Study Report

Observational Single-cohort Data Base Study of Dapagliflozin Utilization in Europe

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Table of Contents

1. ABSTRACT

Title

Observational Single-cohort Data Base Study of Dapagliflozin Utilization in Europe

Keywords

Dapagliflozin, drug utilization study, Europe (UK, Germany and Spain)

Rationale and background

This drug utilization study (DUS) is being conducted as part of the Dapagliflozin Risk Management Plan. Per regulatory request, this study is being conducted to describe the patients using dapagliflozin in routine clinical practice in Europe.

Research question and objectives

Primary objective: To describe the characteristics of European patients newly prescribed dapagliflozin by age, sex, dapagliflozin dose, country, selected co-morbidities, and selected concomitant medications.

The proposed drug utilization study will specifically describe dapagliflozin use in:

- patients > 75 years of age,
- combination use with loop diuretics or pioglitazone,
- patients with a known history of moderate or severe renal impairment
- patients with a known history of kidney failure,
- patients lacking a diagnostic code indicating type 2 diabetes.

Study design

This is an observational single-cohort data base study with descriptive data analyses among patients receiving dapagliflozin within electronic medical records (EMRs) in Europe. The study describes the utilization pattern of dapagliflozin during the first 3.5 years after marketing authorization and launch in Europe. This report is the final analysis performed on patients prescribed dapagliflozin from January 2013 through June 2016 except for Germany where data was not available after December 2015.

Setting

The UK, Germany and Spain.

Subjects and study size, including dropouts

All patients identified in the database(s) with at least 12 months presence in the database (baseline period) who received at least one dapagliflozin prescription during the study period with no records of dapagliflozin prescriptions during the baseline period.

Variables and data sources

IMS Health Longitudinal Patient Databases (LPDs) come directly from physicians' EMRs. Participating physicians use the data provider (Cegedim) software to record their daily patient interactions and data are transmitted regularly to the coordinating center where they are cleaned and de-identified.

Outcomes include:

- Patient demographics: age, sex, country,
- Baseline history of type 2 diabetes,
- Baseline history of moderate or severe renal impairment,
- Renal failure
- Concomitant medications at baseline and during dapagliflozin use.

Results

During the study period, we identified 8409 dapagliflozin users in the UK, 1715 in Germany and 1692 in Spain. More than 98% of patients had a type 2 diabetes diagnosis prior to or on the dapagliflozin prescription date and only one patient in Spain was less than 18 years of age. Moderate (3.1%, 9.4% and 6.1% respectively in UK, Germany and Spain) or severe renal impairment (0.1%, 0.2% and 0.2% respectively in UK, Germany and Spain) and renal failure (0.0%, 9.6% and 0.5% respectively in UK, Germany and Spain) were rare as was prescribing of loop diuretics (7.6%, 15.1% and 9.2% respectively in UK, Germany and Spain) and pioglitazone medication (8.1%, 0.5% and 1.1% respectively in UK, Germany and Spain) . In the UK, 5.4% of patients were over 75 years of age, 9% in Spain, and less than 19% of the patients in Germany.

Discussion

In the UK, Germany and Spain, 93.0%, 74.1% and 88.3% of patients were found to have been prescribed dapagliflozin in accordance with the European labeled indications, respectively. Most prescriptions written to patients outside of label recommendations were to patients greater than 75 years old when receiving a dapagliflozin prescription.

Marketing Authorisation Holder(s)

AstraZeneca

Names and affiliations of principal investigators

[redacted]

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomic Therapeutic Chemical
CSD	Cegedim Strategic Data
CrCl	Creatinine Clearance
DPP-4	Dipeptidyl Peptidase 4 Inhibitors
DUS	Drug Utilization Study
eGFR	Estimated Glomerular Filtration Rate
GLP-1	Glucagon-like Peptide 1
GP	General Practitioner
LPD	Longitudinal Patient Databases
OAD	Oral Antidiabetic Drug
SGLT-2	Sodium Glucose Co-transporter
SD	Standard Deviation
sMDRD	Simplified Modification of Diet in Renal Diseases
T2DM	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
UK	United Kingdom

3. INVESTIGATORS

[redacted]
IMS Health
[redacted]

4. OTHER RESPONSIBLE PARTIES

[redacted]
Bristol-Myers Squibb
[redacted]

5. MILESTONES

The first interim analysis included patients newly prescribed dapagliflozin from launch (January 2013) through June 2014. The second interim analysis included patients newly treated with dapagliflozin between July 2014 and June 2015 and patients prescribed dapagliflozin during the first interim analysis 1. This final report includes patients newly prescribed dapagliflozin from July 2015 through June 2016 (December 2015 for Germany, because the German database was not available after December 2015) and patients that were prescribed dapagliflozin during the first and second interim periods.

Table 5-1: Milestones

Milestone	Expected Planned Date	Actual Date	Comments
Registration in the EU PAS register	12-Jun-2013	21-Apr-2016	
Interim report 1	04-Dec-2015	04-Dec-2015	Actual date is date of PBRER submission
Interim report 2	15-Mar-2016	18-Nov 2016	
Final report of study results	28-Feb-2017		

6. RATIONALE AND BACKGROUND

Dapagliflozin is a highly potent, selective, and reversible inhibitor of the human renal sodium glucose co-transporter (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion making it a member of an emerging therapeutic class in the treatment of type 2 diabetes mellitus (T2DM).

Dapagliflozin is indicated in adults aged 18 years and older with T2DM to improve glycaemic control as:

- Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom metformin is considered inappropriate due to intolerance.
- Add-on combination therapy in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

According to the summary of product characteristics (SmPC), the recommended posology and method of administration are the following:

- The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose lowering medications including insulin. When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.
- Dapagliflozin can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

The following precautions for use must be taken for the following special populations:

- Renal impairment: The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2). No dosage adjustment is indicated in patients with mild renal impairment.

- Hepatic impairment: No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.
- Elderly (≥ 65 years of age): In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.
- Patients at risk for hypotension due to effect of dapagliflozin on diuresis and blood pressure: Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients. For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Two products containing dapagliflozin have market approval, Forxiga™ in 5 and 10 mg tablets and Xigduo™ a fixed dose combination (FDC) tablet containing dapagliflozin and metformin in 5 mg / 850 mg (metformin hydrochloride) and 5 mg / 1,000 mg (metformin hydrochloride) tablets. This DUS is being conducted as part of the Dapagliflozin Risk Management Plan. Per regulatory request, this study is being conducted to describe the patients using dapagliflozin in routine clinical practice in Europe, specifically the countries reporting to IMS Health' data source: Belgium, France, Germany, Italy, Spain and United Kingdom. IMS Health Longitudinal Patient Databases, LPDs (LPDs) were selected because they include data across 6 different European countries. However, a post-approval analysis of dapagliflozin patients is not possible until country-level reimbursement for dapagliflozin is widely granted. Reimbursement for dapagliflozin was achieved in 2013 for the United Kingdom and Germany. Reimbursement has yet to be granted for Belgium and France and has only recently been granted for Italy and Spain. Spain has been included in the study while the number of patients in Italy was not enough as of the date of this report to allow a robust analysis.

7. RESEARCH QUESTION AND OBJECTIVES

Research question 1: What are the baseline characteristics of the patients prescribed dapagliflozin in Europe?

Research question 2: What proportion of patients prescribed dapagliflozin has baseline moderate to severe renal impairment or kidney failure?

Research question 3: What proportion of patients prescribed dapagliflozin is 75 years of age or older at the time of the index prescription?

Research question 4: What proportion of patients prescribed dapagliflozin is also user of loop diuretics or pioglitazone during the baseline period and the available follow-up period?

Research Question 5: What proportion of patients prescribed dapagliflozin does not have a diagnosis of type 2 diabetes mellitus during the baseline period or on the index date?

8. AMENDMENTS AND UPDATES

Initially, analyses were planned at 18, 30 and 42 months from launch of dapagliflozin. Reimbursement has yet to be granted for Belgium and France and has only recently been granted for Italy and Spain. Spain has

been included in the study while the number of patients in Italy was not enough as of the date of this report to allow a robust analysis. Given the date of reimbursement Spain was introduced in the analysis of the second and third wave, thus analyses were done at 18 and 30 months from dapagliflozin launch in Spain. In the German database, data were not available after December 2015 thus analyses were done at 18, 30 and 36 months from dapagliflozin launch in Germany.

9. RESEARCH METHODS

9.1. Study Design

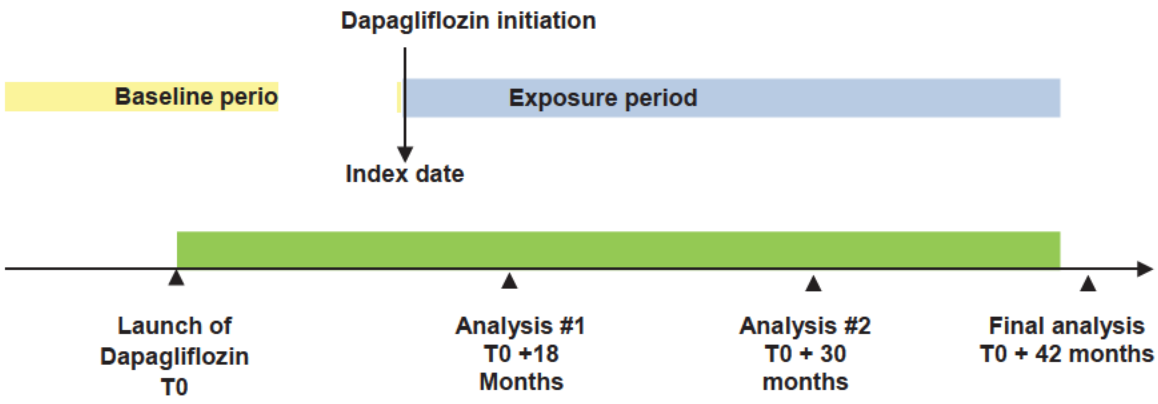
This is a cross-sectional observational cohort study with descriptive data analyses among patients receiving dapagliflozin within the IMS Health LPDs EMRs in Europe. The assessment of combination use with loop diuretics or pioglitazone incorporated longitudinal follow-up. This final study report describes the utilization pattern of dapagliflozin during the first three and a half years after marketing authorization and launch in Europe. Specifically the countries reporting to the data source include the UK, Germany and Spain. Initially analyses were planned at 18, 30 and 42 months from launch of dapagliflozin. However in Spain analyses were done at 18 and 30 months from dapagliflozin launch and analyses were done at 18, 30 and 36 months from dapagliflozin launch in Germany.

9.2. Setting

This study took place in primary care setting in the UK, Germany and Spain.

Relevant dates for the study are presented in Figure 9.2-1.The “prescription index date” for each patient included in the study was defined as the date a patient is first prescribed dapagliflozin. This report is the final analysis performed on patients included in the period between January 2013 and June 2016 or December 2015 for Germany.

Figure 9.2-1: Study Period



9.3. Subjects

Inclusion and Exclusion Criteria

The study population consisted of new users of dapagliflozin who met the inclusion criteria noted below. New users of dapagliflozin are defined as patients who do not have any previous prescriptions for dapagliflozin recorded in the medical record.

- All patients identified in the database who received at least one dapagliflozin prescription during the study period (between T0 and T0+30 months).
- Enrolled in the IMS Health databases for at least 1 year prior to the first prescription of dapagliflozin (baseline time period).

There were no study exclusion criteria.

Follow-up of subjects

The follow-up period was used to identify concomitant use of dapagliflozin with loop diuretics or pioglitazone to address research question 4. Follow-up begins on the date a patient is prescribed dapagliflozin (i.e., index date) and continues until the discontinuation of dapagliflozin (i.e., the final day of the days' supply for the last prescription for dapagliflozin). Because a person may not start taking the prescription on the day the prescription is recorded, 30 days were added to the follow-up time. Once a new user of dapagliflozin discontinues his/her treatment at any time (could also include an interruption in treatment), he/she is not identified in future analyses. The baseline period was defined as one year prior to the index date of each individual.

9.4. Variables

Demographic, medical history, treatment, clinical and clinical laboratory data on patients included in this study were collected from each database.

9.4.1. Assessment of independent variables

All patients included in this study had exposure to dapagliflozin. For eligible patients, use of dapagliflozin (Forxiga™ or Xigduo™) was defined by the date of first dapagliflozin prescription in the database.

9.4.2. Assessment of dependent variables

Table 9.4.2-1 includes the characteristics and definitions of how dapagliflozin users are categorized and described.

