Type 2 diabetes mellitus treatment patterns across Europe: a population-based multi-database study

ABSTRACT

Purpose: The aim of this study was to determine the similarities and differences of type 2 diabetes mellitus (T2DM) treatment patterns in daily practice in five European countries and whether these reflect differences in the guidelines.

Methods: Prescriptions for drugs used in diabetes during a 5-year study period were obtained from electronic databases. Patients initiating T2DM treatment during the study period were included. A SAS analysis tool was developed to create episodes of use of drug classes, which resulted in treatment patterns.

Findings: A total of 253,530 persons initiating T2DM treatment during the study period were included; 52-55% was male and mean age ranged from 62 to 67 years. Metformin was the most common initial treatment in all countries. After initial therapy most patients in the Netherlands, Spain and the UK switched to a combination of metformin + SU. In Italy metformin in combination with SU was outnumbered by 'other treatment', mainly because of repaglinide use. In France treatments including DPP-4i were most frequent as second and fourth line treatment. Metformin monotherapy was again most commonly observed as third treatment in all countries. Fourth treatment was a combination of metformin + SU in the Netherlands and Spain, while in the UK and France this was DPP-4i.

Implications: This study provides a comprehensive overview of T2DM treatment patterns among patients initiating T2DM treatment in five European countries. Differences are present, especially regarding the (uptake of) newer incretin-based treatments, which are usually prescribed as a second and/or third treatment in line with the local guidelines. These differences reflected the differences between the national guidelines of these countries.

Key words: diabetes mellitus, type 2; hypoglycemic agents; treatment pattern; guidelines; Europe

Abbreviations AGI = Alpha glucosidase inhibitors; ATC = Anatomical therapeutic chemical; BMI = Body mass index; DPP-4i = dipeptidyl peptidase-4 inhibitors; EGB = Echantillon Généraliste de Bénéficiaires; ES = Spain; FR = France; GLP-1ra = glucagon-like peptide-1 receptor agonists; HSD = Health Search longitudinal patient Database; IT = Italy; NL = Netherlands; SD = Standard deviation; SIDIAP = Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària; SU = sulphonylurea derivatives; T2DM = Type 2 diabetes mellitus; THIN = The Health Improvement Network; TZD = thiazolidinediones; UK = United Kingdom.

INTRODUCTION

Changes in lifestyle and ageing of the population have led to an increasing prevalence of type 2 diabetes mellitus (T2DM) worldwide[1-3]. Hyperglycaemia is a risk factor for excess micro- and macrovascular complications and mortality[4]. Although initially glycaemic control may be achieved through diet and exercise[5], pharmacological intervention is necessary at some stage in most patients. Most European countries have a national guideline on T2DM and the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have developed a consensus approach to the management of hyperglycaemia to help guide healthcare providers in choosing the most appropriate interventions for their patients with T2DM[6].

At the time of conducting this study, eight different blood glucose lowering drug classes were approved for the treatment of T2DM in Europe: metformin, sulphonylurea derivatives (SU), alpha glucosidase inhibitors (AGI), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4i), meglitinides, glucagon-like peptide-1 receptor agonists (GLP-1ra), and insulin.

The (inter)national guidelines for use of these therapies share the common goal to prevent and treat complaints and micro- and macrovascular complications by achieving/sustaining glycaemic control[6-11]. In general, these guidelines recommend starting pharmacological treatment with metformin and intensification of treatment as the disease progresses or treatment fails to achieve or sustain the glycaemic goals (see Table 1). However, the guidelines differ in recommendations with regard to the type of intensification. Disparities in recommendations in guidelines can differ for several reasons, such as the influence of professional bodies and characteristics of health care systems[12]. Intensification by adding an SU is well established in the ADA/EASD consensus[6], the Netherlands[8], Spain[9] and the UK[7], whereas the guidelines from Italy[10] and France[11] are less strict and give multiple treatment options as early as second line treatment. Guidance for third line treatment also differs with strict approaches recommended by the ADA/EASD consensus, the Netherlands and the UK (e.g. by adding insulin), compared to the addition of a third oral drug, GLP-1ra or insulin in Spain.

