BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008531
Article Type:	Research
Date Submitted by the Author:	17-Apr-2015
Complete List of Authors:	Christiansen, Christian; Aarhus University Hospital, Department of Clinical Epidemiology Ehrenstein, Vera; Aarhus University Hospital, Department of Clinical Epidemiology Skovbo, Stine; Aarhus University Hospital, Department of Clinical Epidemiology Nørrelund, Helene; Aarhus University Hospital, Department of Clinical Epidemiology Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology Li, Lin; Boston University School of Public Health, Boston Collaborative Drug Surveillance Program Jick, Susan; Boston University,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Renal medicine, Epidemiology, Health services research
Keywords:	Chronic renal failure < NEPHROLOGY, DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Diabetes & endocrinology < INTERNAL MEDICINE

Metformin Use in Patients with Renal Impairment: A drug utilization study in Denmark and the United Kingdom

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Key words: Chronic Kidney Disease, Diabetes Mellitus, Drug Utilization, Glomerular Filtration Rate, Metformin

Word count: 2,941

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Abstract

Objectives: To estimate prevalence of renal impairment in metformin users, and to examine utilization of metformin among diabetes patients with renal impairment.

Design, setting and participants: We conducted this two-country drug utilization study using routine data from northern Denmark and the UK during 2000-2011. We included patients aged ≥30 years with medically treated diabetes.

Main outcome measures: Using cross-sectional analysis, we described patients' demographics, comorbidities, and co-medications according to metformin use and renal function by estimated glomerular filtration rates (eGFR). We also examined changes in metformin use within 90 days after first decline in eGFR after study start.

Results: We included 172,052 diabetes patients in Denmark and the UK. Users of metformin were overall younger and had lower prevalence of comorbidities and metformin contraindications including renal impairment than users of other antidiabetic drugs. Prevalence of eGFR <60 ml/min/1.73m^2 among new metformin users was 11.0% in Denmark and 25.2% in the UK. In contrast, eGFR values <45 ml/min/1.73m^2 were less prevalent (2.7% of new metformin users in Denmark and 4.9% in the UK). Most metformin users continued taking the medication after the first decline in eGFR to 45-59 ml/min/1.73m^2 (66% in Denmark and 86% in the UK). A considerable proportion of patients continued metformin use even when the first decline in the study period was to an eGFR below 30 ml/min/1.73m^2 (43% in Denmark and 64% in the UK).

There was no clinically significant dose reduction with decreasing eGFR level discernible from the data.

Conclusions: Mild to moderate renal impairment was common among metformin users, many of whom continued metformin after developing severe renal impairment – against current recommendations.

Article summary

Strengths and limitations of the study:

- The study describes metformin utilization in a large population of patients with medically treated diabetes
- The study includes comparable data from electronic databases in two European Union member states: Denmark and the United Kingdom
- The data include comprehensive individual-level prescription data, laboratory data, and data on medical history, all linked at the individual level
- The cross-sectional design limited the description of the dynamic change in renal impairment along the clinical course of diabetes

Introduction

Metformin was approved in European countries in the 1950s for treatment of type 2 diabetes.[1,2] While metformin is a first-line treatment, it is contraindicated in patients with certain acute and chronic conditions – such as severe infections, cardiac or respiratory failure, shock, or chronic renal or hepatic dysfunction – because of the feared, although not convincingly demonstrated, risk of lactic acidosis.[3-7]

Because metformin is eliminated through renal excretion,[8] patients with renal impairment may be vulnerable to its side effects. Current guidelines recommend cautious use of metformin in patients with renal impairment, and metformin is contraindicated in patients with severe renal impairment.[4] Guidelines recommend discontinuation of metformin in patients with an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73m^2, but recommended eGFR thresholds that should trigger cautious use and dose reduction vary between 60 and 45 ml/min/1.73m^2.[2,4,9-11] Reported prevalence of patients with eGFR below 60 ml/min/1.73m^2 among metformin users ranges from 4.5% to 25%,[12-17] with most evidence originating from studies that were small,[12-14,17] hospital-based,[12,17] or restricted to patients with poorly controlled diabetes.[12] Given the lack of clear-cut recommendations, the observed utilisation patterns, and the limitations of previous studies, the use and safety of metformin in patients with renal impairment should be further examined in a population-based setting among a broad range of diabetes patients.

This study was commissioned by the European Medicines Agency (EMA) with the goal of assessing the utilization of metformin in patients with and without renal insufficiency in current clinical practice in at least two European Union Member States. The study was undertaken to inform potential reassessment and unified recommendations' by the regulator of guidelines for metformin use in patients with renal insufficiency. In a series of epidemiologic analyses among pharmacologically-treated type 2 diabetes patients, we examined 1) prevalence of renal impairment and other contraindications among new and prevalent users of metformin, 2) utilisation of metformin in patients

with type 2 diabetes by stage of renal impairment, and 3) utilisation of metformin after worsening of renal impairment.

Patients and methods

Study design and study period

We undertook a cross-sectional analysis of metformin utilisation patterns. The study period was defined, based on data availability in northern Denmark (including 2000-2010 in the former counties of Aarhus and North Jutland, 2007-2010 in the former county of Ringkjobing, 2009-2012 in the former county of Viborg), and in the United Kingdom (UK) (including 2000-June 2011).

Source population and data sources

The source population for the study was residents of northern Denmark and the UK – the two EU Member States with relevant routine databases. In Denmark, we individually linked data from four registries using the unique personal identification number, assigned at birth or upon immigration by the Danish Central Personal Registry.[18,19] This registry, covering the entire Danish population, has recorded vital status and migrations of Danish residents since 1968. We obtained data from the Aarhus University Prescription Database (AUPD) on reimbursed prescriptions for antidiabetic and other drugs dispensed in the community outpatient pharmacies of northern Denmark.[20] Data on creatinine, blood glucose and glycated haemoglobin were obtained from the Danish Laboratory Information System for the North and Central Denmark (LABKA) database,[21] which tracks all hospital-based laboratory tests in the study region, including those sent to hospital laboratories by general practitioners. The Danish National Registry of Patients[22] provided data on comorbidities and prevalence of contraindications. This registry covers the entire Danish population and has registered hospitalizations since 1977 and outpatient visits since 1995. Up to 20 discharge diagnoses are recorded for each hospital contact, using the *International Classification of Diseases,* 8th revision (ICD-8) until 1994 and the ICD-10 thereafter.

In the UK, the source population was restricted to eligible patients treated by general practitioners (GPs) participating in the Clinical Practice Research Datalink (CPRD).[23,24] The CPRD is an ongoing longitudinal database that has collected data from over 500 general practices in the UK since 1987. It covers approximately 8 million individuals (~6% of the UK population) whose age and sex distribution is representative of the UK population. We accessed the database through the Boston Collaborative Drug Surveillance Program (BCDSP). The BCDSP has received anonymised raw data generated by the GPs since the CPRD was first established. Validation studies have shown greater than 90% concordance between information from the original paper records and information recorded on the computer file. Further, the indication for newly prescribed drugs is recorded more than 95% of the time.[23] The CPRD data housed at the BCDSP are updated annually, so that the most recent data available are never more than 15 months out-of-date. The data are recorded using multiple data screens or files, including registration, drug, and laboratory data, event files, and files containing additional clinical details.

Study population

The study population consisted of persons aged 30 years or older at study entry with medically treated type 2 diabetes, as defined by at least one prescription for an antidiabetic medication during the study period. The study population was restricted to patients aged 30 years or older to exclude those with metformin-treated polycystic ovary syndrome or type 1 diabetes, both of which are frequently diagnosed before age 30 years.[25,26] The study was also restricted to patients with at least one year of prescription history before study entry, in order to allow for an observable washout period to identify new users. In addition, we required patients to have at least one measurement of serum creatinine on or before study entry in order to assess baseline renal function.

Use of metformin and other antidiabetic agents

Metformin users were identified from records of issued prescriptions provided by GPs in the UK and from outpatient-dispensed prescriptions in Denmark. We identified all patients with at least one prescription for metformin during the study period, and included both new and prevalent users in the main analyses.[27] New users of metformin were defined as patients without a prescription for

metformin within a washout period of 365 days before the first metformin prescription during the study period. Other metformin users were considered prevalent users. Users of other antidiabetic drugs were defined as all patients who received a prescription for a non-metformin antidiabetic drug (including sulfonylureas, insulin, glitazones, and other antidiabetics) in the absence of a prescription for metformin during the study period.

For new users, the index date (start of follow-up) was the date of the first antidiabetic drug prescription during the study period. For prevalent users, the index date was 1 January 2000. For each patient with at least two prescriptions for metformin in Denmark, we estimated the daily dose of metformin on the index date. Mean daily dose was calculated as the ratio of the total amount of metformin dispensed on the index date to the number of days until the second metformin dispensation. In the UK, where prescribed daily dose is recorded, we estimated the mean daily dose using the cumulative prescribed dose dispensed from all prescriptions on the index date divided by the number of days of use. In Denmark, we assumed that the last filled prescription provided a 43-day supply, which was the mean duration of all metformin prescriptions in the data set. In the UK, we calculated the length of the last prescription in the CPRD using the amount dispensed in the last issued prescription divided by the prescribed daily dose whenever available. Otherwise we assumed that the last prescription provided a 42-day supply, which was the mean duration of all metformin prescriptions in the CPRD.