Table 9.4.2-1: Categorization of Dapagliflozin Users

Characteristic	Definition
Patient Demographics, at initiation of dapagliflozin use:	
Age categories	< 45, 45-59, 60-74, ≥75
Sex	Male or Female
BMI	< 18, 18-25, ≥ 25
Country	UK, Germany and Spain
Concomitant medications during the baseline period:≥	Loop diuretics Pioglitazone (Actos, Glustin) Biguanides Sulfonamide derivates Dipeptidyl peptidase 4 inhibitors (DPP-4s) Glucagon-like peptide 1 (GLP-1) Alpha glucosidase inhibitors Insulin
Co-morbidities during the baseline period:	
Baseline history of moderate renal impairment	CrCl or eGFR[a] value between 30 and 60
Baseline history of severe renal impairment	CrCl or eGFR[a] value < 30
Type 2 diabetes mellitus	Diagnosis codes for T2DM or prescription for an antiglycemic medication[b]
Others co-morbidities recorded during the patient's entire history:	
Congestive heart failure	Diagnosis codes for congestive heart failure
Hypertension	Diagnosis codes for hypertension
Baseline history of renal failure	Diagnosis codes for end stage renal disease or dialysis
Dapagliflozin Dose, at initiation of dapagliflozin use:	Forxiga • 10 mg • 5 mg Xigduo • 5 mg / 850 mg (metformin hydrochloride) • 5 mg / 1,000 mg (metformin hydrochloride)
Study populations	Patients meeting one of the following criteria: • Less than 18 years old on index date • 75 years of age or older on index date • No diagnostic codes for type 2 diabetes mellitus, at or before the initiation of dapagliflozin use[b] • Baseline history of moderate renal impairment (see definition above)

Table 9.4.2-1: Categorization of Dapagliflozin Users

Characteristic	Definition
	• Baseline history of severe renal impairment (see definition above) • Baseline history of renal failure (see definition above)

[a] If there was no measurement within one year before index date (baseline period), the renal impairment was set as missing. eGFR was estimated by the creatinine clearance calculated by means of the Cockcroft & Gault formula[1] when not available in the data base.

[b] T2DM patients were identified in the LPD bases using the following algorithm:

Step 1: If a patient has a diagnosis for T2DM or a prescription for an oral hyperglycemic medication (OAD) or glucagon-like peptide 1 receptor agonist (GLP-1) recorded during the baseline period, the patient is identified as T2DM.

Step 2: If a patient has a type 1 diagnosis or a prescription for insulin but does not have a prescription for an OAD or GLP-1 recorded during the baseline period, the patient is identified as type 1 diabetes.

Step 3: If a patient does not fall into either of the categories above, the patient's diabetic status is identified as unknown.

9.5. Data Sources and Measurement

This study requires data sources that longitudinally capture patient demographics, prescription information, diagnosis codes, and available laboratory data, in order to assess concurrent use during baseline period and follow up.

LPDs owned by IMS Health include data from 5.8 million active patients in Belgium, France, Germany, Italy, the UK and Spain. In the UK, the database is known as The Health Improvement Network (THIN).

Physicians using proprietary software for management of their practice are asked to take part in LPDs. If the practice agrees to participate, they are asked to provide additional services and in return receive a discount on the price for their software subscription. A nationally representative panel in terms of age, gender and geographical region is extracted from the pool of all participating physicians using the quota sampling method. All LPD data are strictly anonymous and no direct interaction is possible with the physician, who is free to prescribe any product he/she deems necessary for his/her patient.

The LPDs collect medical information from the proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in EMRs. In each country, a panel of physicians using this software volunteer to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in these countries. The panel of contributing physicians is maintained as a representative sample of the primary care physician population in each country according to age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, in most countries, the patient population is representative of the respective country population according to age and sex distribution, as provided by national statistical authorities.

Content of the LPDs

Data are entered during usual patient care and submitted daily to the coordinating center, cleaned and de-identified. The following anonymized patient data collected from General Practitioners (GP) were extracted from the databases:

- Demographics (year of birth, gender, registration dates);
- Medical History (event dates, diagnosis, symptoms, risk factors, co-morbidities, prescription);
- Treatments (indication, molecule/brand, dosage, posology, date and length of prescription);
- Clinical Data (height, weight, blood pressure, life habits);
- Clinical laboratory tests, X-ray and other investigations (not available in Germany).

Patient data collected by IMS Health in each country participating in the LPDs varies to some extent to accommodate local needs. However, all countries collect data on medical co-morbidities and outcomes, prescriptions, demographics, and physician characteristics.

Table 9.5-1: Physician and patient populations, and data coding conventions in IMS Health LPD Germany, UK and Spain

	Germany	UK	Spain
Number of physicians in the panel	550	1780	300
Average number of patients who consulted GP at least once in a year	620,000	3,200,000	320,000
Percent of the national population (Eurostat :http://epp.eurostat.ec.europa.eu)	0.8%	5.0%	0.7%
Drug code dictionary	Abdata	Multilex	Vademecum
Therapy classification	ATC[a]	British National Formulary (BNF)	ATC
Disease classification	ICD-10[b]	Read Codes	CIAP Mapped to ICD-9

[a]ATC = Anatomical Therapeutic Chemical classification system

[b]ICD = International Classification of Disease

9.6. Bias

Selection Bias

In order to more precisely describe the characteristics of European patients prescribed dapagliflozin (specifically baseline renal impairment), a minimum of 12 months (365 days) of medical history in the LPD is required prior to index date. Health care utilization patterns are best described when they include data from all potential prescribers of the drug. In this instance, the LPD data source does not capture prescriptions written in the specialist setting/hospitals; therefore, selection bias is possible if GPs prescribe dapagliflozin to a different patient population than a physician in a specialist setting. In the UK, the GP is a 'gatekeeper' of information for the patient and thus may be aware of and receive reports of health care visits or events taking place outside the GP setting. Thus, in the UK this selection bias may be less pronounced and the UK THIN database can be used to estimate that selection bias in other databases.

Misclassification Bias

Misclassification bias can arise if study subjects are not categorized correctly with regards to exposure or selected patient characteristics. We expect minimal misclassification with respect to exposure since this is determined from each database's prescribing records. However, actual adherence to dapagliflozin or other antidiabetic agent cannot be confirmed. Further, misclassification as to whether the patient is a new initiator could exist (1) if providers supplied samples of dapagliflozin for varying duration to patients, at no cost, and with no record in the database and (2) if dapagliflozin was initiated by a specialist. This will vary by country and database, and could result in varying results across countries.

9.7. Study Size

This is a descriptive study that describes and quantifies dapagliflozin use according to selected patient characteristics; therefore, no formal sample size calculations were conducted.

9.8. Data Transformation

Calculation of BMI: If the body mass index (BMI) was not available for a patient but a measure of weight was available within 12 months prior to the first dapagliflozin dispensing and a measure of height was available at any time prior to the first dapagliflozin dispensing, BMI was calculated using the following formula:

BMI= Weight (Kg) / Height (m) ^{2}

Calculation of estimated Glomerular Filtration Rate (eGFR): eGFR was estimated by the creatinine clearance calculated by means of the Cockcroft & Gault formula[1] when not available in the database.

Since race information was not available in the LPDs, when GFR was not available as such in the database, it was estimated by creatinine clearance (CR_{cl}). When CR_{cl} was not available in the LPD, it was estimated by means of the Cockcroft and Gault formula:

CR_{cl} = Estimated creatinine clearance (ml/min.)
Age = Age in years
Weight = Body weight (Kg)
[Cr] = creatinine Serum (µmol/L)
k = 1.23 for men, 1.04 for women

$$Cl_{Cr} = \frac{(140 - Age) \xi Weight}{[Cr]} \xi k$$

Alternatively, and in order to be able to estimate a renal impairment for patients for whom a creatinine serum value was available while no value of weight could be found in the baseline period, we used the Simplified Modification of Diet in Renal Diseases (sMDRD) equation.[2]

$$\text{s}MDRD = \left(186 \xi Serum\_Creatinine[mg/dl]^{-1\,154} \xi Age[years]^{-0\,203} \xi 0.742[if\_female]\right)$$

Creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4.

9.9. Statistical Methods

9.9.1. Main Summary Measures

The study is strictly descriptive; no formal statistical testing was done. All analyses were conducted using Statistical Analysis Software (SAS) Enterprise Guide 6.1 (SAS 9.2) by IMS Health France.

9.9.2. Main Statistical Methods

9.9.2.1. Primary Objective

This is a study describing the characteristics of European patients newly prescribed dapagliflozin by age, sex, dapagliflozin dose, country, selected co-morbidities, and selected concomitant medications.

The study will specifically describe dapagliflozin use in:

- patients > 75 years of age,
- combination use with loop diuretics or pioglitazone,
- patients with a known history of moderate or severe renal impairment,
- patients with a known history of kidney failure,
- patients lacking a diagnostic code indicating type 2 diabetes.

Descriptive statistics were calculated to describe baseline characteristics among dapagliflozin initiators. These characteristics include age group, sex, initial dapagliflozin dose, country, BMI, eGFR, selected co-morbidities, selected concomitant medications, and available results of laboratory testing.

Categorical variables were described by frequencies and percentages (relative to the non-missing data). For each class, number of missing values was presented. Quantitative variables were described with number of observed data, mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), and number of missing values.

9.9.2.2. Secondary Objectives

Not applicable.

9.9.3. Missing Values

Missing data were not imputed. Analyses were performed on data available. Variables in Table 9.4.2-1 were examined for missing versus non-missing data on BMI and eGFR.

9.9.4. Sensitivity Analyses

In order to assess the effect of excluding patients prescribed dapagliflozin but not included because of enrollment less than one year before index date, these patients were counted and their main characteristics at index date (age, gender, BMI) were described together with the characteristics of patients included in the study.

In order to assess the impact of missing data, key variables (e.g, BMI and eGFR) were checked by describing patients with and without missing values, respectively, regarding basic characteristics available for all or most patients, including age, gender, country, co-medication and co-morbidity.

Because of the likelihood of some degree of allocation bias, comparative statistical testing was not performed, avoiding the danger of spurious statistically significant findings with the numbers of people studied.

9.9.5. Amendments to the Statistical Analysis Plan

Not applicable.

9.10. Quality Control

Data collected are collected by physicians in usual routine practice into the patient EMR. Since data are collected directly by physicians and uploaded in an anonymized way, it is not possible to refer back to patient files and perform any site quality control.

Information is recorded by the physicians whenever they deem it relevant for their clinical practice and some information may be partially available.

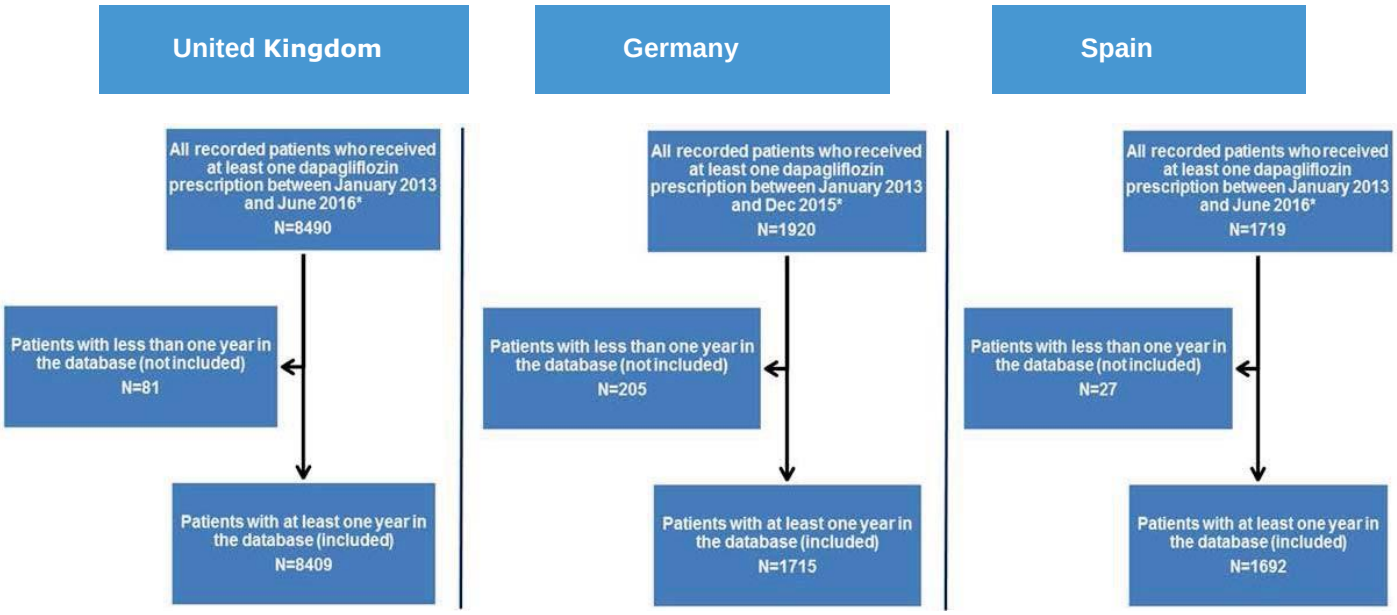
10. RESULTS

10.1. Participants

During the final analysis period (January 2013 through June 2016 for UK and Spain; January 2013 through December 2015 for Germany), 8490 patients were identified in the UK, 1920 in Germany and 1719 in Spain as having received at least one prescription of dapagliflozin (and without a previous prescription of dapagliflozin in their medical records during the baseline period) (Figure 10.1-1). Among these patients, 81 patients in the UK , 205 patients in Germany and 27 patients in Spain had less than one year of history in the database prior to the first prescription of dapagliflozin and were excluded from the analyses.

Therefore, 11816 patients including 8409 in the UK, 1715 in Germany and 1692 in Spain met the inclusion criteria.