Furthermore, the newer incretin-based classes of DPP-4i and GLP-1ra, which were introduced in the last decade, have different places in the different guidelines[6-11], partly due to limited safety information and higher cost of these classes. With this in mind, we studied the similarities and differences of T2DM treatment patterns in actual practice in five European countries and whether these reflected differences in the (inter)national guidelines.

METHODS

Setting

All data for this observational cohort study were obtained from population-based electronic healthcare databases from five European countries: the PHARMO Database Network[13] in the Netherlands, the Health Search longitudinal patient Database[14,15] (HSD) in Italy, the Sistema d' Informació per al Desenvolupament de la Investigació en Atenció Primària[16,17] (SIDIAP) in Catalonia (Spain), the Echantillon Généraliste de Bénéficiaires[18] (EGB) in France, and The Health Improvement Network[19,20] (THIN) in the United Kingdom (UK). The PHARMO Database Network is a population-based patient-centric data tracking system that currently includes demographic and healthcare databases, including patient demographics, mortality, drug dispensing, hospital morbidity, clinical laboratory, pathology and general practitioner information. HSD contains patient demographic details that are linked using an encrypted patient code with medical records, drug prescription information, prevention records, hospital admission, and date of death. The SIDIAP Database includes common clinical variables (smoking, alcohol drinking, body mass index, blood pressure, etc.), primary care laboratory results (HbA1c, glucose, etc.), pharmacy invoice data and hospital discharge information. THIN is an observational database of electronic healthcare records from primary care practices throughout the UK. Demographic and administrative data, primary and secondary care diagnoses and prescription treatments are routinely recorded against date in individual patient records. EGB is a permanent 1/97 random sample of the nationwide claims and hospitalisation database (SNIIRAM) which covers more than 98% of French population from birth (or immigration) to death (or emigration), even if a subject changes occupations or retires, and includes general characteristics, outpatient reimbursed healthcare and discharged summary for all public and private hospitalisations. Data from all countries except France were electronic health records from routine primary care. Data from France were collected for health insurance reimbursement claims.

Study population

The study population included all adult patients with T2DM initiating glucose lowering treatment, further referred to as T2DM treatment, during the most recent five-year period that was available in each database at the time of analysis: 1 January 2007 to 31 December 2011 for the Netherlands, Spain, Italy and France, and from 1 January 2008 to 31 December 2012 for UK. Patients with T2DM were defined as having a diagnosis code for T2DM, or at least two prescriptions for blood glucose lowering drugs, excluding insulins within a six-month period at any time in the available medication records. The date of the first prescription for T2DM treatment during the study period was defined as the index date. T2DM patients were required to have ≥12 months of continuous enrolment immediately preceding the index date; patients with any prescription for blood glucose lowering drugs in these 12 months were excluded as they were not treatment initiators. Patients with a recorded diagnosis code for type 1 diabetes mellitus or for gestational diabetes were also excluded. All included patients were followed from index date to end of registration in the database, death or end of study period, whichever occurred first.

Data management

All data were analysed at the site of the database holder using a common data model. In order to ensure a homogeneous analysis within the different databases, a SAS analysis tool creating treatment patterns was developed and validated. All database holders were asked to prepare specified input files following the common data model that complied with the tool.

Treatment pattern

The tool converted prescription records (one record per prescribed drug including date, encrypted patient id and ATC code) first into one record per drug class per calendar month, subsequently into episodes of use of each drug class, combination therapies and ultimately into aggregated therapies. Formulations of oral combinations were split into their individual drugs before processing.

Drug classes

To characterize treatment patterns, the following drug classes were identified from the electronic records: metformin, SU, TZD, DPP-4i, GLP-1ra, insulin, and 'other treatment' (e.g. AGI and metaglinides).