We defined discontinuation after an eGFR decline as presence of a metformin prescription within 90 days before the date of the eGFR decline combined with absence of a metformin prescription within 90 days after the date of the eGFR decline. We defined switching as a prescription for a non-metformin antidiabetic drug within 90 days after the date of eGFR decline, with no metformin prescription recorded within this 90-day time window. Patients were considered to have stopped metformin use before an eGFR decline if the last prescription prior to the eGFR ended more than 90 days before the date of the decline. Patients with fewer than 90 days of follow-up after the date of eGFR decline were categorized as having incomplete follow-up.

Renal function and renal impairment

For each patient, we identified all recorded serum creatinine (S_{cr}) laboratory values in the LABKA database in Denmark[21] and in the CPRD's laboratory file. We did not evaluate measurements during hospital inpatient admissions, to avoid confounding by acute illness. Creatinine values were used to assess renal function in the calculation of the eGFR[28] at baseline and during follow-up. We used the 4-variable Modification of Diet in Renal Disease (MDRD) equation, which estimates eGFR based on S_{cr}, age, race, and sex.[28,29] Because neither study database collects data on race, the eGFR calculation assumed Caucasian race for all persons in the study, as they represent majority of Danish and UK residents. Based on eGFR, kidney function was classified as follows (corresponding to the criteria for chronic kidney disease): eGFR ≥ 60 ml/min/1.73m^2 (corresponding to Stage 1 and 2 chronic kidney disease or normal renal function); eGFR 45-59 ml/min/1.73m^2 (Stage 3a chronic kidney disease); eGFR 30-44 ml/min/1.73m^2 (Stage 3b chronic kidney disease); eGFR 15-29 ml/min/1.73m^2 (Stage 4 chronic kidney disease); and eGFR <15 ml/min/1.73m^2 (Stage 5 chronic kidney disease).

Covariates

We identified the following characteristics from the available data sources: age on the index date; sex; glycated haemoglobin A1c (HbA1c) level measurement within 12 months before the index date; time from the first recorded antidiabetic drug prescription until the study entry date, as a proxy for diabetes duration in Denmark, or time from either the first recorded antidiabetic drug prescription or first recorded diabetes diagnosis, whichever was earlier, until the index date in the UK (categorized as first prescription,< 1 year; 1-<3 years; 3+ years); history of potential contraindications for metformin within 5 years before the index date, including diagnoses of diabetic ketoacidosis, liver disease, severe infections, shock, respiratory failure, and alcohol-related diseases; history of other chronic diseases within 5 years before the index date, including each of the conditions in the Charlson Comorbidity Index (except for diabetes and diabetes with organ complications);[30,31] and concomitant use (within 90 days before the index date) of other antidiabetic medications, non-steroidal anti-inflammatory drugs (NSAIDs), anti-hypertensives, antiretroviral medications, or aspirin (acetylsalicylic acid).

Statistical analyses

First, we described characteristics of the study population at baseline (index date). (See Table 1 for the list of characteristics.)

Table 1. Renal impairment and other characteristics of metformin users and users of other antidiabetic (AD) drugs during the study period.

	Northern Denmark				UK			
	Metformin users			Users of other AD drugs	Metformin users			Users of other AD drugs
	New users N = 36 018	Prevalent users N = 2417	All users N = 38 435	Non-users N = 14 092	New users N = 101 992	Prevalent users N = 8348	All users N = 110 340	Non-users N = 9185
eGFR (most recent within a year before index date) - n (%)								
>= 60 ml/min/1.73m^2	32051 (88.99)	1938 (80.18)	33989 (88.43)	9603 (68.15)	76 304 (74.81)	5454 (65.33)	81 758 (74.10)	4370 (47.58)
45-59 ml/min/1.73m^2	2987 (8.29)	337 (13.94)	3324 (8.65)	2491 (17.68)	20 648 (20.24)	2143 (25.67)	22 791 (20.66)	2571 (27.99)
30-44 ml/min/1.73m^2	844 (2.34)	116 (4.80)	960 (2.50)	1378 (9.78)	4620 (4.53)	668 (8.00)	5288 (4.79)	1655 (18.02)
15-29 ml/min/1.73m^2	130 (0.36)	23 (0.95)	153 (0.40)	486 (3.45)	408 (0.40)	80 (0.96)	488 (0.44)	508 (5.53)
<15 ml/min/1.73m^2	6 (0.02)	3 (0.12)	9 (0.02)	134 (0.95)	12 (0.01)	3 (0.04)	15 (0.01)	81 (0.88)
Metformin daily dose (mg) at study inclusion, mean (SD)[a,b]	1453.27 (2507.61)	2095.43 (6355.22)	1454.70 (2522.53)	N/A	1104.63 (426.64)	1567.45 (596.32)	1141.38 (459.84)	N/A
Metformin daily dose during study period (mg), mean (SD)[a]	1413.17 (537.82)	1455.37 (600.86)	1413.27 (537.98)	N/A	1265.86 (634.70)	1637.67 (607.75)	1293.99 (640.29)	N/A
Demographics								
Age (years) - median (IQR)	62 (53 - 71)	63 (54 - 71)	62 (53 - 71)	71 (58 - 79)	63 (54-72)	66 (58-73)	63 (54-72)	74 (64-81)
Age (years) - n(%)								
30-39	1968 (5.46)	83 (3.43)	2051 (5.34)	809 (5.74)	4542 (4.45)	108 (1.29)	4650 (4.21)	305(3.32)
40-49	4472 (12.42)	270 (11.17)	4742 (12.34)	1192 (8.46)	12 566 (12.32)	616 (7.38)	13 182 (11.95)	416 (4.53)
50-59	8584 (23.83)	628 (25.98)	9212 (23.97)	1912 (13.57)	23 228 (22.77)	1613 (19.32)	24 841 (22.51)	808 (8.80)
60-69	11000 (30.54)	719 (29.75)	11719 (30.49)	2800 (19.87)	29 098 (28.53)	2812 (33.68)	31 910 (28.92)	1776 (19.34)
70-79	7070 (19.63)	543 (22.47)	7613 (19.81)	3956 (28.07)	23 507 (23.05)	2344 (28.08)	25 851 (23.43)	3041 (33.11)
>= 80	2924 (8.12)	174 (7.20)	3098 (8.06)	3423 (24.29)	9051 (8.87)	855 (10.24)	9906 (8.98)	2839 (30.91)
Female gender – n (%)	15973 (44.35)	1265 (52.34)	17238 (44.85)	6520 (46.27)	45 361 (44.48)	4085 (48.93)	49 446 (44.81)	4145(45.13)
Male gender – n (%)	20045 (55.65)	1152 (47.66)	21197 (55.15)	7572 (53.73)	56 631 (55.52)	4263 (51.07)	60 894 (55.19)	5040(54.87)
Duration of type 2 diabetes* - n(%)								
First prescription at index date	23 491 (65.22)	N/A	23 491 (61.12)	8008 (56.83)	18766 (18.40)	N/A	18766 (17.01)	1529 (16.65)
<1 year	2153 (5.98)	249 (10.30)	2402 (6.25)	420 (2.98)	32868 (32.23)	461 (5.52)	33329 (30.21)	2538 (27.63)
1-3 years	2952 (8.20)	471 (19.49)	3423 (8.91)	971 (6.89)	19211 (18.84)	1386 (16.60)	20 597 (18.67)	1440 (15.68)
>= 3 years	7422 (20.61)	1697 (70.21)	9119 (23.73)	4693 (33.30)	31 147 (30.54)	6501 (77.87)	37 648 (34.12)	3678 (40.04)
Glycated haemoglobin A (HbA1c), %, mean (SD) (a)	8.26 (1.83)	8.20 (1.65)	8.26 (1.82)	8.26 (1.91)	8.67 (1.80)	8.12 (1.65)	8.62 (1.79)	8.22 (1.96)
History of potential contraindications for metformin within 5 years before index date - n(%)								
Diabetic ketoacidosis	58 (0.16)	12 (0.50)	70 (0.18)	206 (1.46)	69 (0.07)	17 (0.20)	86 (0.08)	29 (0.32)
Liver disease	372 (1.03)	27 (1.12)	399 (1.04)	348 (2.47)	1034 (1.01)	29 (0.35)	1063 (0.96)	144 (1.57)
Severe infections	2651 (7.36)	180 (7.45)	2831 (7.37)	2286 (16.22)	27 621 (27.08)	2383 (28.55)	30 004 (27.19)	2217 (24.14)
Severe infections[c]	N/A	N/A	N/A	N/A	1078 (1.06)	90 (1.08)	1168 (1.06)	308 (3.35)