Figure 10.1-1: Flowchart of the study population in each country



The characteristics of the patients that were excluded because they had less than one year of baseline in the databases were compared to the ones that were included in the study (Table 10.1-1). No statistical testing was performed due to the low sample size of excluded patients (N=81, 0.95% for the UK; N=205, 10. 7% for Germany and N=27, 1.57% for Spain).

Table 10.1-1 Characteristics of patients with and without one year of baseline

		UK		Germany		Spain	
		Patients included N=8409 n (%)	**Patients not included N=81 n (%)**	**Patients included N=1715 n (%)**	**Patients not included N=205 n (%)**	**Patients included N=1692 n (%)**	**Patients not included N=27 n (%)**
Age (years)	N	8409 (100.0%)	81 (100.0%)	1687 (98.4%)	205 (100.0%)	1688 (99.8%)	26 (96.3%)
	Mean (SD)	58.2 (10.7)	55.7 (12.3)	64.3 (11.1)	61.3 (11.7)	61.4 (10.4)	57.8 (15.0)
	Median	58.0	57.0	65.0	61.0	62.0	58.5
	Q1 - Q3	[51.0 , 66.0]	[50.0 , 64.0]	[57.0 , 72.0]	[54.0 , 70.0]	[55.0 , 69.0]	[52.0 , 65.0]
	Missing (N)	0	0	28	0	4	1
Age group (years)	<45	837 (10.0%)	16 (19.8%)	69 (4.1%)	17 (8.3%)	103 (6.1%)	4 (15.4%)
	45-59	3413 (40.6%)	29 (35.8%)	426 (25.3%)	62 (30.2%)	514 (30.5%)	9 (34.6%)
	60-74	3709 (44.1%)	32 (39.5%)	884 (52.4%)	101 (49.3%)	917 (54.3%)	10 (38.5%)
	≥ 75	450 (5.4%)	4 (4.9%)	308 (18.3%)	25 (12.2%)	154 (9.1%)	3 (11.5%)
	Missing (N)	0	0	28	0	4	1
Sex	Male	4875 (58.0%)	49 (60.5%)	979 (57.2%)	119 (58.0%)	968 (57.6%)	18 (90.0%)
	Female	3532 (42.0%)	32 (39.5%)	734 (42.8%)	86 (42.0%)	713 (42.4%)	2 (10.0%)
	Missing (N)	2	0	2	0	11	7
BMI (kg/m²)	N	7822 (93.0%)	47 (58.0%)	485 (28.3%)	31 (15.1%)	1040 (61.5%)	13 (48.1%)
	Mean (SD)	34.4 (6.7)	33.3 (7.9)	33.0 (6.0)	36.2 (8.4)	33.2 (5.9)	31.9 (7.8)
	Median	33.4	32.0	32.2	35.8	32.3	32.5
	Q1 - Q3	[29.6 , 38.3]	[28.3 , 35.8]	[28.8 , 36.4]	[30.8 , 39.5]	[29.1 , 36.4]	[24.9 , 35.0]
	Missing (N)	587	34	1230	174	652	14
BMI (kg/m²)	<18	1 (0.0%)	0	0	0	0	0
	18-25	420 (5.4%)	4 (8.5%)	29 (6.0%)	1 (3.2%)	55 (5.3%)	4 (30.8%)
	≥ 25	7401 (94.6%)	43 (91.5%)	456 (94.0%)	30 (96.8%)	985 (94.7%)	9 (69.2%)
	Missing (N)	587	34	1230	174	652	14

10.2. Descriptive Data

Research question 1: What are the baseline characteristics of the patients prescribed dapagliflozin in Europe?

Table 10.2-1 shows the characteristics of the subjects included by country. Most patients received a prescription for Forxiga (99.0% in the UK, 72.0% in Germany and 67.0% in Spain) and most often received the 10 mg dosage (100,0% in Spain, 85.9% in the UK, 95.5% in Germany). Among patients receiving Xigduo, the main dosage prescribed was 5 mg of dapagliflozin combined with 1,000 mg of metformin hydrochloride in the UK and Germany.

The median age of patients was higher in Germany than in Spain and the UK (65 years versus 62 and 58 years in Spain and the UK, respectively). Only 29.3% (N=495) of patients were under 60 years of age in Germany versus 36.5%.2 (N=617) in Spain and 50.5% (N=4250) in the UK. A smaller proportion of the patients prescribed dapagliflozin were aged 75 years or over in the UK (N=450, 5.4%) than in Spain (N=154, 9.1%) and Germany (N=308, 18.3%). Over half of the dapagliflozin users were men (58.0% in the UK, 57.2% in Germany and 57.6% in Spain) and the majority of the study population (94.6% in the UK, 94.0% in Germany and 94.7% in Spain) were overweight (BMI ≥25 kg/m2).

The majority of dapagliflozin users were identified as T2DM patients (N=8374, 99.6% in the UK, N=1683, 98.1% in Germany and N=1669, 98.6% in Spain). A small proportion of patients were found to meet the criteria for type 1 diabetes 0.3% (N=28) in the UK, 0.9% (N=15) in Germany and 1.1% (N=18) in Spain. Additionally, 17 (1.0%) patients in Germany, 5 (0.3%) patients in Spain and 7(0.1%) patients in the UK had no known history of either Type 1 or Type 2 diabetes (“unknown” status in Table 10.2-1**)**.

More than half of patients in the UK (N=4522, 53.8%) and a large majority of the patients in Germany (N=1435, 83.7%) had a diagnosis of hypertension while the corresponding proportion was 39.2% (N=663) in Spain. None of the patients in Germany, 60 (3.5%) in Spain and 53 (0.6%) patients in the UK had been diagnosed with congestive heart failure.

Table 10.2-1: Description of the population at inclusion

		United Kingdom N=8409 n (%)	Germany N=1715 n (%)	Spain N=1692 n (%)
Initial exposure	Forxiga	8327 (99.0%)	1234 (72.0%)	1133 (67.0%)
	Xigduo [a]	82 (1.0%)	481 (28.0%)	559 (33.0%)
Initial dapagliflozin dose	Forxiga			
	10 mg	7153 (85.9%)	1178 (95.5%)	1133 (100.0%)
	5 mg	1174 (14.1%)	56 (4.5%)	0 (0.0%)
	Xigduo			
	5 mg/1,000 mg	69 (84.1%)	409 (85.0%)	275 (49.2%)
	5 mg/850 mg	13 (15.9%)	72 (15.0%)	284 (50.8%)
Age (years)	N	8409 (100.0%)	1687 (98.4%)	1688 (99.7%)
	Mean (SD)	58.2 (10.7)	64.3 (11.1)	61.4 (10.4)
	Median	58.0	65.0	62.0
	Q1 - Q3	[51.0 , 66.0]	[57.0 , 72.0]	[55.0 , 69.0]
	Missing (N)	0	28	4
Age group (years)	<45	837 (10.0%)	69 (4.1%)	103 (6.1%)
	45-59	3413 (40.6%)	426 (25.3%)	514 (30.5%)
	60-74	3709 (44.1%)	884 (52.4%)	917 (54.3%)
	≥ 75	450 (5.4%)	308 (18.3%)	154 (9.1%)
	Missing (N)	0	28	4
Sex	Male	4875 (58.0%)	979 (57.2%)	968 (57.6%)
	Female	3532 (42.0%)	734 (42.8%)	713 (42.4%)
	Missing (N)	2	2	11
BMI (kg/m²)	<18	1 (0.0%)	0 (0.0%)	0 (0.0%)
	18-25	420 (5.4%)	29 (6.0%)	55 (5.3%)
	≥ 25	7401 (94.6%)	456 (94.0%)	985 (94.7%)
	Missing (N)	587	1230	652
Type 2 diabetes mellitus[b]	No	28 (0.3%)	15 (0.9%)	18 (1.1%)
	Yes	8374 (99.6%)	1683 (98.1%)	1669 (98.6%)
	Unknown	7 (0.1%)	17 (1.0%)	5 (0.3%)
Congestive heart failure	No	8356 (99.4%)	1715 (100.0%)	1632 (96.5%)
	Yes	53 (0.6%)	0 (0.0%)	60 (3.5%)
Hypertension	No	3887 (46.2%)	280 (16.3%)	1029 (60.8%)
	Yes	4522 (53.8%)	1435 (83.7%)	663 (39.2%)

[a] Dapagliflozin and metformin hydrochloride in 5mg/850mg and 5mg/1000mg tablets

[b] Yes = Type 2 diabetes mellitus, No = Type 1 diabetes, Unknown = Unknown reported diagnosis over the baseline period

Table 10.2-2 shows the frequency of select concomitant medications prescribed during the baseline period. During the baseline period, 7.6% (N=640) in the UK, 9.2% (N=156) in Spain and 15.1% (N=259) of the patients in Germany received loop diuretics. Pioglitazone was prescribed during the baseline period to 8.1% (N=678) of the patients in the UK, and to 1.1% (N=19) and to 0.5% (N=9) of the patients in Spain and Germany, respectively.

In the UK, a majority of patients (N=7259, 86.3%) received a biguanide. Sulfonamide derivates, dipeptidyl peptidase 4 inhibitors (DPP-4s) and GLP-1s were prescribed to 47.6% (N=4004), 39.0% (N=3281) and 18.8% (N=1577) of UK patients, respectively. Insulin was prescribed to 22.2% (N=1864) of patients.

In Germany, biguanide was prescribed to less than half of the patients (N=759, 44.3%) and more than a third of patients (N=586, 34.2%) received insulin. Sulfonamide derivates, DPP-4s and GLP-1s were prescribed to 15.8% (N=271), 18.5% (N=317) and 9.2% (N=157) of the German patients, respectively.

In Spain, a majority of patients (N=980, 57.9%) received a biguanide. Sulfonamide derivates, DPP-4s and GLP-1s were prescribed to 30.4% (N=515), 12.9% (N=218) and 6.3% (N=106) of Spanish patients, respectively. Insulin was prescribed to 26.2% (N=444) of the patients

Table 10.2-2: Frequencyof select concomitant medications prescribed during the baseline period

		United Kingdom N=8409 n (%)	Germany N=1715 n (%)	Spain N=1692 n (%)
Loop diuretics	Yes	640 (7.6%)	259 (15.1%)	156 (9.2%)
Pioglitazone	Yes	678 (8.1%)	9 (0.5%)	19 (1.1%)
Biguanide	Yes	7259 (86.3%)	759 (44.3%)	980 (57.9%)
Sulfonamide derivates	Yes	4004 (47.6%)	271 (15.8%)	515 (30.4%)
Dipeptidyl peptidase 4 Inhibitors	Yes	3281 (39.0%)	317 (18.5%)	218 (12.9%)
Glucagon-like peptide 1	Yes	1577 (18.8%)	157 (9.2%)	106 (6.3%)
Alpha glucosidase inhibitors	Yes	23 (0.3%)	38 (2.2%)	19 (1.1%)
Insulin	Yes	1864 (22.2%)	586 (34.2%)	444 (26.2%)

Kidney function was assessed with creatinine serum to estimate the GFR calculated using the Cockcroft and Gault formula (Table 10.2-3). No creatinine serum results could be found in the 12 month period preceding dapagliflozin initiation for 5.2% (N=436) of the patients in the UK, 23.1% (N=396) of the patients in Germany and 55.2% (N=934) of the patients in Spain. The median creatinine serum rate was 73 µmol/l (interquartile range [IQR]: 63.0 - 85.0) for patients in the UK and 76 µmol/l (IQR: 65.0 - 90.2) for patients in Germany and 70.7 µmol/l (IQR: 63.6 - 80.4) for patients in Spain. Based on weight, gender and age, the median eGFR was 123.6 ml/min for patients in the UK, 110.7 ml/min for patients in Germany and 109.8 ml/min for patients in Spain.

Table 10.2-3: Biological values recorded during the baseline period

		United Kingdom N=8409 n (%)	Germany N=1715 n (%)	Spain N=1692 n (%)
Number of Creatinine serum tests[a]	No tests	436 (5.2%)	396 (23.1%)	934 (55.2%)
	1	2547 (30.3%)	372 (21.7%)	488 (28.8%)
	2	2891 (34.4%)	250 (14.6%)	222 (13.1%)
	≥ 3	2535 (30.1%)	697 (40.6%)	48 (2.8%)
Creatinine serum (µmol/l)	N	18078 (100%)	3574 (100%)	1082 (100%)
	Mean (SD)	75.2 (17.2)	79.6 (22.0)	73.5 (14.6)
	Median (Range)	73.0 (15.0-169.0)	76.0 (17.7-169.7)	70.7 (36.2-141.4)
	Q1 - Q3	[63.0 , 85.0]	[65.0 , 90.2]	[63.6 , 80.4]
Estimated GFR (ml/min) [b]	N	17423 (96.4%)	1131 (31.6%)	811 (74.9%)
	Mean (SD)	131.7 (49.1)	116.5 (46.0)	114.2 (39.4)
	Median (Range)	123.6 (26.4-665.3)	110.7 (28.4-311.5)	109.8 (27.0-292.2)
	Q1 - Q3	[97.5 , 158.0]	[82.2 , 143.1]	[85.2 , 137.9]
	Missing (N)	655 (3.6%)	2443 (68.3%)	271 (25.0%)

[a] It is possible to have more than one value per patient

[b] eGFR is estimated with Cockcroft and Gault formula..