Episodes of use

As the duration of use of an individual prescription was not available in all databases, an algorithm was used to create treatment episodes. Prescriptions for blood glucose lowering drugs may cover up to three or even six months. However, low compliance or short time referral to specialist care may lead to a longer interval between prescriptions recorded in primary care. Therefore prescriptions of the same drug class which were nine months apart or less, were considered to represent an episode of uninterrupted use of that drug class. If no subsequent prescription was found within nine months, treatment with the drug class was assumed to have stopped one month after the last prescription date. Multiple episode per patients, even of the same drug class, were possible. Overlapping episodes of multiple drug classes were interpreted as concomitant use, i.e. combination therapy. However, if the start of an episode of one drug class occurred in the month after the last prescription of another class, this was interpreted as a switch, and the prior class was cut short at the time of start of the episode of the new class. The time to change was defined as the duration of each treatment, either monotherapy or combination therapy.

Aggregation of drug classes

For presentation purposes it was necessary to decrease the large number of different treatments. The following therapies were aggregated in the following order: 1) all insulin-containing combination therapies, 2) the DPP-4i containing therapies and 3) the GLP-1ra containing therapies. The remaining therapies (i.e. metformin, SU, TZD, and 'other treatment') or combinations thereof were shown separately if they represented >5% of each study population; otherwise they were aggregated into the group 'other'.

Statistical analyses

Proportions of all patients using specific glucose lowering drug classes were determined in January of each calendar year of the study period (cross-sectional) by country. For the patients initiating T2DM treatment general characteristics, proportion of patients per aggregated T2DM therapy and switching destinations per treatment sequence are reported descriptively per country, presenting proportions for categorical variables, and mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables.

The median time to change in treatment was estimated per therapy per country using Kaplan Meier survival analysis, using change in treatment as the outcome event. Patients were right censored at the end of follow-up in the database records or end of the study period. The time at which 50% of the patients had changed therapy was presented as the median time to treatment change.

All data were analysed using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

RESULTS

General characteristics

A total of 253,530 persons initiating T2DM treatment during the study period were included: 19,512 (8%) from the Netherlands, 25,018 (10%) from Italy, 145,882 (58%) from Spain, 6,721 (3%) from France and 56,397 (22%) from the UK. Males represented 52-55% of the study population and the overall mean age at initiation ranged from 62 years (France) to 67 years (Italy). Median follow-up was approximately 3 years (ranging from 2 years (Italy) to 4 years (Spain)).

Overall use of glucose lowering drug classes

Across all countries, metformin (alone or in combination) was the most commonly used drug and its use increased over time (Fig. 1). Second most common drug class was SU, although, in contrast to metformin, its use decreased over time. The use of insulin was quite stable during the study period and very limited in France compared to the other countries (5-8% in France versus 17-22% in the other countries). TZD use decreased during the study period except in Italy, especially in 2011 when

rosiglitazone was withdrawn in all countries, and all TZDs were withdrawn in France. Clear differences between the participating countries were seen for incretin-based treatments. DPP-4i use substantially increased during the study period in France (0% to 27%), the UK (<1% to 9%) and Spain (0% to 9%), but use remained limited in the Netherlands (4%) and Italy (2%). For GLP-1ra use, although the proportions were low in all countries, a similar pattern was observed; the use increased substantially in France and the UK over time, while the uptake was limited in the Netherlands, Italy and Spain.

Proportion of patients on specific T2DM treatments per treatment sequence

At least one change to another T2DM treatment was observed during the study period for 32% (Italy) to 46% (Spain) of newly treated patients. The proportion of patients with at least one change was the highest among the country with the longest follow-up.

Metformin monotherapy was the most common initial treatment in all countries (ranging from 65% in Italy to 88% in the UK) (Fig. 2). As a second treatment, combination of metformin and SU was most common in the Netherlands (47% of patients changing treatment), the UK (45%) and Spain (24%). Treatment cessation after first treatment, temporary or not, was often observed (11% in the UK to 35% in Italy and was highly variable depending on the amount of follow-up available in the countries. In Italy, the second treatment often consisted of 'other treatments' (22%); this is an aggregated group consisting of many diverse treatments. DPP-4i monotherapy or in combination with other therapies was common in France for the second through fourth treatment (32% to up to 42%). Also in the UK DPP-4i mono- or combination therapy was common as a third treatment class (28%). However, metformin monotherapy was most commonly used as third treatment, ranging from 33% in France to 48% in Spain. In the Netherlands, a common third treatment was any combination with insulin (15%) and in Italy 'other treatment' was the second most common third treatment (17%). Fourth treatment was most often a combination of metformin and SU in the Netherlands (27%) and in Spain (21%), while in the UK and France this was a DPP-4i mono- or combination therapy (29% and 42%, respectively). In Italy, the fourth most common treatment was an 'other treatment' (27%).