	Northern Denmark				UK			
	Metformin users			Users of other AD drugs	Metformin users			Users of other AD drugs
	New users N = 36 018	Prevalent users N = 2417	All users N = 38 435	Non-users N = 14 092	New users N = 101 992	Prevalent users N = 8348	All users N = 110 340	Non-users N = 9185
Shock	16 (0.04)	1 (0.04)	17 (0.04)	18 (0.13)	72 (0.07)	3 (0.04)	75 (0.07)	10 (0.11)
Respiratory failure	323 (0.90)	10 (0.41)	333 (0.87)	283 (2.01)	79 (0.08)	5 (0.06)	84 (0.08)	15 (0.16)
Alcohol-related diseases	246 (0.68)	18 (0.74)	264 (0.69)	374 (2.65)	1070 (1.05)	68 (0.81)	1138 (1.03)	190 (2.07)
Co-medication within 90 days before index date - n(%)								
Other antidiabetic medications	11 201 (31.10)	1879 (77.74)	13 080 (34.03)	14 092 (100.0)	20 141 (19.75)	4985 (59.71)	25 126 (22.77)	9185 (100.00)
NSAIDs	5764 (16.00)	327 (13.53)	6091 (15.85)	1773 (12.58)	11 965 (11.73)	1103 (13.21)	13 068 (11.84)	926 (10.08)
Anti-hypertensives	19 631 (54.50)	1280 (52.96)	20 911 (54.41)	7257 (51.50)	64 112 (62.86)	5162 (61.84)	69 274 (62.78)	6138 (66.83)
Antiretroviral medications	0	0	0	0	5 (0.00)	0	5 (0.00)	3 (0.03)
Aspirin	26 444 (73.42)	2203 (91.15)	28 647 (74.53)	14 091 (99.99)	28 954 (28.39)	2034 (24.37)	30 988 (28.08)	2798 (30.46)
Charlson Comorbidity Index Score - n(%) (a)								
0	24 743 (68.70)	1641 (67.89)	26 384 (68.65)	6841 (48.55)	57 993 (56.86)	4693 (56.22)	62 686 (56.81)	3700 (40.28)
1	6354 (17.64)	443 (18.33)	6797 (17.68)	2902 (20.59)	24 592 (24.11)	2296 (27.50)	26 888 (24.37)	2225 (24.22)
2	3091 (8.58)	213 (8.81)	3304 (8.60)	2174 (15.43)	11 870 (11.64)	883 (10.58)	12 753 (11.56)	1624 (17.68)
3	1079 (3.00)	66 (2.73)	1145 (2.98)	1049 (7.44)	4704 (4.61)	318 (3.81)	5022 (4.55)	880 (9.58)
>=4	751 (2.09)	54 (2.23)	805 (2.09)	1126 (7.99)	2833 (2.78)	158 (1.89)	2991 (2.71)	756 (8.23)
Lifestyle factors (when available)								
Obesity [d]	N/A	N/A	N/A	N/A	54 100 (53.04)	3801 (45.53)	57 901 (52.48)	1879 (20.46)
Smoking								
Current	N/A	N/A	N/A	N/A	17 505 (17.16)	1351 (16.18)	18 856 (17.09)	1444 (15.72)
Former	N/A	N/A	N/A	N/A	41 660 (40.85)	2475 (29.65)	44 135 (40.00)	3241 (35.29)
Never	N/A	N/A	N/A	N/A	40 957 (40.16)	4189 (50.18)	45 146 (40.92)	4010 (43.66)
Missing	N/A	N/A	N/A	N/A	1870 (1.83)	333 (3.99)	2203 (2.00)	490 (5.33)

IQR: interquartile range; N/A: Not available/applicable

* In the UK, duration was defined as time since first antidiabetic prescription or first diagnosis of type 2 diabetes, whichever was earlier[a] Based on non-missing values

[b] For prevalent users the daily dose was estimated based on the dosage of the first prescription of metformin and period from first to second prescription after cohort entry (Jan 1, 2000)

[c] Defined as having a hospitalization code within 7 days before or after diagnosis of severe infections

[d] Defined as a body mass index ≥ 30 kg/m^2

Second, we described the patient characteristics according to the five categories of chronic renal disease at baseline. Third, we assessed continued use and discontinuation of metformin after the first decline in eGFR, from the baseline eGFR (based on last available outpatient serum creatinine measurement within 1 year before or on the index date). Appendix 1 lists codes for diagnoses, drugs, and laboratory measurements used in the study. Both study sites used SAS Statistical Software Version 9 (Cary, NC, USA) for data management and analyses.

Results

The study included 52,527 patients in Denmark and 119,525 patients in the UK medically treated for diabetes.

Drug utilisation

Table 1 provides characteristics of metformin users and users of other antidiabetic drugs. Metformin users comprised 73% of the patient population in Denmark and 92% in the UK. The proportion of metformin users with duration of diabetes of 3 or more years was 24% in Denmark and 34% in the UK. There was no clinically important difference in mean glycated haemoglobin between users of metformin and users of other antidiabetic drugs or between countries.

The overall mean daily dose of metformin was 1413 mg in Denmark and 1294 mg in the UK. Among prevalent users, the mean daily dose was 1455 mg in Denmark and 1638 mg in the UK. The median age of metformin users was 62 years in Denmark and 63 years in the UK, while users of other antidiabetic drugs were older (ages 71 and 74 years, respectively). The prevalences of diabetic ketoacidosis, liver disease, shock, respiratory failure, or alcohol-related diseases were low. As expected, these contraindications for metformin use were more prevalent among users of other antidiabetic drugs than among metformin users. Compared with metformin users, a larger proportion of users of other antidiabetic drugs had a high Charlson Comorbidity Index score. (Table 1)

The prevalence of chronic kidney disease with eGFR values below 60 ml/min/1.73m^2 was lower among metformin users than among users of other antidiabetic drugs (11.6% vs. 31.9% in Denmark

and 25.9% vs. 52.4% in the UK). (Table 1) Nevertheless, eGFR values below 60 ml/min/1.73m^2 was common among new users of metformin (11.0% and 25.2% in Denmark and the UK, respectively), while a baseline eGFR below 45 ml/min/1.73m^2 was less common (2.7% in Denmark and 4.9% in the UK). As expected, the proportion of patients with a baseline eGFR level below 30 ml/min/1.73m^2 was markedly lower among new metformin users (0.38% in Denmark and 0.41% in the UK). (Table 1)

Drug utilisation according to eGFR level

Danish metformin users were more likely to have concurrent use of other antidiabetic drugs, in particular insulin and sulfonylureas, as baseline eGFR levels decreased. These differences were less pronounced in the UK patients. As expected, more patients with a low baseline eGFR had diabetes duration of 3 or more years. Still, approximately 48% of the metformin users in Denmark and around 35% in the UK with an eGFR below 45 ml/min/1.73m^2 had a diabetes duration of less than 1 year. We observed no substantial decrease in mean daily metformin dose with decreasing eGFR. NSAIDs were prescribed in more than 10% of patients within 90 days before study entry, even in patients with low baseline eGFR levels (Table 2).

Table 2. Drug utilisation study. Metformin use and other characteristics according to level of renal function at cohort entry.

	Northern Denmark					UK				
	Estimated glomerular filtration rate (eGFR)					Estimated glomerular filtration rate (eGFR)				
eGFR (using last creatinine measurement within a year before inclusion, ml/min/1.73m^2)	>= 60 (N=33989)	45-59 (N=3324)	30-44 (N=960)	15-29 (N=153)	<15 (N=9)	**≥ 60 (n = 81 758)**	**45-59 (n =22 791)**	**30-44 (n =5288)**	**15-29 (n =488)**	**<15 (n =15)**
Antidiabetic drug use - n (%) (These are not mutually exclusive categories)										
Metformin	33989 (100.0)	3324 (100.0)	960 (100.0)	153 (100.0)	9 (100.0)	81 758 (100)	22 791 (100)	5288 (100)	488 (100)	15 (100)
Insulin	1327 (3.90)	189 (5.69)	73 (7.60)	22 (14.38)		549 (0.67)	212 (0.93)	78 (1.48)	10 (2.05)	0
Sulfonylureas	6165 (18.14)	901 (27.11)	286 (29.79)	39 (25.49)	3 (33.33)	6371 (7.79)	2313 (10.15)	754 (14.26)	92 (18.85)	5 (33.33)
Glitazones	154 (0.45)	15 (0.45)	7 (0.73)	0	0	280 (0.34)	65 (0.29)	18 (0.34)	3 (0.61)	0
Other antidiabetic drugs	449 (1.32)	69 (2.08)	17 (1.77)	1 (0.65)	1 (11.11)	344 (0.42)	98 (0.43)	23 (0.43)	3 (0.61)	0
Metformin daily dose (mg) at study inclusion, mean (SD)[a,b]	1438.72 (2502.22)	1580.67 (2753.02)	1598.42 (2460.93)	2327.38 (2990.09)	793.65 (.)	1151.71 (460.02)	1117.19 (459.30)	1089.98 (454.07)	1106.84 (434.10)	1171.43 (555.64)
Metformin daily dose during study period (mg), mean (SD)[a]	1425.96 (540.68)	1314.29 (502.67)	1235.00 (472.59)	1382.71 (541.95)	986.63 (242.85)	1320.10 (663.56)	1239.68 (549.99)	1139.76 (598.26)	1128.59 (611.88)	1239.28 (704.46)
Demographics										
Age (years) - median (IQR)	61 (52 - 69)	73 (66 - 80)	78 (71 - 83)	77 (71 - 85)	64 (54 - 71)	60 (51, 69)	71 (64, 77)	76 (71, 82)	77 (72, 83)	70 (54, 80)
Age(years) - n(%)										
30-39	2035 (5.99)	14 (0.42)	1 (0.10)	0	1 (11.11)	4539 (5.55)	100 (0.44)	8 (0.15)	3 (0.61)	0
40-49	4687 (13.79)	44 (1.32)	7 (0.73)	3 (1.96)	1 (11.11)	12 533 (15.33)	600 (2.63)	43 (0.81)	4 (0.82)	2 (13.33)
50-59	8895 (26.17)	280 (8.42)	30 (3.13)	5 (3.27)	2 (22.22)	21 944 (26.84)	2667 (11.70)	210 (3.97)	17 (3.48)	3 (20.00)
60-69	10656 (31.35)	874 (26.29)	166 (17.29)	22 (14.38)	1 (11.11)	24 169 (29.56)	6777 (29.74)	896 (16.94)	66 (13.52)	2 (13.33)
70-79	5929 (17.44)	1270 (38.21)	354 (36.88)	58 (37.91)	2 (22.22)	14 807 (18.11)	8555 (37.54)	2282 (43.15)	203 (41.60)	4 (26.67)
>= 80	1787 (5.26)	842 (25.33)	402 (41.88)	65 (42.48)	2 (22.22)	3766 (4.61)	4092 (17.95)	1849 (34.97)	195 (39.96)	4 (26.67)
Female gender - n(%)	14520 (42.72)	2025 (60.92)	585 (60.94)	104 (67.97)	4 (44.44)	32 262 (39.46)	13 163 (57.76)	3691 (69.80)	320 (65.57)	10 (66.67)
Male gender - n(%)	19469 (57.28)	1299 (39.08)	375 (39.06)	49 (32.03)	5 (55.56)	49 496 (60.54)	9628 (42.24)	1597 (30.20)	168 (34.43)	5 (33.33)
Duration of type 2 diabetes* – n (%)										
First prescription at index date	21432 (63.06)	1597 (48.04)	402 (41.88)	57 (37.25)	3 (33.33)	14814 (18.12)	3173 (13.92)	701 (13.26)	72 (14.75)	6 (40.00)