10.3. Outcome Data

Not applicable.

10.4. Main Results

This section addresses Research questions 2 to 5. Table 10.4-1 summarizes the use of dapagliflozin in study populations by country.

Table 10.4-1: Use of dapagliflozin by country

		United Kingdom N=8409 n (%)	Germany N=1715 n (%)	Spain N=1692 n (%)
No T2DM diagnosis	No	8374 (99.6%)	1683 (98.1%)	1669 (98.6%)
	Yes	35 (0.4%)	32 (1.9%)	23 (1.4%)
Age <18 years	No	8409 (100.0%)	1687 (100.0%)	1687 (99.9%)
	Yes	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Missing (N)	0	28	4
Age ≥ 75 years	No	7959 (94.6%)	1379 (81.7%)	1534 (90.9%)
	Yes	450 (5.4%)	308 (18.3%)	154 (9.1%)
	Missing (N)	0	28	4
Severe renal impairment	No	7643 (99.9%)	416 (99.8%)	556 (99.8%)
	Yes	4 (0.1%)	1 (0.2%)	1 (0.2%)
	Missing (N)	762	1298	1135
Moderate renal impairment	No	7411 (96.9%)	378 (90.6%)	523 (93.9%)
	Yes	236 (3.1%)	39 (9.4%)	34 (6.1%)
	Missing (N)	762	1298	1135
Renal Failure	No	8408 (100.0%)	1551 (90.4%)	1683 (99.5%)
	Yes	1 (0.0%)	164 (9.6%)	9 (0.5%)

10.4.1. Primary Objective

Research question 2: What proportion of patients prescribed dapagliflozin has baseline moderate to severe renal impairment?

In the 12 months preceding dapagliflozin initiation among those with non-missing eGFR values, moderate renal impairment (eGFR value between 30 and 60) was found in 3.1% (N=236 of 7647 non-missing) of the patients in the UK, 6.1% (N=34 of 557 non-missing) in Spain and 9.4% (N=39 of 417 non-missing) of patients in Germany (Table 10.4-1). Severe renal impairment (eGFR value < 30) was found in 4 patients (0.1%) in the UK, 1 patient in Germany (0.2%) and 1 patient in Spain (0.2%). In Germany, estimation of eGFR using Cockcroft and Gault formula[1] was limited due to large number of missing values for weight in electronic medical records during the baseline period. In Spain, less than half of the patients had a recorded creatinine serum test available (Table 10.2-3).

In an attempt to quantify those patients for whom an eGFR value could not be deduced from Cockcroft and Gault formula, we used the simplified Modification of Diet in Renal Diseases (sMDRD) formula [Appendix 1].

We tested the sMDRD equation on the UK cohort, where eGFR was well documented, using Cockcroft and Gault formula to compare the estimated population of moderate to severe renal impairment groups. We identified 473 patients (5.9%) who had a moderate impairment using sMDRD versus 236 (3.2%) using the Cockcroft and Gault formula. Four patients (0.1%) were identified as having severe renal impairment using the Cockcroft and Gault formula, and only one (0.01%) was identified using sMDRD. Therefore based on these two equations, between 3.2% and 5.9% of patients had moderate renal impairment in the UK, and between 0.1% and 0.01% of patients had severe renal impairment (Table 10.4.1-1). In the UK, 5.4% of the patients are 75 years old or older. Among the 236 patients identified with moderate impairment using the Cockcroft and Gault formula, 133 (56.3%) were aged 75 years and older. Likewise, the four patients identified as having severe renal impairment using the Cockcroft and Gault formula were aged 75 years and older. Moreover, among the 473 patients identified with moderate impairment using the sMDRD formula, 117 (24.7%) were aged 75 years and older. The unique, patient identified as having severe renal impairment using the sMDRD formula was aged 75 years and older.

In the German database, we identified 207 patients (16.0%) who had moderate impairment using sMDRD versus 39 (9.4%) using the Cockcroft and Gault formula. One patient (0.2%) was identified as having severe renal impairment (<30 ml/min) using Cockcroft and Gault formula whereas three patients (0.2%) were identified as having severe renal impairment using sMDRD. Therefore based on these two equations, between 9.4% and 16.0% of patients had moderate renal impairment in Germany, and 0.2% of patients had severe renal impairment (Table 10.4.1-1). In Germany, 18.3% of the patients are 75 years and older. Among the 39 patients identified with moderate impairment using the Cockcroft and Gault formula, 27 (69.2%) were aged 75 years and older. Likewise, the patient identified as having severe renal impairment using the Cockcroft and Gault formula was aged 75 years and older. Among the 207 patients identified with moderate impairment using the sMDRD formula, 84 (40.5%) were aged 75 years and older. Two out of three patients identified as having severe renal impairment using the sMDRD formula formula were aged 75 years and older.

In Spain, we identified 26 patients (3.5%) who had moderate impairment using sMDRD versus 34 (6.1%) using the Cockcroft and Gault formula. One patient (0.2%) was identified as having severe renal impairment (<30 ml/min) using Cockcroft and Gault formula whereas no patient was identified as having severe renal impairment using sMDRD. Therefore based on these two equations, between 3.5% and 6.1% of patients had moderate renal impairment in Spain, and 0% to 0.2% of patients had severe renal impairment (Table 10.4.1-1). In Spain 9.1% of the patients are 75 years and older. Among the 26 patients identified with moderate impairment using the sMDRD formula, 7 (26.9%) were aged 75 years and older. In addition among the 34 patients identified with moderate impairment using the Cockcroft and Gault formula, 19 (55.9%) were aged 75 years and older The one patient identified with the Cockcroft and Gault formula was aged 75 years and older.

Table 10.4.1-1: Evaluation of moderate to severe renal impairment by Cockcroft and Gault formula and sMDRD formula

		United Kingdom N=8409		Germany N=1715		Spain N=1692	
		sMDRD formula	Cockcroft and Gault formula	sMDRD formula	Cockcroft and Gault formula	sMDRD formula	Cockcroft and Gault formula
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Moderate renal impairment	No	7499 (94.1%)	7411 (96.9%)	1087 (84.0%)	378 (90.6%)	727 (96.5%)	523 (93.9%)
	Yes	473 (5.9%)	236 (3.1%)	207 (16.0%)	39 (9.4%)	26 (3.5%)	34 (6.1%)
	Missing (N)	437	762	421	1298	939	1135
Severe renal impairment	No	7971 (99.9%)	7643 (99.9%)	1291 (99.7%)	416 (99.8%)	753 (100%)	556 (99.8%)
	Yes	1 (0.2%)	4 (0.1%)	3 (0.2%)	1 (0.2%)	0 (0%)	1 (0.2%)
	Missing (N)	437	762	421	1298	939	1135

One patient with a diagnosis of renal failure (based on ICD10 codes) was found in the UK database, however, 9 patients were identified in the Spanish (0.5%) and 164 patients in the German databases (9.6%) (Table 10.4-1). Of the 164 patients for whom the diagnosis of renal failure could be deduced from ICD 10 codes in Germany, 137 had a creatinine serum test available. Of these, 3 (2%) had an eGFR < 30 ml/min, 52 (38%) had an eGFR between 30 and 59 ml/min (using sMDRD equation), and 82 patients (60%) had an eGFR >60 ml/min. In Spain, among 9 patients with a diagnosis of renal failure, creatinine serum test was available only for 4 patients, of whom one exhibited an eGFR between 30 and 59 ml/min and three had an eGFR >60 ml/min. Based on a comparison between ICD diagnosis codes and the available laboratory data, between 2% and 9.6% of patients had renal failure in Germany, This number was between 0% and 0.5% in Spain, and was 0.01% in the UK.

Research question 3: What proportion of patients prescribed dapagliflozin is 75 years of age or older at the time of the index prescription?

The percentage of patients aged 75 years and older prescribed dapagliflozin was 5.4% in the UK (N=450), 9.1% in Spain (N=154) and 18.3% in Germany (N=308) (Table 10.4-1).

In the UK, 27.0% (N=117) of patients 75 and older had an eGFR indicating moderate renal impairment, 1 patients (0.2%) had an eGFR< 30 ml/min and 317 (73.0%) had an eGFR> 60 ml/min.

In Germany, 34.0% (N=84) of patients 75 and older had an eGFR indicating moderate renal impairment, two patients had an eGFR< 30 ml/min and 161 (65.2%) had an eGFR> 60 ml/min.

In Spain, 10.0% (N=7) of patients 75 and older had an eGFR indicating moderate renal impairment, none was found with an eGFR< 30 ml/min and 63 (90.0%) had an eGFR> 60 ml/min.

Research question 4: What proportion of patients prescribed dapagliflozin is also users of loop diuretics or pioglitazone during the baseline period and the available follow-up period?

During the baseline period, 7.6% (N=640), 9.2% (N=156) and 15.1% (N=259) of the patients were prescribed loop diuretics, in the UK, Spain and Germany respectively (Table 10.2-2**).** In the follow-up period, 7.2% (N=602), 8.8% (N=149) and 14.9% (N=255) of the patients in the UK, Spain and Germany respectively, were prescribed loop diuretics after dapagliflozin treatment initiation (Table 10.4.1-2).

Pioglitazone was prescribed to 8.1% (N=678) of the patients in the UK, 1.1 % (N=19) of the patients in Spain and 0.5% (N=9) of the patients in Germany during the baseline period (Table 10.2-2). During the follow up period, after dapagliflozin initiation, 3.8% (N=318), 0.8% (N=14) and 0.2% (N=3) of the patients were prescribed pioglitazone in the UK, Spain and Germany respectively (Table 10.4.1-2).

Table 10.4.1-2: Frequency of select co-medications prescribed during the follow-up period

		United Kingdom N=8409 n (%)	Germany N=1715 n (%)	Spain N=1692 n (%)
Loop diuretics	Yes	602 (7.2%)	255 (14.9%)	149 (8.8%)
Pioglitazone	Yes	318 (3.8%)	3 (0.2%)	14 (0.8%)

Research Question 5: What proportion of patients prescribed dapagliflozin does not have a diagnosis of type 2 diabetes mellitus during the baseline period or on the index date?

Most patients prescribed dapagliflozin were identified as T2DM patients (N=8374 (99.6%) in the UK, N=1683 (98.1%) in Germany and N= 1669 (98.6%) in Spain). The proportion of patients identified as having type 1 diabetes was low (N=28 (0.3%) in the UK, N=18 (1.1%) in Spain and N=15 (0.9%) in Germany). A diagnosis for type 1 diabetes or T2DM could not be determined in N= 7 (0.1%), N=5 (0.63%) and N=17 (1.0%) of the patients in the UK, Spain and Germany respectively (Table 10.2-1).

10.4.2. Secondary Objectives

Not applicable.

10.5. Other Analyses

In order to assess the impact of missing data, key variables (e.g., BMI and eGRF) were checked by describing patients with and without missing values, respectively, regarding basic characteristics available for all or most patients, including age, gender, country, co-medication and co-morbidity.

10.5.1. Sensitivity analyses based on BMI values

The proportion of patients with a missing BMI value was lower in the UK (N=587, 6.9%) than in Spain (N= 652, 38.5%) and in Germany (N=1230, 71.7%).

The characteristics of the patients with a BMI value were compared to those without BMI value in each country (Table 10.5.1-1). Overall the two groups of patients in all three countries appear similar concerning patient characteristics except in Spain where % of female is slightly higher in the BMI reported group than in the BMI missing group (45.6% and 37.4% respectively) also in the UK there are more patients of 75 years and older on the BMI missing group (8.5%) compare to the BMI reported group (5.1%). Hypertension is more frequent in the BMI reported group than in the BMI missing group notably in Spain with a difference of 10% (44.0% and 34.0% respectively).

In addition the number of missing creatinine serum tests is higher in the BMI missing group than in the BMI reported group in the three countries (12.1% *vs* 4.7% in the UK, 26.5% *vs* 14.4% in Germany and 67.6% *vs* 47.4% in Spain).

Additionally, overall, the frequency of select concomitant medications prescribed during the baseline period in the three countries is similar in the two groups (Table 10.5.1-2). Of note in Spain, Biguanide and Sulfonamide derivates are more frequent in the BMI reported group, 60.8% of the patients in the BMI

reported group have been prescribed Biguanide compared to 53.4% in the BMI missing group and 32.7% of the patients in the BMI reported group have been prescribed Sulfonamide derivates compared to 26.8% in the BMI missing group.

The assessment of missing BMI data on study populations in the three countries is given in Table 10.5.1-3.