Switching destinations per sequential treatment

Patients with metformin monotherapy as the initial treatment most often switched to combination of metformin and SU in the Netherlands (56%), the UK (48%) and Spain (29%), but to DPP-4i mono- or combination therapy in France (41%) and to other treatment in Italy (24%) (Fig. 3a). When the second treatment was a combination of metformin and SU, patients most often resumed metformin in the Netherlands (38%), Spain (34%) and Italy (42%) (Fig. 3b). The same was observed for patients with a temporary stop after their initial treatment (62%-80% of the patients switched (back) to metformin). In France and the UK, patients most often switched to a DPP-4i mono- or combination therapy (both 35%). Patients with DPP-4i mono- or combination therapy as second treatment (which was the most common second treatment in France) most often remained on DPP-4i when they switched but combined with another treatment (ranging from 44% in Italy to 64% in France) (Fig. 3c). In the Netherlands, Spain and the UK, patients with metformin as third treatment most often switched to a combination of metformin and SU (44%, 32% and 38%, respectively) while in France and Italy metformin users switched to DPP-4i mono- or combination treatment (46%) or 'other treatment' (27%), respectively.

Time to change

In all countries, the median time until treatment change declined with the number of sequential changes (Fig. 4). Differences in median time spent on treatment between countries were large for the first treatment (40 months for the UK, 37 for the Netherlands, 31 for Italy, 24 for Spain and 22 for France), but smaller for subsequent treatments (second treatment ranged from 16 to 23 months, third from 15 to 21 and fourth from 13 to 17).

DISCUSSION

This study describes the overall use of glucose lowering drug classes and treatment patterns in five European countries. Metformin was the most common initial treatment in all countries, as recommended by (inter)national guidelines[6-11]. After initial therapy, the choice of drug class(es) differed between the countries. The combination of metformin and SU was most common in the Netherlands, Spain and the UK, which is in line with the ADA/EASD consensus[6] and the respective national guidelines[7-9]. The guidelines from Italy[10] and France[11] are less strict and give multiple treatment options as early as second line treatment. This is reflected in the greater variation in second line treatment that was observed.

Although the use of incretin-based treatments is discouraged in the Netherlands[21], these newer treatments were observed in all countries. The proportion of DPP-4i users was particularly high in France, even as second treatment. Furthermore, use of GLP-1ra substantially increased in the UK and France. Also these differences can be partly explained by the guidelines. GLP-1ra is mainly recommended/reimbursed for patients with a minimum BMI threshold and since the proportion of patients who are overweight is the highest in the UK, as reported by the World Obesity Federation[22], this guide explains the observation for the UK. For France, the explanation would be the lack of guidance as the French guideline only states 'bitherapy'.

An interesting finding was that many patients switched back and forth between monotherapy and dual therapy, despite the recommendation of guidelines to intensify when glycaemic control remains insufficient. Even with our lenient definition of treatment continuation (allowing repeat prescriptions as much as 8 months apart), many interruptions were observed. Whether treatment interruptions and de-intensifications reflect non-compliance, intolerance, or physicians de-intensifying treatment because of reaching glycaemic control could not be determined from this study.

The median time to change differed between the countries. However, this cannot be interpreted in terms of quality of care as the reason for change is not available. A short time to change in treatment may indicate that patients are actively managed and receive more intensive treatment because the prior treatment proved ineffective. But a short time to change may also indicate that patients do not tolerate the prior treatment very well. A long time to change in treatment might indicate inertia when change is actually due, or it may indicate that patients are well controlled and change in treatment is not needed. Since HbA1c and other possible triggers for treatment change were not documented for all patients in all databases, it was outside the scope of this study to assess the factors associated with time to change in treatment.

