short start-up times. However, the number of sites and the fact that more than 50% of the Spanish Autonomous Communities (including those with larger populations) were included should provide a fair representativeness of the country's reality. Because of the existence of payers' restrictions to GLP-1 Ra use in Spain, first prescription of these compounds by the Primary

Care Physicians was clearly minor at the time of conducting the study. Hence, the predominance of specialist sites may have resulted in some patient selection bias towards a more advanced, complex patient type. However, most guidelines and algorithms tend to place GLP-1 Ra late in the course of the disease, mainly for cost reasons, and most pivotal clinical trials of currently available studies have been conducted with patients with long duration of diabetes, so the bias may not have had as much impact as could be anticipated.

On the other hand, this study is the first effort to assess the clinical and sociodemographic profile of patients receiving an initial prescription of GLP-1 Ra in Spain, in a relevant number of patients and sites. Moreover, its cross-sectional nature brings a new and different perspective since the published data so far come from retrospective analyses of databases mostly aiming at assessing comparative efficacy, or to physician surveys providing perceptions of what is behind the decision to prescribe or not a GLP-1 Ra. As such, it should provide valuable insight in learning about such treatment patterns.

In conclusion, this study provides an updated description of DM2 patients initiating GLP-1Ra treatment in Spain. Their worse than the average DM2 patient clinical picture probably reflects clinicians behavior towards limiting GLP-1Ra to more advanced disease, consistent with payers' restrictions but potentially not totally aligned with the mechanistic background (which would call probably for use earlier in the course of the disease). Also, it may be worth reflecting further on whether emphasis being placed on the weight loss properties of this class of drugs is leading to somewhat forgetting that the primary aim of their use should be, in line with the approved indications, improving glycemic control, with weight loss as a highly desirable added benefit, rather than their major feature.

Acknowledgements

We are indebted to all investigators participating in the study. CEMKA-EVAL and IMS Health provided support in conducting the study. CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM) is an initiative from Instituto de Salud Carlos III. We gratefully acknowledge Dr. Manuel García-Losa of IMS Health for his contribution in medical writing of the manuscript; as an employee of IMS Health, Dr. Garcia's editorial assistance was funded by GlaxoSmithKline.

Competing interests

All authors have read and understood BMJ policy on declaration of interests and have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf and declare financial support for the submitted work from GlaxoSmithKline and the following interests:

IC: reports receiving lecturing and consulting fees from Medtronic Inc., Bayer AG, GlaxoSmithKline, Eli Lilly & Co., NovoNordisk A/S, Sanofi-Aventis, Novartis, Astra Zeneca and MSD.

DM: speaking and/or consulting fees from Abbott, AstraZeneca, Bristol & Myers Squibb, GlaxoSmithKline, Medtronic, Merck Sharp Dohme, Eli Lilly, Novartis, NovoNordisk and Sanofi.

RO: employed by GlaxoSmithKline, a pharmaceutical company owner of a GLP-1 receptor agonist, which was not in the market at the time of this study.

BD: is employed by CEMKA-EVAL, a consultancy team working for numerous private companies and public national and international institutions in health care.

Funding

This study was funded by GlaxoSmithKline.

Author's contributions

Concept/design: DM, IC, RO, BD; Data analysis/interpretation: DM, IC, RO, BD; Drafting article: DM, IC, RO; Critical revision of article: DM, IC, RO, BD; Approval of article: DM, IC, RO, BD; Statistics: BD; Funding secured by: RO; Data collection: DM, IC.

Data Sharing

No additional data available.

References

[1] Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5):1047-53.

[2] Soriguer F, Goday A, Bosch-Comas A, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. *Diabetologia* 2012; 55(1):88-93.

[3] Espelt A, Borrell C, Palència L, et al. Socioeconomic inequalities in the incidence and prevalence of type 2 diabetes mellitus in Europe. *Gac Sanit* 2013; 27 (6):494-501.

[4] Hall GC, McMahon AD, Dain MP, et al. Primary-care observational database study of the efficacy of GLP-1 receptor agonists and insulin in the UK. *Diabet Med* 2013; 30 (6):681-6.

[5] Pawaskar M, Bonafede M, Johnson B et al. Medication utilization patterns among type 2 diabetes patients initiating Exenatide BID or insulin glargine: a retrospective database study. *BMC Endocrine Disorders* 2013, 13:20.

[6] Evans M, McEwan P, O'Shea R et al. A Retrospective, Case-Note Survey of Type 2 Diabetes Patients Prescribed Incretin-Based Therapies in Clinical Practice. Diabetes Ther (2013) 4:27–40.

[7] Nyeland ME, Ploug UJ, Richards A et al. Evaluation of the effectiveness of liraglutide and sitagliptin in type 2 diabetes: a retrospective study in UK primary care. Int J Clin Pract, March 2015, 69, 3, 281–91.

[8] Matza LS, Curtis S, Jordan J et al. Physician Perceptions of GLP-1 Receptor Agonists in the UK. Curr Med Res Opin. 2016 Jan 25:1-33. [Epub ahead of print]

[9] Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289 (19): 2560-72. Epub 2003 May 14.

[10] Vinagre I, Mata-Cases M, Hermosilla E, et al. Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). Diabetes Care 2012; 35 (4): 774-9.

[11] Mata-Cases M, Roura-Olmeda P, Berengué-Iglesias M, et al. Fifteen years of continuous improvement of quality care of type 2 diabetes mellitus in primary care in Catalonia, Spain. *Int J Clin Pract* 2012; 66 (3): 289-98.

[12] Rodriguez-Poncelas A, Garre-Olmo J, Franch-Nadal J, et al. Prevalence of chronic kidney disease in patients with type 2 diabetes in Spain: PERCEDIME2 study. *BMC Nephrol* 2013; 14:46.

[13] Victoza European Prescribing Information, available at http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf Last accessed 29 September 2014.

[14] Lyxumia European Prescribing Information, available at http://ec.europa.eu/health/documents/community-register/2013/20130201125120/anx_125120_es.pdf Last accessed 29 September 2014.

[15] Byetta European Prescribing Information, available at http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf Last accessed 29 September 2014.

[16] Bydureon European Prescribing Information, available at http://ec.europa.eu/health/documents/community-register/2011/20110617103730/anx_103730_es.pdf Last accessed 29 September 2014.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N / A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	N /A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	N / A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	N / A
		(c) Consider use of a flow diagram	N / A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	N / A
Outcome data	15*	Report numbers of outcome events or summary measures	N / A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N / A
		(*b*) Report category boundaries when continuous variables were categorized	N / A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N / A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Correction

Conget I, Mauricio D, Ortega R on behalf of the CHADIG Study investigators, *et al*. Characteristics of patients with type 2 diabetes mellitus newly treated with GLP-1 receptor agonists (CHADIG Study): a cross-sectional multicentre study in Spain. *BMJ Open* 2016;**6:**e010197. doi: 10.1136/bmjopen-2015-010197

Four of the Collaborator names were written incorrectly. 'Francisco Merino Torres' should have been written 'Juan Francisco Merino-Torres', 'Fernando Gómez Peralta' as 'Fernando Gomez-Peralta', 'Diego Bellido Guerrero' as 'Diego Bellido' and 'Miguel Ángel Mangas' as 'Miguel Angel Mangas-Cruz'.

BMJ Open 2017;**7**:e010197corr1. doi:10.1136/bmjopen-2015-010197corr1