Table 10.5.1-1: Description of the population at inclusion: Assessment of the impact of missing data for BMI

		UK		Germany		Spain	
		BMI reported N=7822 n (%)	BMI missing N=587 n (%)	BMI reported N=485 n (%)	BMI missing N=1230 n (%)	BMI reported N=1040 n (%)	BMI missing N=652 n (%)
Age (years)	N	7822 (100.0%)	587 (100.0%)	481 (99.1%)	1206 (98.0%)	1040 (100.0%)	648 (99.4%)
	Mean (SD)	58.2 (10.6)	58.0 (11.6)	63.9 (11.3)	64.4 (11.0)	61.8 (10.1)	61.0 (10.8)
	Median	58.0	58.0	65.0	65.0	62.0	61.0
	Missing	0 (0.0%)	0 (0.0%)	4 (0.8%)	24 (1.9%)	0 (0.0%)	4 (0.6%)
Age group (years)	<45	769 (9.8%)	68 (11.6%)	18 (3.7%)	51 (4.2%)	60 (5.8%)	43 (6.6%)
	45-59	3159 (40.4%)	254 (43.3%)	131 (27.2%)	295 (24.5%)	301 (28.9%)	213 (32.9%)
	60-74	3494 (44.7%)	215 (36.6%)	241 (50.1%)	643 (53.3%)	587 (56.4%)	330 (50.9%)
	≥ 75	400 (5.1%)	50 (8.5%)	91 (18.9%)	217 (18.0%)	92 (8.8%)	62 (9.6%)
	Missing	0	0	4	24	0	4
Sex	Male	4537 (58.0%)	338 (57.6%)	284 (58.6%)	695 (56.6%)	563 (54.4%)	405 (62.6%)
	Female	3283 (42.0%)	249 (42.4%)	201 (41.4%)	533 (43.4%)	471 (45.6%)	242 (37.4%)
	Missing	2	0	0	2	6	5
Type 2 diabetes mellitus[a]	No	26 (0.3%)	2 (0.3%)	2 (0.4%)	13 (1.1%)	8 (0.8%)	10 (1.5%)
	Yes	7791 (99.6%)	583 (99.3%)	479 (98.8%)	1204 (97.9%)	1030 (99.0%)	639 (98.0%)
	Unknown	5 (0.1%)	2 (0.3%)	4 (0.8%)	13 (1.1%)	2 (0.2%)	3 (0.5%)
Congestive heart failure	Yes	47 (0.6%)	6 (1.0%)	0 (0.0%)	0 (0.0%)	9 (2.2%)	7 (3.5%)
Hypertension	Yes	4233 (54.1%)	289 (49.2%)	431 (88.9%)	1004 (81.6%)	177 (44.0%)	68 (34.0%)

Table 10.5.1-1: Description of the population at inclusion: Assessment of the impact of missing data for BMI

		UK		Germany		Spain	
		BMI reported N=7822 n (%)	BMI missing N=587 n (%)	BMI reported N=485 n (%)	BMI missing N=1230 n (%)	BMI reported N=1040 n (%)	BMI missing N=652 n (%)
Creatinine serum tests (number)	No tests	365 (4.7%)	71 (12.1%)	70 (14.4%)	326 (26.5%)	493 (47.4%)	441 (67.6%)
	1	2343 (30.0%)	204 (34.8%)	119 (24.5%)	253 (20.6%)	336 (32.3%)	152 (23.3%)
	2	2710 (34.6%)	181 (30.8%)	84 (17.3%)	166 (13.5%)	175 (16.8%)	47 (7.2%)
	≥ 3	2404 (30.7%)	131 (22.3%)	212 (43.7%)	485 (39.4%)	36 (3.5%)	12 (1.8%)
Creatinine serum (µmol/l)	N	17031 (100.0%)	1047 (100.0%)	1117 (100.0%)	2457 (100.0%)	798 (100.0%)	284 (100.0%)
	Mean (SD)	75.2 (17.2)	76.0 (18.1)	79.5 (22.3)	79.6 (21.8)	73.0 (14.5)	74.9 (14.8)
	Median (Range)	73.0 (15.0-166.0)	74.0 (38.0-169.0)	75.1 (35.0-167.1)	76.9 (17.7-169.7)	70.7 (36.2-141.4)	71.6 (47.7-132.6)
	Q1 - Q3	[63.0 , 85.0]	[64.0 , 85.0]	[65.0 , 90.2]	[65.0 , 90.2]	[62.8 , 79.6]	[64.5 , 82.2]
Estimated GFR (ml/min) [b]	N	17022 (99.9%)	401 (38.3%)	1110 (99.3%)	21 (0.8%)	793 (99.3%)	18 (6.3%)
	Mean (SD)	131.8 (49.1)	127.8 (45.6)	116.5 (45.5)	116.0 (70.9)	114.5 (39.1)	100.2 (48.6)
	Median (Range)	123.6 (26.4-665.3)	123.8 (45.5-282.9)	110.8 (28.4-311.5	96.4 (40.9-251.0)	110.2 (27.0-292.2)	95.3 (37.0-249.2)
	Q1 - Q3	[97.6 , 158.3]	[94.6 , 148.4]	[82.6 , 143.1]	[68.9 , 138.6]	[85.6 , 138.2]	[63.4 , 116.2]
	Missing (N)	9 (0.05%)	646 (61.7%)	7 (0.6%)	2436 (99.1%)	5 (0.6%)	266 (93.6%)

[a] Yes = Type 2 diabetes mellitus, No = Type 1 diabetes, Unknown = Unknown reported diagnosis over the baseline period.

[b] eGFR is estimated with Cockcroft and Gault formula.

Table 10.5.1-2: Frequency of select concomitant medications prescribed during the baseline period: Assessment of the impact of missing data for BMI

		UK		Germany		Spain	
		BMI reported N=7822 n (%)	BMI missing N=587 n (%)	BMI reported N=485 n (%)	BMI missing N=1230 n (%)	BMI reported N=1040 n (%)	BMI missing N=652 n (%)
Loop diuretics	Yes	587 (7.5%)	53 (9.0%)	82 (16.9%)	177 (14.4%)	95 (9.1%)	61 (9.4%)
Pioglitazone	Yes	631 (8.1%)	47 (8.0%)	1 (0.2%)	8 (0.7%)	9 (0.9%)	10 (1.5%)
Biguanide	Yes	6778 (86.7%)	481 (81.9%)	210 (43.3%)	549 (44.6%)	632 (60.8%)	348 (53.4%)
Sulfonamide derivates	Yes	3734 (47.7%)	270 (46.0%)	84 (17.3%)	187 (15.2%)	340 (32.7%)	175 (26.8%)
Dipeptidyl peptidase 4 Inhibitors	Yes	3068 (39.2%)	213 (36.3%)	83 (17.1%)	234 (19.0%)	139 (13.4%)	79 (12.1%)
Glucagon-like peptide 1	Yes	1488 (19.0%)	89 (15.2%)	44 (9.1%)	113 (9.2%)	72 (6.9%)	34 (5.2%)
Alpha glucosidase inhibitors	Yes	21 (0.3%)	2 (0.3%)	9 (1.9%)	29 (2.4%)	14 (1.3%)	5 (0.8%)
Insulin	Yes	1707 (21.8%)	157 (26.7%)	168 (34.6%)	418 (34.0%)	287 (27.6%)	157 (24.1%)

Table 10.5.1-3: Use of dapagliflozin by country: Assessment of the impact of missing data for BMI

		UK		Germany		Spain	
		BMI Reported N=7822 n (%)	BMI missing N=587 n (%)	BMI Reported N=485 n (%)	BMI missing N=1230 n (%)	BMI Reported N=1040 n (%)	BMI missing N=652 n (%)
No T2DM diagnosis	No	7791 (99.6%)	583 (99.3%)	479 (98.8%)	1204 (97.9%)	1030 (99.0%)	639 (98.0%)
	Yes	31 (0.4%)	4 (0.7%)	6 (1.2%)	26 (2.1%)	10 (1.0%)	13 (2.0%)
Age <18 years	No	7822 (100.0%)	587 (100.0%)	481 (100.0%)	1206 (100.0%)	1040 (100%)	647 (99.8%)
	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Missing (N)	0	0	4	24	0	4
Age ≥ 75 years	No	7422 (94.9%)	537 (91.5%)	390 (81.1%)	989 (82.0%)	948 (91.2%)	586 (90.4%)
	Yes	400 (5.1%)	50 (8.5%)	91 (18.9%)	217 (18.0%)	92 (8.8%)	62 (9.6%)
	Missing (N)	0	0	4	24	0	4
Severe renal impairment	No	7449 (99.9%)	194 (100%)	410 (99.8%)	6 (100.0%)	543 (99.8%)	13 (100.0%)
	Yes	4 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Missing (N)	369	393	74	1224	496	639
Moderate renal impairment	No	7223 (96.9%)	188 (96.9%)	373 (90.8%)	5 (83.3%)	511 (93.9%)	12 (92.3%)
	Yes	230 (3.1%)	6 (3.1%)	38 (9.2%)	1 (16.7%)	33 (6.1%)	1 (7.7%)
	Missing (N)	369	393	74	1224	496	639
Renal Failure	No	7821 (100.0%)	587 (100.0%)	424 (87.4%)	1127 (91.6%)	1032 (99.2%)	651 (99.8%)
	Yes	1 (0.0%)	0 (0.0%)	61 (12.6%)	103 (8.4%)	8 (0.8%)	1 (0.2%)

10.5.2. Sensitivity analyses based on eGFR values

When not available directly in the database, the value of eGFR can be estimated with the Cockcroft and Gault formula using creatinine serum value, age, and weight. As a consequence of the limited documentation of weight in the German database, the proportion of missing eGFR values was higher in Germany (N=1298, 75.7%) than in Spain (N=1135, 67.1%) and in the UK (N=762, 9.1%). In Spain, on the other hand, missing eGFR values were mainly resulting from the fact that only half of the patients had a recorded creatinine serum test available (N=758, 44.8%).

The characteristics of the patients with an eGFR value were compared to those without an eGFR value (Table 10.5.2-1). Overall the two groups of patients in all three countries appear similar concerning patient characteristics, however in the UK there are more patients aged between 60 and 74 years old in the eGFR reported group than in the eGFR missing group (44.7% and 38.2% respectively) also in the same country there are more patients with hypertension in the eGFR reported group than in the eGFR missing group (54.4% and 47.7% respectively).

Additionally, the lack of information on eGFR does not seem to have any impact on the frequency of selected concomitant medications prescribed during the baseline period in Germany and Spain. However in the UK more patients in the eGFR reported group have been prescribed Biguanide, Sulfonamide derivates and DPP4 compared to the eGFR missing group (87.7% *vs* 73.0%, 48.6% *vs* 37.7% and 48.6% *vs* 37.7% respectively). In the UK more patients in the eGFR missing group (28.5%) have been prescribed Insulin compared to the patients in the eGFR reported group (21.5%) (Table 10.5.2-2)

The assessment of missing eGFR data in the study populations in each country is given in Table 10.5.2-3.

Table 10.5.2-1: Description of the population at inclusion: Assessment of the impact of missing data for eGFR

		UK		Germany		Spain	
		eGFR Reported N=7647 n (%)	eGFR missing N=762 n (%)	eGFR Reported N=417 n (%)	eGFR missing N=1298 n (%)	eGFR Reported N=557 n (%)	eGFR missing N=1135 n (%)
Age (years)	N	7647 (100.0%)	762 (100.0%)	417 (100.0%)	1270 (97.8%)	557 (100.0%)	1131 (99.6%)
	Mean (SD)	58.2 (10.6)	57.2 (11.4)	64.1 (11.2)	64.3 (11.0)	62.1 (10.4)	61.1 (10.4)
	Median	58.0	57.0	65.0	65.0	63.0	62.0
	Missing	0	0	0	28	0	4
Age group (years)	<45	744 (9.7%)	93 (12.2%)	13 (3.1%)	56 (4.4%)	32 (5.7%)	71 (6.3%)
	45-59	3082 (40.3%)	331 (43.4%)	118 (28.3%)	308 (24.3%)	158 (28.4%)	356 (31.5%)
	60-74	3418 (44.7%)	291 (38.2%)	208 (49.9%)	676 (53.2%)	309 (55.5%)	608 (53.8%)
	≥ 75	403 (5.3%)	47 (6.2%)	78 (18.7%)	230 (18.1%)	58 (10.4%)	96 (8.5%)
	Missing	0	0	0	28	0	4
Sex	Male	4450 (58.2%)	425 (55.9%)	245 (58.8%)	734 (56.6%)	308 (55.3%)	660 (58.7%)
	Female	3197 (41.8%)	335 (44.1%)	172 (41.2%)	562 (43.4%)	249 (44.7%)	464 (41.3%)
	Missing	0	2	0	2	0	11
BMI (kg/m²)	<18	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	18-25	383 (5.1%)	37 (10.0%)	22 (5.4%)	7 (9.5%)	35 (6.4%)	20 (4.0%)
	≥ 25	7069 (94.8%)	332 (90.0%)	389 (94.6%)	67 (90.5%)	509 (93.6%)	476 (96.0%)
	Missing (N)	194	393	6	1224	13	639
Type 2 diabetes mellitus[a]	No	23 (0.3%)	5 (0.7%)	2 (0.5%)	13 (1.0%)	4 (0.7%)	14 (1.2%)
	Yes	7622 (99.7%)	752 (98.7%)	413 (99.0%)	1270 (97.8%)	553 (99.3%)	1116 (98.3%)
	Unknown	2 (0.0%)	5 (0.7%)	2 (0.5%)	15 (1.2%)	0 (0.0%)	5 (0.4%)
Congestive Heart Failure	No	7600 (99.4%)	756 (99.2%)	417 (100.0%)	1298 (100.0%)	544 (97.7%)	1088 (95.9%)
	Yes	47 (0.6%)	6 (0.8%)	0 (0.0%)	0 (0.0%)	13 (2.3%)	47 (4.1%)
Hypertension	No	3486 (45.6%)	401 (52.6%)	49 (11.8%)	231 (17.8%)	338 (60.7%)	691 (60.9%)

Table 10.5.2-1: Description of the population at inclusion: Assessment of the impact of missing data for eGFR

		UK		Germany		Spain	
		eGFR Reported N=7647	**eGFR missing N=762**	**eGFR Reported N=417**	**eGFR missing N=1298**	**eGFR Reported N=557**	**eGFR missing N=1135**
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Creatinine serum (µmol/l) [b]	Yes	4161 (54.4%)	361 (47.4%)	368 (88.2%)	1067 (82.2%)	219 (39.3%)	444 (39.1%)
	N	17423 (100.0%)	655 (100.0%)	1131 (100.0%)	2443 (100.0%)	811 (100.0%)	271 (100.0%)
	Mean (SD)	75.2 (17.1)	76.5 (19.5)	79.5 (22.2)	79.6 (21.9)	73.0 (14.7)	74.8 (14.3)
	Median (Range)	73.0 (15.0-166.0)	74.0 (38.0-169.0)	75.1 (35.0-167.1)	76.9 (17.7-169.7)	70.7 (36.2-141.4)	71.6 (47.7-132.6)
	Q1 - Q3	[63.0 , 85.0]	[64.0 , 86.0]	[64.5 , 90.2]	[65.0 , 90.2]	[62.8 , 79.6]	[64.5 , 82.2]

[a]Yes = Type 2 diabetes mellitus, No = Type 1 diabetes, Unknown = Unknown reported diagnosis over the baseline period
[b]eGFR is estimated with Cockcroft and Gault formula.