Differences in rates of micro- and macrovascular complications and HbA1c at time of diagnosis and at time of treatment change might also hamper interpretation of the differences in time to change between countries. In another study[23], large variations in HbA1c at start of an intensification of treatment between the countries were observed. In general, patients in the Netherlands seem to intensify treatment at a lower HbA1c-level (7.8-8.0%), whereas patients in the UK intensify treatment at a higher HbA1c-level (8.5-9.1%).

To our knowledge, no other multi-country study has been published regarding T2DM treatment patterns using a similar approach. Most studies did not follow patients over time, but simply presented cross-sectional data per year and most studies predated our study period, thereby excluding new drug classes such as DPP-4i and GLP-1ra[24-29]. Per country, overall use of glucose lowering drug classes over time was more often studied and similar results as in our study were observed. During 2004-2013 the use of metformin and SU in the Netherlands increased, while the use of TZD decreased. The use of DPP-4i remained low[30]. Use of metformin did not change during 2010-2012 in Italy, use of SU and TZD decreased and use of GLP-1ra and DPP-4i increased[31]. In Spain, metformin was the most common drug class and DPP-4i use increased (in relative terms) the most during 2008-2012[32]. In France, the use of metformin increased during Q4 2007-Q4 2013 and all TZD

and some SU treatments were replaced by DPP-4i and to a much lesser extend by GLP-1ra[33]. For the period of 2006-2010, metformin as initial treatment increased and SU as initial treatment decreased in the UK[34]. Another study also showed a stable prevalence of insulin use between 2000 and 2013 and a decrease in TZD use since 2007[35].

Strengths and limitations

A major strength of this study is its design. This multi-country observational and longitudinal study regarding T2DM treatment patterns used the same statistical program applied to all countries (common data model), which ensured a homogenous analysis along the countries. Over a quarter million persons initiating T2DM treatment during 2007/2008-2011/2012 were included.

As recent data were not available during the study, there is limited information regarding newer T2DM treatments. We do expect differences regarding the uptake of these newer treatments, particularly in second line and beyond, as current guidelines differ in recommending these newer drugs. Furthermore, patients included in the study could only be described in terms of demographic characteristics. Unfortunately clinical information such as HbA1c, micro- and macrovascular complications, co-medication or, comorbiditieswas not available for all five countries.

A proxy for duration of use of a prescription was used as the actual duration was not available in all databases. An algorithm was used assuming continued use of a drug class as long as there was a repeat prescription within nine months. This was done to avoid creation of gaps in treatment if patients were temporarily treated by a specialist, but continued their original treatment as not all specialist prescriptions may be visible in the GP databases. However, in most countries the GP is the main treating physician for patients with T2DM.

For this study drug classes for the treatment of T2DM were defined a priori by the PHARMO Institute: metformin, SU, TZD, DPP-4i, GLP-1ra, other OADs and insulin. The drug class ‘other OADs’ combined meglitinides, guar gum, benfluorex, pramlintide and AGI. However, the use of meglitinides and AGI differed per country. For example acarbose is more often prescribed in France, where it is mentioned

as an alternative to metformin as first line treatment[11]. Furthermore, repaglinide was often prescribed in Italy. Generally meglitinides are suggested as an alternative to SU only in case of high risk of SU induced hypoglycaemia, as meglitinides are at higher cost and have a more frequent dosing schedule compared to SU. This made comparisons between the countries regarding this group difficult.

Future directions

This study provides a comprehensive overview of T2DM treatment patterns among patients initiating T2DM treatment in five European countries. Furthermore, it may serve as background material when interpreting other diabetes studies across Europe and to put these in perspective. Also, as our study does not provide reasons for initiating or discontinuing treatment, further research should focus on these reasons to put our results more in perspective.