<1 year	2139 (6.29)	189 (5.69)	57 (5.94)	17 (11.11)	0	26041 (31.85)	6030 (26.46)	1163 (21.99)	95 (19.47)	0
1->3 years	2968 (8.73)	353 (10.62)	93 (9.69)	9 (5.88)	0	15 454 (18.90)	4205 (18.45)	874 (16.53)	62 (12.70)	2 (13.33)
>= 3 years	7450 (21.92)	1185 (35.65)	408 (42.50)	70 (45.75)	6 (66.67)	25 449 (31.13)	9383 (41.17)	2550 (48.22)	259 (53.07)	7 (46.67)
Glycated haemoglobin A (HbA1c), %, mean (SD) (a)	8.26 (1.82)	8.27 (1.81)	8.13 (1.71)	8.28 (1.95)	7.43 (1.91)	8.66 (1.80)	8.51 (1.74)	8.54 (1.82)	8.65 (2.06)	9.66 (3.90)
History of potential contraindications for metformin within 5 years before index date – n (%)										
Diabetic ketoacidosis	63 (0.19)	6 (0.18)	1 (0.10)	0	0	62 (0.08)	15 (0.07)	8 (0.15)	1 (0.20)	0
Liver disease	367 (1.08)	22 (0.66)	8 (0.83)	2 (1.31)	0	868 (1.06)	164 (0.72)	27 (0.51)	4 (0.82)	0
Severe infections	2279 (6.71)	376 (11.31)	148 (15.42)	25 (16.34)	3 (33.33)	22 542 (27.57)	5930 (26.02)	1398 (26.44)	130 (26.64)	4 (26.67)
Shock	17 (0.05)	0	0	0	0	56 (0.07)	16 (0.07)	3 (0.06)	0	0
Respiratory failure	271 (0.80)	45 (1.35)	15 (1.56)	2 (1.31)	0	61 (0.07)	14 (0.06)	8 (0.15)	1 (0.20)	0
Alcohol-related diseases	244 (0.72)	14 (0.42)	6 (0.63)	0	0	999 (1.22)	114 (0.50)	22 (0.42)	3 (0.61)	0
Co-medication within 90 days before index date - n(%)										
Other antidiabetic medications	10947 (32.21)	1546 (46.51)	501 (52.19)	82 (53.59)	4 (44.44)	16 508 (20.19)	6489 (28.47)	1929 (36.48)	193 (39.55)	7 (46.67)
NSAIDs	5313 (15.63)	574 (17.27)	170 (17.71)	33 (21.57)	1 (11.11)	9577 (11.71)	2749 (12.06)	682 (12.90)	58 (11.89)	2 (13.33)
Anti-hypertensives	17778 (52.31)	2278 (68.53)	723 (75.31)	124 (81.05)	8 (88.89)	46 631 (57.04)	17550 (77.00)	4644 (87.82)	435 (89.14)	14 (93.33)
Antiretroviral medications	0	0	0	0	0	5 (0.01)	0	0	0	0
Aspirin	24727 (72.75)	2889 (86.91)	880 (91.67)	143 (93.46)	8 (88.89)	20 358 (24.90)	8240 (36.15)	2182 (41.26)	202 (41.39)	6 (40.00)

IQR: interquartile range; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation
*In the UK, duration was defined as time since first of fist antidiabetic prescription or first diagnosis of type 2 diabetes, whichever was earlier.
[a]Based on non-missing values
[b]For prevalent users the initial daily dose was estimated based on the first prescription of metformin after cohort entry (Jan 1, 2000)

Metformin use after decline in eGFR

Most patients continued metformin use after a decline in eGFR from ≥60 ml/min/1.73m^2 to 45-59 ml/min/1.73m^2 (66.2% in Denmark and 86.2% in the UK) (Table 3). Even when the first decline in the study period was to an eGFR below 30 ml/min/1.73m^2, 43% (271/627) of metformin users in Denmark and 64% (1366/2140) in the UK had a prescription for metformin within 90 days after the decline date (cumulated proportion across baseline levels ≥ 30 ml/min/1.73m^2 in Table 3).

Table 3. Metformin use after first estimated glomerular filtration rate (eGFR) decline.

		Northern Denmark, N (%)							UK, N (%)						
Baseline eGFR, ml/min/1.73m^2	First eGFR decline, ml/min/1.73 m^2	Number of patients	Number who continued use (%)	Number who discontinued use (%)	Number who switched use (%)	Metformin users who stopped before eGFR decline (%)	Metformin users who stopped before eGFR decline but restarted after eGFR decline	Incomplete follow-up: outcome unknown	Number of patients	Number who continued use (%)	Number who discontinued use (%)	Number who switched use (%)	Metformin users who stopped before eGFR decline	Metformin users who stopped before eGFR decline but restarted after eGFR decline	Incomplete follow-up: out-come unknown (%)
>=60	45-59	5552	3675 (66.19)	379 (6.83)	99 (1.78)	1064 (19.16)	263 (4.74)	72 (1.30)	20709	17855 (86.22)	1152 (5.56)	200 (0.97)	954 (4.61)	338 (1.63)	210 (1.01)
>=60	30-44	461	263 (57.05)	69 (14.97)	15 (3.25)	73 (15.84)	18 (3.90)	23 (4.99)	1092	836 (76.56)	113 (10.35)	33 (3.02)	48 (4.40)	11 (1.01)	51 (4.67)
>=60	15-29	101	53 (52.48)	13 (12.87)	8 (7.92)	17 (16.83)	0	10 (9.90)	182	93 (51.10)	36 (19.78)	20 (10.99)	13 (7.14)	3 (1.65)	17 (9.34)
>=60	<15	22	11 (50.00)	7 (31.82)	2 (9.09)	1 (4.55)	0	1 (4.55)	57	20 (35.09)	16 (28.07)	8 (14.04)	2 (3.51)	1 (1.75)	10 (17.54)
45-59	30-44	1482	902 (60.86)	133 (8.97)	36 (2.43)	313 (21.12)	55 (3.71)	43 (2.90)	7986	6603 (82.68)	606 (7.59)	153 (1.92)	390 (4.88)	123 (1.54)	111 (1.39)
45-59	15-29	78	31 (39.74)	16 (20.51)	4 (5.13)	11 (14.10)	3 (3.85)	13 (16.67)	297	195 (65.66)	48 (16.16)	14 (4.71)	19 (6.40)	2 (0.67)	19 (6.40)
45-59	<15	4	2 (50.00)	0	0	1 (25.00)	0	1 (25.00)	41	20 (48.78)	8 (19.51)	5 (12.20)	1 (2.44)	0	7 (17.07)
30-44	15-29	411	170 (41.36)	62 (15.09)	14 (3.41)	130 (31.63)	14 (3.41)	21 (5.11)	1533	1026 (66.93)	238 (15.53)	94 (6.13)	104 (6.78)	23 (1.50)	48 (3.13)
30-44	<15	11	4 (36.36)	2 (18.18)	1 (9.09)	2 (18.18)	0	2 (18.18)	30	12 (40.00)	10 (33.33)	1 (3.33)	1 (3.33)	0	6 (20.00)
15-29	<15	46	7 (15.22)	10 (21.74)	3 (6.52)	22 (47.83)	1 (2.17)	3 (6.52)	49	11 (22.45)	20 (40.82)	3 (6.12)	12 (24.49)	0	3 (6.12)

Discussion

We described utilisation of metformin in Denmark and in the UK according to the level of renal function among 172,052 patients with medically treated type 2 diabetes. Although renal impairment was less prevalent in metformin users than among users of other antidiabetic drugs, we identified a considerable number of new metformin users with baseline eGFRs below 45 ml/min/1.73m^2, in particular in the UK. Despite guideline recommendations, 43%-64% of metformin users continued metformin within 90 days after their eGFR dropped below 30 ml/min/1.73m^2.