Table 10.5.2-2: Frequency of select concomitant medications prescribed during the baseline period: Assessment of the impact of missing data for eGFR

		UK		Germany		Spain	
		eGFR reported N=7647 n (%)	eGFR missing N=762 n (%)	eGFR reported N=417 n (%)	eGFR missing N=11298 n (%)	eGFR reported N=557 n (%)	eGFR missing N=1135 n (%)
Loop diuretics	Yes	571 (7.5%)	69 (9.1%)	76 (18.2%)	183 (14.1%)	50 (9.0%)	106 (9.3%)
Pioglitazone	Yes	622 (8.1%)	56 (7.3%)	1 (0.2%)	8 (0.6%)	2 (0.4%)	17 (1.5%)
Biguanide	Yes	6703 (87.7%)	556 (73.0%)	187 (44.8%)	572 (44.1%)	339 (60.9%)	641 (56.5%)
Sulfonamide derivates	Yes	3717 (48.6%)	287 (37.7%)	74 (17.7%)	197 (15.2%)	182 (32.7%)	333 (29.3%)
Dipeptidyl peptidase 4 Inhibitors	Yes	3049 (39.9%)	232 (30.4%)	68 (16.3%)	249 (19.2%)	76 (13.6%)	142 (12.5%)
Glucagon-like peptide 1	Yes	1431 (18.7%)	146 (19.2%)	37 (8.9%)	120 (9.2%)	16 (2.9%)	90 (7.9%)
Alpha glucosidase inhibitors	Yes	22 (0.3%)	1 (0.1%)	5 (1.2%)	33 (2.5%)	4 (0.7%)	15 (1.3%)
Insulin	Yes	1647 (21.5%)	217 (28.5%)	151 (36.2%)	435 (33.5%)	119 (21.4%)	325 (28.6%)

Table 10.5.2-3: Use of dapagliflozin by country: Assessment of the impact of missing data for eGFR

		UK		Germany		Spain	
		eGFR reported N=7647 n (%)	eGFR missing N=762 n (%)	eGFR reported N=417 n (%)	eGFR missing N=1298 n (%)	eGFR reported N=557 n (%)	eGFR missing N=1135 n (%)
No T2DM diagnosis	No	7622 (99.7%)	752 (98.7%)	413 (99.0%)	1270 (97.8%)	553 (99.3%)	1116 (98.3%)
	Yes	25 (0.3%)	10 (1.3%)	4 (1.0%)	28 (2.2%)	4 (0.7%)	19 (1.7%)
Age <18 years	No	7647 (100.0%)	762 (100.0%)	417 (100.0%)	1270 (100.0%)	557 (100.0%)	1130 (99.9%)
	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Missing (N)	0	0	0	28	0	4
Age ≥ 75 years	No	7244 (94.7%)	715 (93.8%)	339 (81.3%)	1040 (81.9%)	499 (89.6%)	1035 (91.5%)
	Yes	403 (5.3%)	47 (6.2%)	78 (18.7%)	230 (18.1%)	58 (10.4%)	96 (8.5%)
	Missing (N)	0	0	0	28	0	4
Severe renal impairment	No	7643 (99.9%)	0 (0.0%)	416 (99.8%)	0 (0.0%)	233 (99.6%)	0 (0.0%)
	Yes	4 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
	Missing (N)	0	762	0	1298	0	368
Moderate renal impairment	No	7411 (96.9%)	0 (0.0%)	378 (90.6%)	0 (0.0%)	556 (99.8%)	0 (0.0%)
	Yes	236 (3.1%)	0 (0.0%)	39 (9.4%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
	Missing (N)	0	762	0	1298	0	1135
Renal Failure	No	7646 (100.0%)	762 (100.0%)	364 (87.3%)	1187 (91.4%)	554 (99.5%)	1129 (99.5%)
	Yes	1 (0.0%)	0 (0.0%)	53 (12.7%)	111 (8.6%)	3 (0.5%)	6 (0.5%)

10.6. Adverse Events/Adverse Reactions

Not applicable.

11. DISCUSSION

11.1. Key Results

11.1.1. Primary Objective

This study is the final analysis of the drug utilization study (DUS) being conducted as part of the Dapagliflozin Risk Management Plan. In this study reflecting real life experience, we examined dapagliflozin use in a cohort of 8409, 1715 and 1692 patients in the UK, Germany and Spain, respectively, during a period spanning from January 2013 to June 2016 for UK and Spain and to December 2015 for Germany (after 2015)

In all three countries, dapagliflozin users were predominantly male (~ 60%) and overweight (>90%). The median age of dapagliflozin users in Germany was 65 years, 62 years for the Spanish users and 58 years for the UK users. Among the German patients 83.7% had been diagnosed with hypertension. The corresponding proportion was 53.8% in the UK and 39.2% in the Spanish counterparts. The proportion of patients prescribed loop diuretics was 15.1% in Germany, 7.6% and 9.2% in the UK and Spain, respectively. Patients were commonly treated with biguanide in all countries, the percentage of patients treated was 44.3% in Germany, 57.9% in Spain and 86.3% in the UK. In addition, insulin treatment was prescribed to more than a third of the German cohort (34.2%), less than a quarter (22.2%) of the UK cohort and about a quarter (26.2%) of the Spanish cohort. Finally, pioglitazone was prescribed to 0.5% of the users in Germany and 1.1% in Spain and 8.1% in the UK. These results stem from the use of different guidelines/recommendations in these countries [NICE (National Institute for Health and Care Excellence] in the UK, DDG / DGIM (Deutschen Diabetes Gesellschaft/Deutschen Gesellchaft für Innere Medizin) and DEGAM/AkdÄ (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin/arzneimittelkommission der Deutschen ärzteschaft) in Germany, and AUnETS (Agencias y Unidades de Evaluación de Technologias Sanitarias) in Spain] or different regulations (e.g.: since June 2011, German regulatory agency suspended the use of pioglitazone and its use have be restrained since 2008 in Spain).

During the study period, a T2DM diagnosis was found for 99.6% of the identified dapagliflozin patients in the UK, 98.6% of the patients in Spain and 98.1% in Germany. A small proportion of patients was found to have a type 1 diagnosis (0.3% in the UK, 0.9% in Germany and 1.1% in Spain), or have an undefined status (0.1% in the UK, 1.0% in Germany and 0.3% in Spain).

We identified 640 patients (7.6%) in the UK, 259 patients (15.1%) in Germany and 156 patients (9.2%) in Spain being prescribed loop diuretics during the baseline period. After treatment initiation the proportions treated with loop diuretics decreased slightly to 7.2% (N=602) for the UK, 14.9% (N= 255) in Germany and 8.8% (N=149) in Spain. The higher proportion of patients treated with loop diuretics in the German cohort may reflect a higher percentage of patients with hypertension or kidney impairment.

At baseline, pioglitazone was prescribed to 8.1% of patients in the UK, 1.1% of the patients in Spain and 0.5% of the patients in Germany. After dapagliflozin initiation, 318 patients (3.8%) in the UK 14 patients (0.8%) in Spain, and 3 patients (0.2%) in Germany were prescribed pioglitazone.

Severe and moderate renal impairment were deduced from eGFR values using Cockcroft and Gault formula. In the UK, 3.1% (N=236) and 0.1% (N=4) patients were determined to have moderate and severe

renal impairment, respectively. Among the 417 patients with eGFR values determined from the Cockcroft and Gault equation, 39 (9.4%) were determined to have moderate impairment. However, in the German database, estimation of eGFR using Cockcroft and Gault formula was difficult due to missing data for weight in the EMRs. Among the 1294 patients with eGFR determined from the sMDRD, 207 (16.0%) were determined to have moderate impairment. One patient was determined to have severe renal impairment using Cockcroft and Gault formula and 3 patients using sMDRD formula. In Spain, 6.1% (N=34) patients out of 557 patients with eGFR values and 0.2% (N=1) patient were determined to have moderate and severe renal impairment, respectively using Cockcroft and Gault formula. However, in Spain, less than half of the patients had a recorded creatinine serum test and the use of sMDRD equation to capture missing information on renal status only marginally changed the results. The number of patients with moderate renal impairment was 26 (3.5%) of 753 patients with eGFR values instead of 34 with Cockcroft and Gault formula and no patient with severe renal impairment was found (vs. 1 with Cockcroft and Gault formula).

One patient with a diagnosis of renal failure was identified in the UK cohort; however, 164 patients (9.6%) and 9 patients (0.5%) were identified in the German and Spanish cohort respectively. In Germany, of those patients with an ICD 10 diagnosis of renal failure , three had an eGFR < 30 ml/min, 52 patients (38.0%) had an eGFR between 30 and 59 ml/min, and 82 (60.0%) had an eGFR >60 ml/min, based on the sMDRD equation. In Spain, among 9 patients with a diagnosis of renal failure, a creatinine serum test was available only for 4 patients, of whom one had an eGFR between 30 and 59 ml/min and three had an eGFR >60 ml/min.

A higher percentage of patients over 75 years of age prescribed dapagliflozin were identified in Germany (N= 308, 18.3%) than in Spain (N=154, 9.1%) and the UK (N=450, 5.4%). Among these older patients, a majority (65.2%, 73.0% and 90.0% in Germany, the UK and Spain respectively) were determined to have a creatinine clearance > 60 ml/min.

11.1.2. Secondary Objectives

Not applicable.

11.2. Limitations

Limitations are mainly attributable to the real-life nature of clinical practice information recorded in the databases. As the study is based on fully anonymized electronic medical records data, there are limitations inherent to the inability to link data from different databases and to get additional information from the physicians.

Selection bias:.Health care utilization patterns are best described when they include data from all potential prescribers of the drug. In this instance, the LPD data source does not capture prescriptions written in the specialist setting/hospitals; therefore, selection bias is possible if GPs prescribe dapagliflozin to a different patient population than a physician in a specialist setting.

Misclassification bias: Misclassification bias can result if study subjects are not categorized correctly with regards to exposure or patient characteristics. We expect minimal misclassification with respect to exposure, since this has been determined from each database's prescribing records. However, actual adherence to dapagliflozin or other drugs cannot be confirmed. Further, misclassification as to whether the patient is a new initiator could exist (1) if providers supplied samples of dapagliflozin for varying duration to patients, at no cost, and with no record in the database and (2) if dapagliflozin was initiated by a specialist. This may vary by country and database, and could result in varying results across countries.

Potential for missing data: LPDs collect real life clinical practice information from the patients' electronic medical records. Clinical laboratory results are entered by the GPs whenever they deem these results relevant. If GPs fail to enter all creatinine results, the patient's renal function is therefore uncertain in the absence of recent creatinine. Similarly, weight is not recorded on a regular basis by physicians in the German database; only 40% of the German patients had a weight recorded and we could estimate BMI for only 28.7% of German patients. This also impacted the calculation of creatinine clearance using Cockcroft and Gault formula.

11.2.1. Strengths of Research Methods

The LPDs collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in electronic medical records. In each country, a panel of physicians using this software volunteer to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in these countries.