Initial T2DM treatment is similar in the Netherlands, Italy, Spain, France and UK. Differences concern the uptake of newer incretin-based treatments, which are usually prescribed as a second and/or third treatment. As approval, availability and reimbursement are very similar between the selected countries; the different treatment patterns observed are probably driven by guidelines and/or local organisation of diabetes care (e.g. the presence of diabetes clinics and/or diabetes disease management programs). The newer treatments did not (yet) find their way in all guidelines during the study period. For countries with national guidelines not in line with the ADA/EASD consensus (i.e. Italy and France), our results suggest that these countries prefer to follow their national guidelines.

Apparently, despite one European regulatory authority which centrally decides whether a medicine is authorised in Europe, actual T2DM treatment differs per country. These data are of interest to EU healthcare commissioners and policy-makers as they contain key information on sources of heterogeneity in the treatment of T2DM throughout EU member states.

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Conflicts of Interest statement

JO, EH, IB and RH are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies. DPAs research group and/or department have received unrestricted research grants from Bioberica, AMGEN and Servier Laboratoires. PB is an employee of The Bordeaux PharmacoEpi (BPE) - CIC 1401, an academic research team which performs financially supported studies for public and private partners, including several pharmaceutical companies. RL has no conflict of interest to disclose regarding this manuscript. GH has been on the Advisory Group of the THIN database and has received funding for research and consultancy from a number of pharmaceutical companies and from charities. FL provided consultancies in protocol preparation and data analysis for epidemiological studies for AMGEN, Sanofi and Eli-Lilly. EB has no conflict of interest to disclose. NH is an employee of AstraZeneca.

REFERENCES

1. Chittleborough CR, Grant JF, Phillips PJ, Taylor AW (2007) The increasing prevalence of diabetes in South Australia: the relationship with population ageing and obesity. Public Health 121: 92-99
2. Andersson T, Ahlbom A, Magnusson C, Carlsson S (2014) Prevalence and incidence of diabetes in Stockholm County 1990-2010. PLoS One 9: e104033
3. Geiss LS, Wang J, Cheng YJ, et al (2014) Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. JAMA 312: 1218-1226
4. Stratton IM, Adler AI, Neil HA, et al (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321: 405-412
5. (2014) American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care 37 Suppl 1: S14-80
6. Nathan DM, Buse JB, Davidson MB, et al (2009) Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 52: 17-30
7. National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice at NICE. NICE guideline Type 2 diabetes: The management of type 2 diabetes. 2009.
8. Rutten GEHM, De Grauw WJC, Nijpels G, et al (2006) NHG-Standaard Diabetes mellitus type 2 (Tweede herziening). Huisarts Wet 49: 137-152
9. Ariz Arnedo MJ, Artola Menéndez S, Barutell Rubio L, et al. Práctica clínica en la DM2. Barcelona: 2011.
10. (SID) AMDA-SIdD. Standard italiani per la cura del diabete mellito tipo 2. 2011.
11. Agence française de sécurité sanitaire des produits de santé (afssaps) et Haute Autorité de Santé (HAS) (2006) Traitement médicamenteux du diabète de type 2 (Actualisation), recommendations de bonne pratique. Available from http://www.formindep.org/IMG/pdf/recos_diabete-2006.pdf, accessed 24 February 2016
12. Burgers JS, Bailey JV, Klazinga NS, et al (2002) Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. Diabetes Care 25: 1933-1939
13. (2016) PHARMO Institute for Drug Outcomes Research. Available from http://www.pharmo.com, accessed 22 April 2016.
14. Cricelli C, Mazzaglia G, Samani F, et al (2003) Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. J Public Health Med 25: 254-257
15. Filippi A, Vanuzzo D, Bignamini AA, Mazzaglia G, Cricelli C, Catapano AL (2005) The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. Ital Heart J 6: 311-314
16. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, et al (2011) Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Inform Prim Care 19: 135-145
17. Vinagre I, Mata-Cases M, Hermosilla E, et al (2012) Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). Diabetes Care 35: 774-779
18. Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merliere Y (2010) French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique 58: 286-290
19. (2015) The Health Improvement Network (THIN) database. Available from https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database, accessed 29 April 2016.