The study included virtually complete unselected population-based data from a well-defined geographical area in Denmark and a representative sample of general practices in the UK. At the same time, although we had virtually complete laboratory data, estimation of eGFR depends on steady-state serum creatinine level, which is difficult to assess from routine records. Exclusion of inpatient laboratory test results minimized the potential impact of a severe acute illness on eGFR values. Minor misclassification of eGFR cannot be ruled out after the implementation of standardized creatinine measurement in some laboratories during the later years of the study period. A further limitation was the need to restrict of the study population to persons with a baseline creatinine value, since availability of baseline creatinine values may correlate with frequency of medical contacts. According to the guidelines, however, diabetes patients should have their creatinine measured at least once yearly, independent of antidiabetic treatment, and we therefore expect that most patients with diabetes were included. Finally, we used dispensations as a proxy for antidiabetic drug use in the Danish data (as opposed to issued prescriptions in the UK), which is assumed to be reasonable since non-adherence is expected to be low for these drugs; however, some patients may have been diagnosed with type 2 diabetes earlier than the dispensation date. Based on the available data, duration of diabetes was estimated differently in the CPRD, where outpatient diagnoses available enable identification of both date of the first diabetes diagnosis and date of the first diabetes treatment. This may explain the longer observed mean diabetes duration among the UK patients.

Our finding that a considerable proportion of metformin users had renal impairment confirms result from previous smaller studies and suggests that our findings are applicable to other European countries. A Scottish study of 11,297 metformin users from a diabetes register, found that as many as 25% of the users had an eGFR of <60 ml/min/1.73m^2, including 14% with eGFR 50-59 ml/min/m^2, 8.5% with eGFR 40-49 ml/min/1.73m^2, and 2.8% with an eGFR of 30-39 ml/min/1.73m^2.[15] In other smaller studies, the proportion of metformin users with eGFR <60 ml/min/1.73m^2 was consistent across geographic regions, study designs, and types diabetic population: 17% among 558 hospitalized patients with poorly regulated diabetes in Poland;[12] 18% among women and 13% among men in a randomised trial of glycaemic optimisation of 4,838 metformin users;[16] 19% among 308 hospitalised metformin users in Germany;[17] and 18% among 425 general-population diabetes patients in Australia. The latter study even found that the proportion of metformin users with renal impairment increased during follow-up.[14] Our finding that a large proportion of patients continue taking metformin despite renal impairment is also consistent with a US study of 234 patients, reporting that 44% of patients with eGFR <60 ml/min/1.73m^2 continued metformin.[13]

Conclusions

Metformin is widely prescribed in patients with mild renal impairment and in a considerable proportion with moderate renal impairment despite recommendations. We observed no dose reduction with decreasing eGFR level. Rather, most metformin users continued the medication after a decline in eGFR, and a large proportion continued metformin use even after their eGFR dropped below 30 ml/min/1.73m^2.

Acknowledgments

Acknowledgements

The authors would like to thank the Pharmacovigilance Working Party (PhVWP) at the European Medicines Agency for helpful comments during the project. They are grateful to Uffe Heide-Jørgensen for statistical assistance and Hanne Kjeldahl Schlosser, Helle Vester and Kathleen Jick for outstanding administrative support.

Competing interests

The Department of Clinical Epidemiology is a member of the Danish Center for Strategic Research in Type 2 Diabetes (Danish Research Council, Grants no. 09-075724 and 10-079102). C.F. Christiansen, H.T. Sørensen, S. Skovbo, V. Ehrenstein, H. Nørrelund, S. Jick, and L. Li did not report receiving fees, honoraria, grants or consultancies. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study.

Funding

This work was commissioned and funded by the European Medicines Agency (Procurement Procedure No. EMA/2013/08/PV). The study received the ENCePP Study Seal.

Disclaimer

This document expresses the opinion of the authors of the paper, and may not be understood or quoted as being made on behalf or of reflecting the position of the European Medicines Agency or one of its committees or working parties. The EMA had no direct role in preparation of this manuscript.

Contributors

CFC participated in study conception and design, contributed to data analysis and interpretation, and led the writing. VE and SJ participated in the conception and design of the study, and contributed to data analysis. LL and SS contributed to the design of study and conducted the data analyses in CPRD and Denmark, respectively. HN contributed to study design and provided clinical expertise.

HTS oversaw the study, provided clinical expertise, and is responsible for the access to Danish databases. All authors participated in revisions of the manuscript draft for intellectual content. VE is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

In Denmark, the study was approved by the Danish Data Protection Agency (record numbers: 2012-41-0793 and 2013-41-1924). It did not require ethical committee approval due to lack of direct patient contact. In the UK, we obtained ethical approval from the CPRD's Independent Scientific Advisory Committee.

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

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

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

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

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

BMJ Open

Metformin Initiation and Renal Impairment: A cohort study in Denmark and the United Kingdom

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008531.R1
Article Type:	Research
Date Submitted by the Author:	06-Jul-2015
Complete List of Authors:	Christiansen, Christian; Aarhus University Hospital, Department of Clinical Epidemiology Ehrenstein, Vera; Aarhus University Hospital, Department of Clinical Epidemiology Heide-Jørgensen, Uffe; Aarhus University Hospital, Department of Clinical Epidemiology Skovbo, Stine; Aarhus University Hospital, Department of Clinical Epidemiology Nørrelund, Helene; Aarhus University Hospital, Department of Clinical Epidemiology Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology Li, Lin; Boston University School of Public Health, Boston Collaborative Drug Surveillance Program Jick, Susan; Boston University,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Renal medicine, Epidemiology, Health services research
Keywords:	Chronic renal failure < NEPHROLOGY, DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Diabetes & endocrinology < INTERNAL MEDICINE

Metformin Initiation and Renal Impairment: A cohort study in Denmark and the United Kingdom

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Key words: Chronic Kidney Disease, Diabetes Mellitus, Drug Utilization, Glomerular Filtration Rate, Metformin

Word count: 2,958

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Abstract

Objectives: To estimate prevalence of renal impairment, rate of decline in kidney function, and changes in metformin use after decline in kidney function, in metformin initiators.

Design, setting and participants: We conducted this two-country cohort study using routine data from northern Denmark and the United Kingdom (UK) during 2000-2011. We included metformin initiators among patients aged ≥30 years with medically treated diabetes.

Main outcome measures: We described patients' demographics, comorbidity, co-medications, and their estimated glomerular filtration rates (eGFR). Furthermore, we described the patients´ characteristics according to eGFR level. Finally, we examined rate of any decline in eGFR and changes in metformin use within 90 days after first decline in eGFR during follow-up.

Results: We included 124,720 metformin initiators in the two countries. Prevalence of eGFR <60 ml/min/1.73m^2 among metformin initiators was 9.0% in Denmark and 25.2% in the UK. In contrast, prevalence of eGFR values <30 ml/min/1.73m^2 among metformin initiators was 0.3% in Denmark and 0.4% in the UK. Patients with renal impairment were older and more likely to have received cardiovascular drugs. Incidence rate of decline in renal function was 4.92 per 100 person-years (95% CI 4.76-5.09) in Denmark and 7.48 (95%CI: 7.39-7.57) in the UK. The proportion of patients continuing metformin use even after a first decline brought the eGFR below 30 ml/min/1.73m^2 was 44% in Denmark and 62% in the UK. There was no clinically significant dose reduction with decreasing baseline eGFR level discernible from the data.

Conclusions: Mild to moderate renal impairment was common among metformin initiators, while severe renal impairment was uncommon. Patients with severe renal impairment frequently continued receiving/redeeming metformin prescriptions even 90 days after eGFR decline.

Article summary

Strengths and limitations of the study:

- The study describes metformin initiators in a large population of patients with medically treated diabetes
- The study includes comparable and complementary data from electronic databases in two European Union member states: Denmark and the United Kingdom
- The data include comprehensive individual-level prescription data, laboratory data, and data on medical history, all linked at the individual level
- Some misclassification may arise from the use of automated prescription and dispensation data to assess initiation and continuation of metformin

Introduction

Metformin was approved in Europe in the 1950s for treatment of type 2 diabetes.[1,2] While metformin is a first-line treatment, it is contraindicated in patients with certain acute and chronic conditions – such as severe infections, cardiac or respiratory failure, shock, or chronic renal or hepatic dysfunction – because of the feared, although not convincingly demonstrated, risk of lactic acidosis.[3-7]

Because metformin is eliminated through renal excretion,[8] patients with renal impairment may be vulnerable to its side effects. Current guidelines recommend cautious use of metformin in patients with renal impairment, and metformin is contraindicated in patients with severe renal impairment.[4] Guidelines recommend discontinuation of metformin in patients with an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73m^2, but recommended eGFR thresholds that should trigger cautious use and dose reduction, but not discontinuation, vary between 60 and 45 ml/min/1.73m^2.[2,4,9-11] Reported prevalence of eGFR below 60 ml/min/1.73m^2 among metformin users ranges from 4.5% to 25%,[12-17] with most evidence originating from studies that were small,[12-14,17] hospital-based,[12,17] or restricted to patients with poorly controlled diabetes.[12] Given the lack of clear-cut recommendations, the observed utilisation patterns, and the limitations of previous studies, the use and safety of metformin in patients with renal impairment should be further examined in a population-based setting among a broad range of diabetes patients.