11.3. Interpretation

In study populations for whom dapagliflozin is not recommended according to the European label, use in patients ≥75 years of age was the most commonly reported. Management of T2DM in elderly patients is complicated by the clinical and functional heterogeneity of this patient population. Some older patients with T2DM may have developed the disease in middle age and experienced years of comorbidity, whereas others may be newly diagnosed or may have had years of undiagnosed comorbidity or few complications. Older adults also differ with regard to physical robustness, physical and cognitive functioning, health status, and life expectancy. Clinicians who treat elderly patients with T2DM must consider this heterogeneity when setting and prioritizing treatment goals.

The insulin-independent mechanism of action of SGLT2 inhibitors suggest that they are associated with a very low risk of hypoglycemia and can be used in patients with any degree of β-cell function or insulin sensitivity[3]. In addition, dapagliflozin, beside its glucose lowering activity has been shown to be associated with weight loss and act as an osmotic diuretic, resulting in a lowering of blood pressure[4,5]. Because glucosuric efficacy of SGLT2 inhibitors depends on sufficient glomerular filtration, the use of dapagliflozin is not recommended in patients with estimated glomerular filtration rate (eGFR) less than 60 mL/min.

While elderly patients are more likely to have impaired renal function, in the population of patients over 75 years of age prescribed dapagliflozin in our study, we found that a majority had a creatinine clearance > 60 ml/min. Therefore, GPs may have considered it appropriate to prescribe dapagliflozin to these patients.

11.4. Generalisability

The study results will be generalizable to patients in the UK, Germany, and Spain who meet the inclusion and exclusion criteria. However, by including data from the several countries in Europe, the study has the potential to maximize the populations to which these findings can be generalized.

12. OTHER INFORAMTION

Not applicable.

13. CONCLUSION

This study has been conducted upon regulatory request to describe the patients using dapagliflozin in routine clinical practice in Europe.

In conclusion, most patients were found to be using dapagliflozin according to the label in the UK, Germany, and Spain. One patient was reported to be under 18 years of age and few patients had no reported diagnosis of T2DM. Among the study populations for whom dapagliflozin is not recommended according to the European label, use in patients ≥ 75 years of age was the most commonly reported.

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1 APPENDICES

1.1 Methodology used: to determine if sMDRD formula can be used in addition to the CG formula to estimate GFR (based on Datacut 1 (2014) results for UK and Germany cohorts)

COMPLEMENTARY ANALYSES

TABLE OF CONTENTS

List of tables

List of figures

1 Feasibility study

1.1 Objective

The objective of this complement analyses are to determine if the MDRD formulae can be used in addition to the Cockcroft and Gault formulae in estimating the frequency of renal impairment based on Glomerular Filtration Rate in the Dapagliflozin study.

2 Methodology

2.1 Estimation of GFR with Cockcroft and Gault formulae

As race information is not available in the LPD, the GFR will be estimated with creatinine clearance (CR_{cl}) estimated by means of the Cockroft and Gault formula:

Cl_{cr} = Estimated creatinine clearance (ml/min.)

Age = Age in years

Weight = Body weight (Kg)

[Cr] = Serum creatinine (µmol/L)

$$Cl_{Cr} = \frac{(140 - Age) \xi Weight}{7.2 \xi [Cr]} \xi k$$

k = 1.23 for male, 1.04 for female

2.2 Estimation of GFR with MDRD formulae

Assuming that the majority of patients are Caucasian, simplified MDRD formula is:

$$MDRD = \left(186 \xi Serum\_Creatinine[mg/dl]^{-1.154} \xi Age[years]^{-0.203} \xi 0.742[if\ female]\right)$$

Creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4.

2.3 Definition of renal impairment

Renal impairment is defined within 12 months prior to the dapagliflozin dispensing as:

- Moderate if CrCl or eGFR value between 30-60;
- Severe if CrCl or eGFR value < 30;

3 Statistical considerations

The Normality hypothesis of all variables studied has been performed. Then the concordance between estimated values of Creatinine clearance rate (CCr or CrCl) with both available formulae has been studied with the Bland & Altman methods[1].

Therefore, the concordance between identification of moderate and severe real impairment has been studied with the kappa coefficient agreement.

The statistical analysis was performed using the software SAS version 9.2 via SAS Entreprise Guide version 6.1 after data retrieval from the database.

[1] Bland JM and Altman DG. (1986). Statistical methods for assessing agreement between two methods of clinical measurement, *Lancet*, February, pp 307-10.

4 Results

4.1 Descriptive statistics

Table 1 Biological values recorded during the baseline period based on MDRD

		United Kingdom (N=1909)	Germany (N=579)
Number of Creatinine serum tests	No tests	104 (5.4%)	123 (21.3%)
	1	693 (36.3%)	139 (24.0%)
	2	594 (31.1%)	91 (15.7%)
	≥ 3	518 (27.1%)	225 (38.9%)
Creatinine serum (µmol/l)	N	4086 (100.00)	1185 (100.00)
	Mean (SD)	75.8 (18.2)	81.1 (21.5)
	Median (Range)	74.0 (34.0-166.0)	78.0 (22.1-167.1)
	Q1 - Q3	[64.0 , 85.0]	[67.2 , 91.9]
estimated GFR (ml/min/1.73 m2)	N	4086 (100.00)	1173 (100.00)
	Mean (SD)	91.8 (23.3)	85.0 (24.5)
	Median (Range)	89.7 (33.9-287.0)	82.8 (27.1-275.4)
	Q1 - Q3	[76.2 , 104.7]	[68.8 , 99.4]

Analysis sets: data.deriv04_cp

Program: D:/users/MR/France/FR-AZE12005FR/Statistics/Analysis/program/tables/T_03B.sas; Date & time program was run: 14APR2015 16:53

4.2 Normality tests

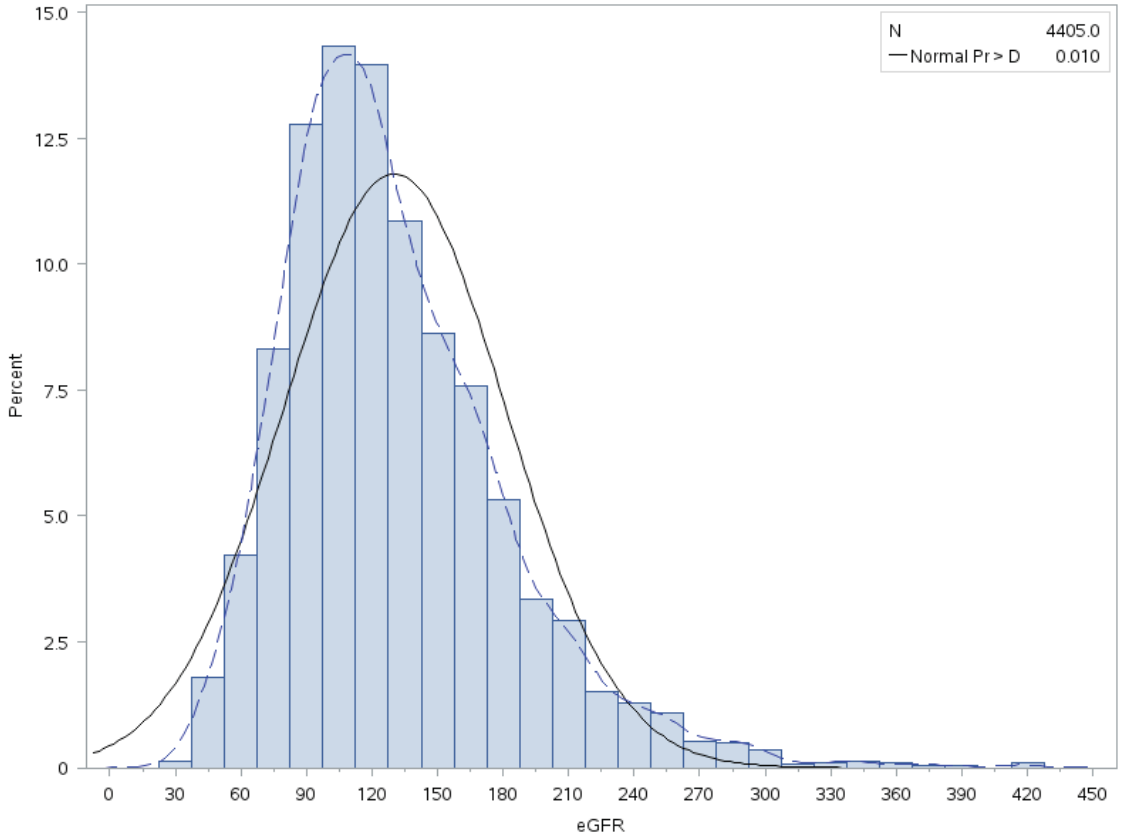


Figure 1 Distribution of eGFR (Cockroft and Gault formulae)

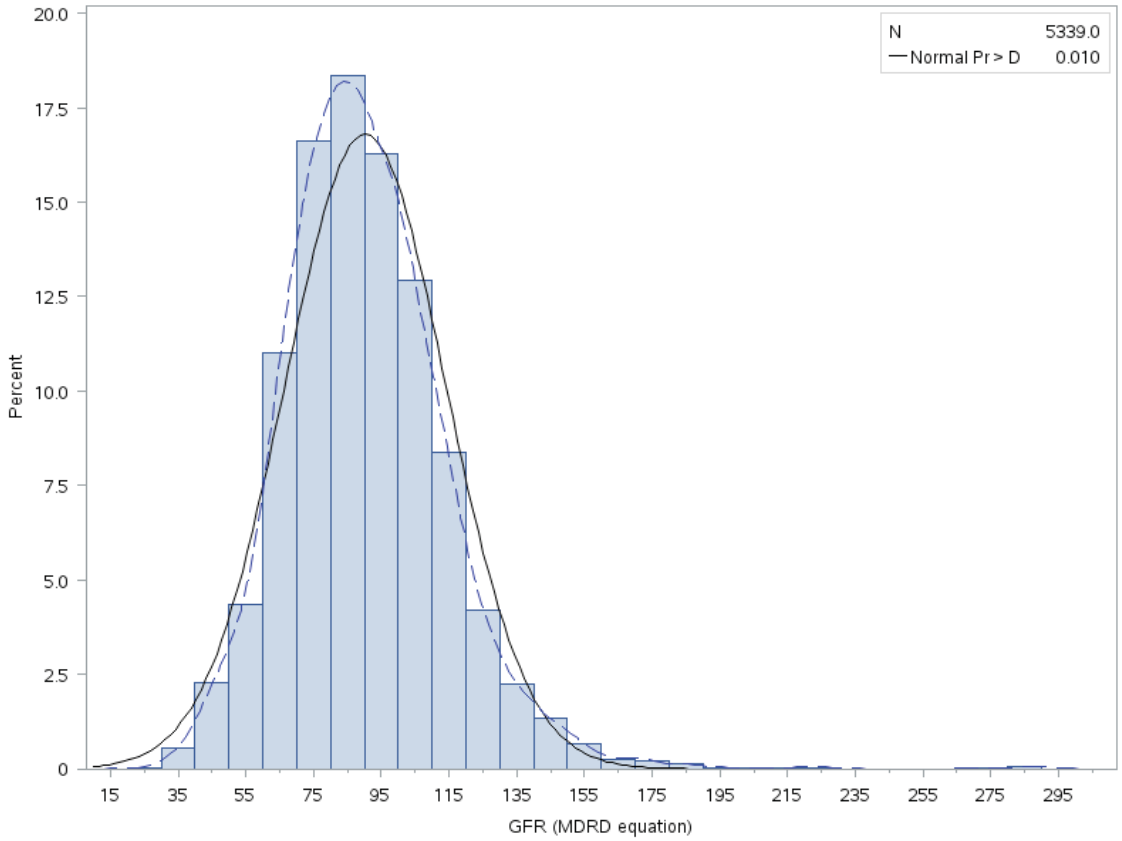


Figure 2 Distribution of GFR (MDRD equation)