20. Blak BT, Thompson M, Dattani H, Bourke A (2011) Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care 19: 251-255
21. Verduijn T, Janssen PG. NHG-Standpunt DPP-4-remmers en GLP-1-agonisten. In: NHG, editor. Utrecht2010.
22. World Obesity Federation. Adult overweight and obesity in the European Union (EU28) based on Measured Height and Weight. World Obesity Federation. , 2015.
23. Overbeek JA, Heintjes EM, Hall GC, Lapi F, Prieto Alhambra D, Bezemer ID (2015) Factors Associated with T2DM Treatment Choice Across Europe. Value Health 18: A600
24. Boyc KS, Yurgin N, Lage MJ (2007) Trends in the prescription of antidiabetic medications in France: evidence from primary care physicians. Adv Ther 24: 803-813
25. Langendam MW, Hooijkaas C, Piepenbrink JF (2006) [The increase in the use of drug treatment for diabetes mellitus in the Netherlands, 1998-2003]. Ned Tijdschr Geneeskd 150: 1396-1401
26. Baviera M, Monesi L, Marzona I, et al (2011) Trends in drug prescriptions to diabetic patients from 2000 to 2008 in Italy's Lombardy Region: a large population-based study. Diabetes research and clinical practice 93: 123-130
27. Arrieta FJ, Calvo MJ, Perez A, et al (2006) [Prevalence and consumption of medication in diabetes mellitus in Madrid (1996-2002)]. Rev Clin Esp 206: 117-121
28. Leal I, Sammon C, Masclee GMC, et al (2015) Trends of use of non-insulin blood glucose lowering drugs in Europe and USA. Pharmacoepidemiol Drug Saf 24: 106-107 (Abstract)
29. Leal I, Sammon C, Masclee GMC, et al (2015) Patterns of use of incretin-based therapies in Europe and USA. Pharmacoepidemiol Drug Saf 24: 106 (Abstract)
30. Torre C, Guerreiro J, de Oliveira Martins S, Raposo JF, Martins AP, Leufkens H (2015) Patterns of glucose lowering drugs utilization in Portugal and in the Netherlands. Trends over time. Prim Care Diabetes:
31. Rafaniello C, Arcoraci V, Ferrajolo C, et al (2015) Trends in the prescription of antidiabetic medications from 2009 to 2012 in a general practice of Southern Italy: a population-based study. Diabetes research and clinical practice 108: 157-163
32. Mancera-Romero J, Hormigo-Pozo A, Fernandez-Arquero J, Baca-Osorio A, Aparicio-Cervantes MJ, Munoz-Gonzalez L (2014) [Use of glucose-lowering drugs in a primary care setting in Malaga during the years 2008-2012]. Semergen 40: 4-11
33. Simon D, Dallongeville J, Charbonnel B, et al (2015) Patterns of Pharmacological Treatment in Type 2 Diabetes in France in 2013. Value Health 18: A599
34. Maguire A, Mitchell BD, Ruzafa JC (2014) Antihyperglycaemic treatment patterns, observed glycaemic control and determinants of treatment change among patients with type 2 diabetes in the United Kingdom primary care: a retrospective cohort study. BMC Endocr Disord 14: 73
35. Sharma M, Nazareth I, Petersen I (2016) Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ open 6: e010210

TABLES

Table 1 Overview of step-wise pharmacological T2DM treatment according to national guidelines per country

FIGURES

NOTE: Per year, proportions of the drug classes combined add up to >100% as oral combination formulations were split into their individual drugs before processing.

Figure 1 Overall use of glucose lowering drug class per year per country

Figure 2 Proportion of patients on specific T2DM treatments per treatment sequence per country

a) Switching destination from first treatment to second treatment
b) Switching destination from second treatment to third treatment
c) Switching destination from third treatment to fourth treatment

NOTE: Switching destination from GLP-1ra was not presented as this treatment was only available for UK and consisted of only 16 patients.

Figure 3 Switching destinations per treatment during study period per country

Figure 4 Median time to change of sequential treatments per country