This study was commissioned by the European Medicines Agency (EMA) with the goal of assessing the utilization of metformin in patients with and without renal insufficiency in current clinical practice in at least two European Union Member States. The study was undertaken to inform potential reassessment and unified recommendations' by the regulator of guidelines for metformin use in patients with renal impairment. In a series of epidemiologic analyses among pharmacologically-treated diabetes patients, we examined 1) prevalence of renal impairment and other contraindications among metformin initiators, 2) characteristics of metformin initiators by stage of

renal impairment, 3) rate of decline in renal function, and 4) utilisation of metformin after worsening of renal impairment.

Patients and methods

Study design and inclusion period

We undertook a cohort study including metformin initiators in northern Denmark and in the UK. The inclusion period was defined, based on data availability in northern Denmark (including 2000-2010 in the former counties of Aarhus and North Jutland, 2007-2010 in the former county of Ringkjobing, 2009-2012 in the former county of Viborg), and in the United Kingdom (UK) (including 2000-June 2011).

Source population and data sources

The source population for the study was residents of northern Denmark and the UK – the two EU Member States with relevant routine databases. In Denmark, we individually linked data from four registries using the unique personal identification number, assigned at birth or upon immigration by the Danish Central Personal Registry.[18,19] This registry, covering the entire Danish population, has recorded vital status and migrations of Danish residents since 1968. We obtained data from the Aarhus University Prescription Database (AUPD) on reimbursed prescriptions for antidiabetic and other drugs dispensed in the community outpatient pharmacies of northern Denmark.[20] Data on creatinine, blood glucose and glycated haemoglobin were obtained from the Danish Laboratory Information System for the North and Central Denmark (LABKA) database,[21] which tracks all hospital-based laboratory tests in the study region, including those sent to hospital laboratories by general practitioners (GPs). The Danish National Registry of Patients[22] provided data on comorbidities and prevalence of contraindications. This registry covers the entire Danish population and has registered hospitalizations since 1977 and outpatient visits since 1995. Up to 20 discharge diagnoses are recorded for each hospital contact, using the *International Classification of Diseases,* 8th revision (ICD-8) until 1994 and the ICD-10 thereafter.

In the UK, the source population was restricted to eligible patients treated by GPs participating in the Clinical Practice Research Datalink (CPRD).[23,24] The CPRD is an ongoing longitudinal database that has collected data from over 500 general practices in the UK since 1987. It covers approximately 8 million individuals (~6% of the UK population), whose age and sex distribution is representative of the UK population. We accessed the database through the Boston Collaborative Drug Surveillance Program (BCDSP). The BCDSP has received anonymised raw data generated by the GPs since the CPRD was first established. Validation studies have shown greater than 90% concordance between information from the original paper records and information recorded on the computer file. Further, the indication for newly prescribed drugs is recorded more than 95% of the time.[23] The CPRD data housed at the BCDSP are updated annually, so that the most recent data available are never more than 15 months out-of-date. The data are recorded using multiple data screens or files, including registration, drug, and laboratory data, event files, and files containing additional clinical details.

Study population

The study population of metformin initiators was derived from a cohort of persons aged 30 years or older at study start, with medically treated diabetes, as defined by at least one prescription for an antidiabetic medication during the study period. The study population was restricted to patients aged 30 years or older to avoid, to the extent possible, inclusion of patients with metformin-treated polycystic ovary syndrome (PCOS) or type 1 diabetes, both of which are frequently diagnosed before age 30 years.[25,26] In addition, we excluded patients with a diagnosis of type 1 diabetes in the UK, while the ICD-10 coding in Denmark did not allow clear distinction between diabetes types. The study was also restricted to patients with at least one year of prescription history before cohort entry, in order to allow for an observable washout period to define new users. In addition, we required patients to have at least one measurement of serum creatinine on or before cohort entry in order to assess baseline renal function. Patients were followed from day of first metformin prescription until death, emigration, end of enrolment in a CPRD practice (the UK only), or end of follow-up on 31 December 2011 in Denmark and 30 June 2012 in the UK.

Use of metformin and other antidiabetic agents

Metformin users were identified from records of issued prescriptions provided by GPs in the UK and from outpatient-dispensed prescriptions in Denmark. We identified all patients with at least one prescription for metformin during the study period, but included only metformin initiators in the main analyses.[27] Metformin initiators were defined as patients with no prescriptions for metformin within a washout period of 365 days before the first metformin prescription during the study period.

The cohort entry (start of follow-up) was the date of the first new metformin prescription during the study period. For each patient with at least two prescriptions for metformin, we estimated the mean daily dose at cohort entry as the ratio of the total amount of metformin dispensed at cohort entry to the number of days until the second metformin dispensation. We estimated the mean daily dose during the follow-up using the cumulative prescribed dose dispensed from all prescriptions during the follow-up divided by the number of days of use. To estimate the last day of use in the UK, we calculated the length of the last metformin prescription in the follow-up using the amount dispensed in the last issued prescription divided by the prescribed daily dose whenever available. Otherwise, we assumed that the last filled metformin prescription in the follow-up covered a period corresponding to the mean duration of all metformin prescriptions in the data set, i.e., 43-day in Denmark and 42-day in the UK.

We defined discontinuation after an eGFR decline as presence of a metformin prescription within 90 days before the date of the eGFR decline combined with absence of a metformin prescription within 90 days after the date of the eGFR decline in patients without rebound in eGFR level within this 90 day period. We defined switching as a prescription for a non-metformin antidiabetic drug within 90 days after the date of persistent eGFR decline, with no metformin prescription recorded within this 90-day time window. Patients were considered to have stopped metformin before a persistent eGFR decline if the last prescription prior to the eGFR ended more than 90 days before the date of the decline. Patients with fewer than 90 days of follow-up after the date of persistent eGFR decline were categorised as having incomplete follow-up.

Renal function and renal impairment

For each patient, we identified all recorded serum creatinine (S_{cr}) laboratory values in the LABKA database in Denmark[21] and in the CPRD's laboratory file. We did not include measurements during hospital inpatient admissions, to avoid confounding by acute illness. Creatinine values were used to assess renal function in the calculation of the eGFR[28] at baseline and during follow-up. We used the 4-item Modification of Diet in Renal Disease (MDRD) equation, which estimates eGFR based on S_{cr}, age, race, and sex.[28,29] Because neither study database collects data on race, the eGFR calculation assumed Caucasian race for all persons in the study, as they represent majority of Danish and UK residents. Based on eGFR, kidney function was classified as follows, in accordance with the criteria for chronic kidney disease: eGFR ≥ 60 ml/min/1.73m^2 (corresponding to Stage 1 and 2 chronic kidney disease or normal renal function); eGFR 45-59 ml/min/1.73m^2 (Stage 3a chronic kidney disease); eGFR 30-44 ml/min/1.73m^2 (Stage 3b chronic kidney disease); eGFR 15-29 ml/min/1.73m^2 (Stage 4 chronic kidney disease); and eGFR <15 ml/min/1.73m^2 (Stage 5 chronic kidney disease).

Covariates

We identified the following characteristics from the available data sources: age at cohort entry; sex; glycated haemoglobin A1c (HbA1c) level measurement within 12 months before cohort entry; time from the first recorded antidiabetic drug prescription until the cohort entry date, as a proxy for diabetes duration in Denmark, or time from either the first recorded antidiabetic drug prescription or first recorded diabetes diagnosis, whichever was earlier, until cohort entry in the UK (categorized as first prescription,< 1 year; 1-<3 years; 3+ years); history of potential contraindications for metformin within 5 years before cohort entry, including diagnoses of diabetic ketoacidosis, liver disease, and alcohol-related diseases; history of other chronic diseases within up to 5 years before cohort entry, including each of the conditions in the Charlson Comorbidity Index (except for diabetes and diabetes with organ complications);[30,31] and concomitant use (within 90 days before cohort entry) of other antidiabetic medications, non-steroidal anti-inflammatory drugs (NSAIDs), anti-hypertensives, or aspirin (acetylsalicylic acid).

Statistical analyses

First, we described characteristics, including eGFR level, of the metformin initiators at cohort entry. (See Table 1 for the list of characteristics.)

Table 1. Renal impairment and other characteristics of metformin initiators during the study period.