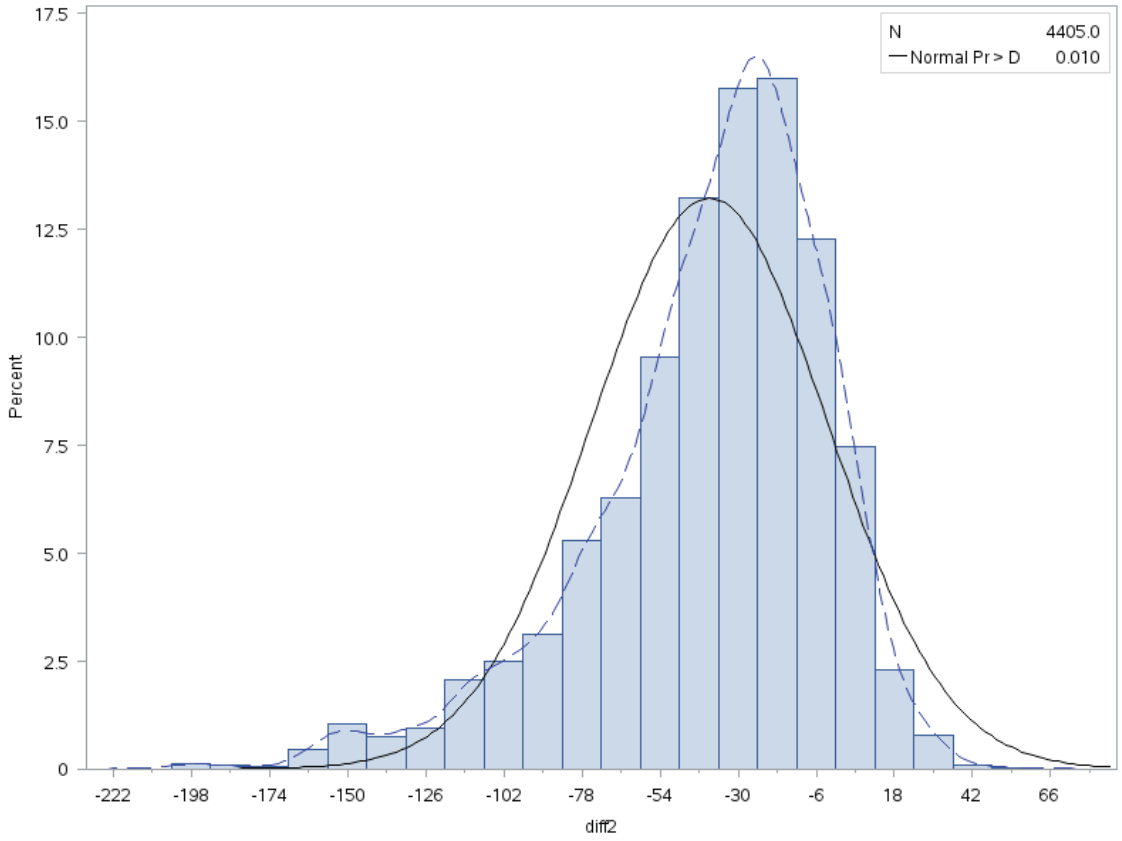


Figure 3 Distribution of difference of GFR between both equations

4.3 Kappa analysis

The most important statistic to look at in this table is the p-value. That is Pr>S = 1.0. When this number is smaller than 0.05, one may conclude that the marginals are not homogeneous. That is, there is not a strong enough evidence to support the fact that the methods (MDRD and Cockcroft and Gault) may have the same rating propensities for severe renal impairment but not for moderate renal impairment where we can observe a good agreement rate.

	Severe renal impairment (MDRD)		
	No	Yes	Total
Severe renal impairment			
No N(%)	2556 (99.9%)	1(0.04%)	2557
Yes N(%)	1 (0.04%)	0(0%)	1
Total N	2557	1	2558

	Moderate renal impairment (MDRD)		
	No	Yes	Total
Moderate renal impairment			
No N(%)	2348(91.7%)	143 (5.59%)	2491
Yes (%)	24 (0.94%)	43 (1.68%)	67
Total N	2372	186	2558

4.4 Per country

A. UK

	Moderate renal impairment (MDRD)		
	No	Yes	Total
Moderate renal impairment			
No N(%)	1774 (92.3%)	81 (4.24%)	1855
Yes N(%)	22 (1.15%)	32 (1.68%)	54
Total N	1796	113	1909

B. Germany

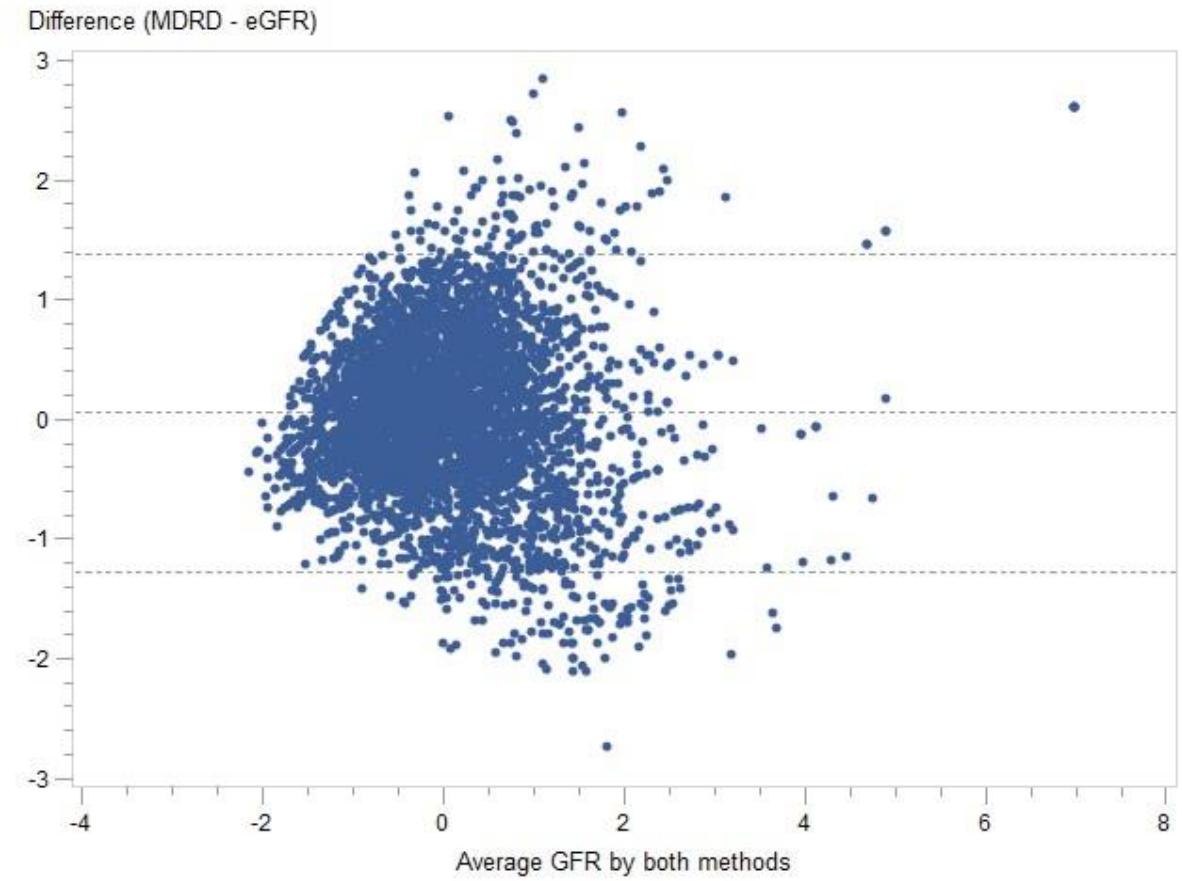
	Moderate renal impairment (MDRD)		
	No	Yes	Total
Moderate renal impairment			
No N(%)	509 (87.9%)	60 (10.3%)	569
Yes N(%)	2 (0.35%)	8 (1.38%)	10
Total	511	68	579

Table 2 Descriptive statistics of absolute variation between both estimation of GFR

Variable	N	Minimum	1st Pctl	5th Pctl	10th Pctl	25th Pctl	50th Pctl	75th Pctl	95th Pctl	99th Pctl	Maximum	Mean	N Miss
Absolute variation	4405	-203.6	-153.0	-110.4	-87.1	-56.7	-31.9	-13.7	8.2	23.3	53.8	-38.8	959
Difference rate (in %)	4405	-65.5	-57.3	-51.6	-46.8	-38.1	-27.2	-14.4	10.9	37.9	79.4	-24.5	959

5 Appendix: supplementary descriptive statistics

5.1 Mean GFR by eFR and MDRD formulae



1.2 Complementary analyses using sMDRD formula (DataCut 3)

Table 1-1-1 Biological values recorded during the baseline period based on sMDRD

		United Kingdom (N=8409)	Germany (N=1715)	Spain (N=1692)
Number of Creatinine serum tests	No tests	436 (5.2%)	396 (23.1%)	934 (55.2%)
	1	2547 (30.3%)	372 (21.7%)	488 (28.8%)
	2	2891 (34.4%)	250 (14.6%)	222 (13.1%)
	>3	2535 (30.1%)	697 (40.6%)	48 (2.8%)
Creatinine serum (µmol/l)	N	18078 (100.0%)	3574 (100.0%)	1082 (100.0%)
	Mean (SD)	75.2 (17.2)	79.6 (22.0)	73.5 (14.6)
	Median (Range)	73.0 (15.0-169.0)	76.0 (17.7-169.7)	70.7 (36.2-141.4)
	Q1 - Q3	[63.0 , 85.0]	[65.0 , 90.2]	[63.6 , 80.4]
estimated GFR (ml/min/1.73 m2)	N	18076 (99.9%)	3501 (97.9%)	1072 (99.0%)
	Mean (SD)	92.0 (22.7)	86.7 (26.1)	91.7 (18.4)
	Median (Range)	89.9 (28.9-493.5)	85.0 (27.1-526.3)	91.4 (34.3-191.8)
	Q1 - Q3	[76.7 , 104.8]	[69.5 , 102.5]	[79.4 , 103.4]
	Missing (N)	2 (0.01)	73 (2.04)	10 (0.92)

Table 1.1.2 Use outside of European label recommendations use based on GFR values estimated with sMDRD

		United Kingdom (N=8409)	Germany (N=1715)	Spain (N=1692)
No T2DM diagnosis	No	8374 (99.6%)	1683 (98.1%)	1669 (98.6%)
	Yes	35 (0.4%)	32 (1.9%)	23 (1.4%)
Age <18 years	No	8409 (100.0%)	1687 (100.0%)	1687 (99.9%)
	Yes	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Missing (N)	0	28	4
Age ≥ 75 years	No	7959 (94.6%)	1379 (81.7%)	1534 (90.9%)
	Yes	450 (5.4%)	308 (18.3%)	154 (9.1%)
	Missing (N)	0	28	4
Renal Failure	No	8408 (100.0%)	1551 (90.4%)	1683 (99.5%)
	Yes	1 (0.0%)	164 (9.6%)	9 (0.5%)
Severe renal impairment (MDRD)	No	7971 (100.0%)	1291 (99.7%)	753 (100.0%)
	Yes	1 (0.0%)	3 (0.2%)	0 (0.0%)
	Missing (N)	437	421	939
Moderate renal impairment (MDRD)	No	7499 (94.1%)	1087 (84.0%)	727 (96.5%)
	Yes	473 (5.9%)	207 (16.0%)	26 (3.5%)
	Missing (N)	437	421	939
Any use outside of label recommendations	No	7567 (90.0%)	1181 (68.9%)	1491 (88.1%)
	Yes	842 (10.0%)	534 (31.1%)	201 (11.9%)

Table 1 Proportion of patients 75 years of age or older with moderate or severe renal impairment - Cockroft and Gault formula

		UK < 75 year (N=7959)	UK ≥ 75 year (N=450)	DE < 75 year (N=1379)	DE ≥ 75 year (N=308)	ES < 75 year (N=1534)	ES ≥ 75 year (N=154)
Severe renal impairment	No	7244 (100.0%)	399 (99.0%)	339 (100.0%)	77 (98.7%)	499 (100.0%)	57 (98.3%)
	Yes	0 (0.0%)	4 (1.0%)	0 (0.0%)	1 (1.3%)	-	1 (1.7%)
	Missing (N)	715	47	1040	230	1035	96
Moderate renal impairment	No	7141 (98.6%)	270 (67.0%)	327 (96.5%)	51 (65.4%)	484 (97.0%)	39 (67.2%)
	Yes	103 (1.4%)	133 (33.0%)	12 (3.5%)	27 (34.6%)	15 (3.0%)	19 (32.8%)
	Missing (N)	715	47	1040	230	1035	96

Table 1.1.4 Proportion of patients 75 years of age or older with moderate or severe renal impairment – sMDRD formula

		UK < 75 years (N=7959)	UK ≥ 75 years (N=450)	DE < 75 years (N=1379)	DE ≥ 75 years (N=308)	ES < 75 years (N=1534)	ES ≥ 75 (N=154)
Severe renal impairment	No	7537 (100.0%)	434 (99.8%)	1046 (99.9%)	245 (99.2%)	683 (100.0%)	70 (100.0%)
	Yes	0 (0.0%)	1 (0.2%)	1 (0.1%)	2 (0.8%)	0 (0.0%)	0 (0.0%)
	Missing (N)	422	15	332	61	851	84
Moderate renal impairment	No	7181 (95.3%)	318 (73.1%)	924 (88.3%)	163 (66.0%)	664 (97.2%)	63 (90.0%)
	Yes	356 (4.7%)	117 (26.9%)	123 (11.7%)	84 (34.0%)	19 (2.8%)	7 (10.0%)
	Missing (N)	422	15	332	61	851	84

Table 1.1.5 Proportion of patients with a renal failure diagnosis having moderate or severe renal impairment (Germany only) – sMDRD formula

		Germany		Spain	
		RF (yes) (N=164)	RF (no) (N=1551)	RF (yes) (N=9)	RF (no) (N=1683)
Severe renal impairment (sMDRD)	No	134 (97.8%)	1157 (100.0%)	4 (100.0%)	749 (100.0%)
	Yes	3 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing (N)	27	394	5	934
Moderate renal impairment (sMDRD)	No	85 (62.0%)	1002 (86.6%)	3 (75.0%)	724 (96.7%)
	Yes	52 (38.0%)	155 (13.4%)	1 (25.0%)	25 (3.3%)
	Missing (N)	27	394	5	934