	Northern Denmark N = 22 728	UK N = 101 992
eGFR (most recent within a year before cohort entry) - n (%)		
>= 60 ml/min/1.73m^2	20 677 (90.98)	76 304 (74.81)
45-59 ml/min/1.73m^2	1576 (6.93)	20 648 (20.24)
30-44 ml/min/1.73m^2	410 (1.80)	4620 (4.53)
15-29 ml/min/1.73m^2	61 (0.27)	408 (0.40)
<15 ml/min/1.73m^2	4 (0.02)	12 (0.01)
Metformin daily dose (mg) at cohort entry, mean (SD)[a]	1433.53 (2410.20)	1104.63 (426.64)
Metformin daily dose during follow-up (mg), mean (SD)[a]	1387.37 (539.86)	1265.86 (634.70)
Demographics at cohort entry		
Age (years) - median (IQR)	61 (51 - 69)	63 (54-72)
Age (years) - n(%)		
30-39	1639 (7.21)	4542 (4.45)
40-49	3186 (14.02)	12 566 (12.32)
50-59	5572 (24.52)	23 228 (22.77)
60-69	6895 (30.34)	29 098 (28.53)
70-79	3971 (17.47)	23 507 (23.05)
>= 80	1465 (6.45)	9051 (8.87)
Female gender – n (%)	10 269 (45.18)	45 361 (44.48)
Male gender – n (%)	12 459 (54.82)	56 631 (55.52)
Duration of type 2 diabetes at cohort entry* - n(%)		
First prescription at cohort entry	21 799 (95.91)	18 766 (18.40)
<1 year	55 (0.24)	32 868 (32.23)
1-3 years	220 (0.97)	19 211 (18.84)
>= 3 years	654 (2.88)	31 147 (30.54)
Glycated haemoglobin A (HbA1c) at cohort entry, %, mean (SD) (a)	8.09 (1.91)	8.67 (1.80)
History of potential contraindications for metformin within 5 years before cohort entry - n(%)		
Diabetic ketoacidosis	10 (0.04)	69 (0.07)
Liver disease	215 (0.95)	1034 (1.01)
Alcohol-related diseases	128 (0.56)	1070 (1.05)

	Northern Denmark N = 22 728	UK N = 101 992
Co-medication within 90 days before cohort entry - n(%)		
Other antidiabetic medications	738 (3.25)	20 141 (19.75)
NSAIDs	3802 (16.73)	11 965 (11.73)
Anti-hypertensives	11 878 (52.26)	64 112 (62.86)
Aspirin	982 (4.32)	28 954 (28.39)
Charlson Comorbidity Index Score at cohort entry- n(%) (a)		
0	16 196 (71.26)	57 993 (56.86)
1	3754 (16.52)	24 592 (24.11)
2	1781 (7.84)	11 870 (11.64)
3	585 (2.57)	4704 (4.61)
≥4	412 (1.81)	2833 (2.78)
Lifestyle factors at cohort entry (where available)		
Obesity [b]	N/A	54 100 (53.04)
Smoking		
Current	N/A	17 505 (17.16)
Former	N/A	41 660 (40.85)
Never	N/A	40 957 (40.16)
Missing	N/A	1870 (1.83)

eGFR: estimated glomerular filtration rate; IQR: interquartile range; N/A: Not available/applicable; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation

In the UK, duration was defined as time since first antidiabetic prescription or first diagnosis of type 2 diabetes, whichever was earlier

[a]Based on non-missing values

[b]Defined as a body mass index ≥ 30 kg/m^2

Second, we described the patient characteristics according to the five categories of chronic renal disease at cohort entry. Third, we assessed the rate of first decline in eGFR level following patients from first new metformin prescription until first decline in eGFR, emigration, or death, whichever came first.

Fourth, we assessed continued use and discontinuation of metformin within 90 days after the first decline in eGFR, from the baseline eGFR (based on last available outpatient serum creatinine measurement within 1 year before or on the cohort entry date) excluding patients with rebound in eGFR level during the 90 day period after first decline. Both study sites used SAS statistical software Version 9 (Cary, NC, USA) for data management and analyses.

Results

Characteristics of metformin initiators

The study included 22 728 metformin initiators in Denmark and 101 992 metformin initiators in the UK. Table 1 provides characteristics of metformin initiators in Denmark and the UK. The median age was 61 years (interquartile range (IQR) 51-69) in Denmark and 63 years (IQR 54-72) in the UK. There was no clinically important difference in mean glycated haemoglobin between countries.

The overall mean daily dose of metformin at cohort entry was 1433 mg in Denmark and 1105 mg in the UK. The prevalences of diabetic ketoacidosis, liver disease, or alcohol-related diseases were low. Most patients had no major comorbidity, as indicated by a Charlson Comorbidity Index Score of 0 (71.3% in Denmark and 56.9% in the UK) (Table 1).

The proportion of patients with chronic kidney disease (eGFR values below 60 ml/min/1.73m^2) was 9.0% in Denmark and 25.2% in the UK (Table 1). The proportion of patients with a baseline eGFR level below 30 ml/min/1.73m^2 was 0.3% in Denmark and 0.4% in the UK (Table 1).

Characteristics of metformin initiators according to eGFR level

The proportion of metformin initiators using other concurrent antidiabetic medication, mainly sulfonylureas, was higher in the UK than in Denmark, and increased with decreasing eGFR levels in both countries. We observed no substantial decrease in mean daily metformin dose with decreasing eGFR at cohort entry. NSAIDs were prescribed in more than 10% of patients within 90 days before cohort entry, even in patients with low baseline eGFR levels (Table 2).

Table 2. Antidiabetic drug use and other characteristics according to level of renal function at cohort entry among metformin initiators.

	Northern Denmark					UK				
	Estimated glomerular filtration rate (eGFR)					Estimated glomerular filtration rate (eGFR)				
eGFR (using last creatinine measurement within a year before cohort entry, ml/min/1.73m^2)	**≥ 60 (N=20 677)**	**45-59 (N=1576)**	**30-44 (N=410)**	**15-29 (N=61)**	**<15 (N=4)**	**≥ 60 (n = 76 304)**	**45-59 (n =20 648)**	**30-44 (n =4620)**	**15-29 (n =408)**	**<15 (n =12)**
Concurrent antidiabetic drug use - n (%) (These are not mutually exclusive categories)										
Metformin	20 677 (100.0)	1576 (100.0)	410 (100.0)	61 (100.0)	4 (100.0)	76 304 (100)	20 648 (100)	4620 (100)	408 (100)	12 (100)
Insulin	183 (0.89)	12 (0.76)	5 (1.22)	3 (4.92)	0	1542 (2.02)	599 (2.90)	195 (4.22)	25 (6.13)	0
Sulfonylureas	455 (2.20)	62 (3.93)	21 (5.12)	3 (4.92)	0	12 649 (16.58)	4813 (23.31)	1423 (30.80)	136 (33.33)	5 (41.67)
Glitazones	7 (0.03)	0	0	0	0	903 (1.18)	276 (1.34)	74 (1.60)	8 (1.96)	0
Other antidiabetic drugs	34 (0.16)	5 (0.32)	1 (0.24)	0	0	449 (0.59)	142 (0.69)	55 (1.19)	1 (0.25)	0
Metformin daily dose (mg) at cohort entry, mean (SD)[a]	1423.24 (2379.07)	1574.50 (2999.11)	1395.60 (1264.01)	2017.26 (2678.15)	793.65 (-)	1118.67 (430.21)	1070.94 (415.64)	1029.79 (402.61)	1046.76 (385.35)	1045.45 (415.60)
Metformin daily dose during follow-up (mg), mean (SD)[a]	1398.75 (543.07)	1282.06 (495.61)	1173.55 (429.39)	1429.44 (548.43)	942.59 (256.33)	1294.23 (659.96)	1202.78 (530.95)	1094.17 (584.86)	1097.94 (615.96)	1253.35 (784.43)
Demographics										
Age (years) - median (IQR)	60 (50 – 67)	72 (65 – 79)	78 (72 – 83)	78 (70 – 86)	65.5 (42.5 – 84)	60 (51, 68)	71 (64, 77)	77 (71, 82)	77 (72, 83)	60.5 (53.5, 77.5)
Age(years) - n(%)										
30-39	1626 (7.86)	11 (0.70)	1 (0.24)	0	1 (25.00)	4436 (5.81)	95 (0.46)	8 (0.17)	3 (0.74)	0
40-49	3149 (15.23)	30 (1.90)	3 (0.73)	3 (4.92)	1 (25.00)	11 963 (15.68)	557 (2.70)	40 (0.87)	4 (0.98)	2 (16.67)
50-59	5413 (26.18)	146 (9.26)	13 (3.17)	0	0	20 593 (26.99)	2435 (11.79)	182 (3.94)	15 (3.68)	3 (25.00)
60-69	6384 (30.87)	439 (27.86)	61 (14.88)	11 (18.03)	0	22 246 (29.15)	6047 (29.29)	752 (16.28)	51 (12.50)	2 (16.67)
70-79	3232 (15.63)	574 (36.42)	147 (35.85)	18 (29.51)	0	13 579 (17.80)	7766 (37.61)	1983 (42.92)	176 (43.14)	3 (25.00)
>= 80	873 (4.22)	376 (23.86)	185 (45.12)	29 (47.54)	2 (50.00)	3487 (4.57)	3748 (18.15)	1655 (35.82)	159 (38.97)	2 (16.67)

Female gender - n(%)	9050 (43.77)	936 (59.39)	238 (58.05)	43 (70.49)	2 (50.00)	29 991 (39.30)	11 882 (57.55)	3218 (69.65)	263 (64.46)	7 (58.33)
Male gender - n(%)	11 627 (56.23)	640 (40.61)	172 (41.95)	18 (29.51)	2 (50.00)	46 313 (60.70)	8766 (42.45)	1402 (30.35)	145 (35.54)	5 (41.67)
Duration of type 2 diabetes at cohort entry* – n (%)										
First prescription at cohort entry	19 855 (96.02)	1505 (95.49)	382 (93.17)	54 (88.52)	3 (75.00)	14 814 (19.41)	3173 (15.37)	701 (15.17)	72 (17.65)	6 (50.00)
<1 year	51 (0.25)	4 (0.25)	0	0	0	25 724 (33.71)	5910 (28.62)	1142 (24.72)	92 (22.55)	0
1->3 years	199 (0.96)	16 (1.02)	3 (0.73)	2 (3.28)	0	14 467 (18.96)	3885 (18.82)	803 (17.38)	54 (13.24)	2 (16.67)
>= 3 years	572 (2.77)	51 (3.24)	25 (6.10)	5 (8.20)	1 (25.00)	21 299 (27.91)	7680 (37.19)	1974 (42.73)	190 (46.57)	4 (33.33)
Glycated haemoglobin A (HbA1c) at cohort entry, %, mean (SD) (a)	8.11 (1.91)	7.90 (1.84)	7.71 (1.62)	7.91 (1.92)	6.68 (1.70)	8.70 (1.81)	8.55 (1.74)	8.63 (1.85)	8.85 (2.11)	9.89 (4.16)
History of potential contraindications for metformin within 5 years before cohort entry – n (%)										
Diabetic ketoacidosis	9 (0.04)	1 (0.06)	0	0	0	54 (0.07)	10 (0.05)	4 (0.09)	1 (0.25)	0
Liver disease	200 (0.97)	10 (0.63)	4 (0.98)	1 (1.64)	0	849 (1.11)	155 (0.75)	26 (0.56)	4 (0.98)	0
Alcohol-related diseases	118 (0.57)	8 (0.51)	2 (0.49)	0	0	950 (1.25)	97 (0.47)	20 (0.43)	3 (0.74)	0
Co-medication within 90 days before cohort entry - n(%)										
Other antidiabetic medications	634 (3.07)	73 (4.63)	26 (6.34)	5 (8.20)	0	13 341 (17.48)	5152 (24.95)	1506 (32.60)	138 (33.82)	4 (33.33)
NSAIDs	3424 (16.56)	288 (18.27)	76 (18.54)	13 (21.31)	1 (25.00)	8855 (11.60)	2474 (11.98)	585 (12.66)	50 (12.25)	1 (8.33)
Anti-hypertensives	10 454 (50.56)	1058 (67.13)	313 (76.34)	50 (81.97)	3 (75.00)	43 595 (57.13)	16 048 (77.72)	4096 (88.66)	362 (88.73)	11 (91.67)
Aspirin	807 (3.90)	124 (7.87)	47 (11.46)	3 (4.92)	1 (25.00)	19 181 (25.14)	7650 (37.05)	1943 (42.06)	174 (42.65)	6 (50.00)

eGFR: estimated glomerular filtration rate; IQR: interquartile range; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation
*In the UK, duration was defined as time since first of fist antidiabetic prescription or first diagnosis of type 2 diabetes, whichever was earlier.
[a]Based on non-missing values

Decline in eGFR and metformin use

Among the 22 728 metformin initiators in Denmark, 3434 had a decline in eGFR level during 69 792 person-years (mean follow-up 3.1 years) (Table 3). Among the 101 992 metformin initiators in the UK, 27 325 had a decline in eGFR within 365 208 person-years (mean follow-up 3.6 years). The corresponding incidence rates were 4.92 (95% CI 4.76-5.09) per 100 person-years in Denmark and 7.48 (7.39-7.57) per 100 person-years in the UK.

Table 3. Incidence rate of first decline in eGFR in metformin new users.

	Northern Denmark				UK			
Baseline eGFR	N (denominator)	Count (first decline in eGFR)	Person-years (to first decline in eGFR)	Incidence rate (95% CI), per 100 person years	N (denominator)	Count (first decline in eGFR)	Person-years (to first decline in eGFR)	Incidence rate (95% CI), per 100 person years
Total	22 728	3434	69 792	4.92 (4.76-5.09)	101 992	27325	365 208	7.48 (7.39 – 7.57)
>=60	20 677	2695	65 088	4.14 (3.99-4.30)	76 304	18936	275 873	6.86 (6.77 – 6.96)
45-59	1576	583	3857	15.12 (13.94-16.40)	20 648	7089	73 832	9.60 (9.38 – 9.83)
30-44	410	143	761	18.80 (15.96-22.15)	4620	1266	14 637	8.65 (8.18 – 9.14)
15-29	61	13	82	15.79 (9.17-27.19)	408	34	866	3.93 (2.76 – 5.42)
<15	4	.	4	. (.-.)	12	0	11	NA

Most patients continued metformin use within 90 days after a persistent decline in eGFR from ≥60 ml/min/1.73m^2 to 45-59 ml/min/1.73m^2: 70.4% in Denmark and 84.7% in the UK (Table 4). Even when the first decline during follow-up was to an eGFR below 30 ml/min/1.73m^2, 44% (45 out of 103) of metformin users in Denmark and 62% (281 out of 450) in the UK had a prescription for metformin within 90 days after the decline date (cumulated proportion across baseline levels ≥ 30 ml/min/1.73m^2 in Table 4).

Table 4. Metformin use after first estimated glomerular filtration rate (eGFR) decline among metformin initiators with first decline that persisted or worsened within 90 days.

		Northern Denmark, N (%)							UK, N (%)						
Base-line eGFR, ml/min /1.73 m^2	First eGFR decline, ml/min /1.73 m^2	Number of patients	Number who continued use (%)	Number who discontinued use (%)	Number who switched use (%)	Metformin users who stopped before eGFR decline (%)	Metformin users who stopped before eGFR decline but restarted after eGFR decline	Incomplete follow-up: outcome unknown	Number of patients	Number who continued use (%)	Number who discontinued use (%)	Number who switched use (%)	Metformin users who stopped before eGFR decline	Metformin users who stopped before eGFR decline but restarted after eGFR decline	Incomplete follow-up: out-come unknown (%)
>=60	45-59	1618	1139 (70.40)	115 (7.11)	20 (1.24)	236 (14.59)	80 (4.94)	28 (1.73)	2460	2083 (84.67)	160 (6.50)	47 (1.91)	103 (4.19)	41 (1.67)	26 (1.06)
>=60	30-44	88	51 (57.95)	7 (7.95)	4 (4.55)	14 (15.91)	3 (3.41)	9 (10.23)	149	107 (71.81)	22 (14.77)	9 (6.04)	6 (4.03)	0	5 (3.36)
>=60	15-29	8	0	1 (12.50)	0	2 (25.00)	0	5 (62.50)	21	6 (28.57)	7 (33.33)	3 (14.29)	0	1 (4.76)	4 (19.05)
>=60	<15	3	1 (33.33)	2 (66.67)	0	0	0	0	2	1 (50.00)	0	0	0	0	1 (50.00)
45-59	30-44	337	239 (70.92)	29 (8.61)	8 (2.37)	39 (11.57)	12 (3.56)	10 (2.97)	1414	1127 (79.70)	144 (10.18)	60 (4.24)	55 (3.89)	19 (1.34)	9 (0.64)
45-59	15-29	14	3 (21.43)	2 (14.29)	1 (7.14)	1 (7.14)	2 (14.29)	5 (35.71)	46	26 (56.52)	12 (26.09)	2 (4.35)	3 (6.52)	0	3 (6.52)
45-59	<15	0	0	0	0	0	0	0	4	1 (25.00)	1 (25.00)	2 (50.00)	0	0	0
30-44	15-29	77	41 (53.25)	10 (12.99)	2 (2.60)	11 (14.29)	5 (6.49)	8 (10.39)	373	246 (65.95)	73 (19.57)	28 (7.51)	14 (3.75)	7 (1.88)	5 (1.34)
30-44	<15	1	0	0	0	0	0	1 (100.0)	4	1 (25.00)	1 (25.00)	0	0	0	2 (50.00)
15-29	<15	8	3 (37.50)	0	0	4 (50.00)	0	1 (12.50)	9	1 (11.11)	4 (44.44)	2 (22.22)	2 (22.22)	0	0

Discussion

Among metformin initiators in Denmark and in the UK, we identified a considerable number of patients with baseline eGFRs below 45 ml/min/1.73m^2, in particular in the UK. However, only few metformin initiators had eGFRs below the absolute contraindicated eGFR of 30 ml/min/1.73m^2. Among the few metformin users whose eGFR dropped below 30 ml/min/1.73m^2, 44% in Denmark and 62% in the UK continued metformin within 90 days after the decline.

The study included virtually complete unselected population-based data from a well-defined geographical area in Denmark and a representative sample of general practices in the UK. At the same time, although the laboratory data were virtually complete, estimation of eGFR depends on steady-state serum creatinine level, which is difficult to assess from routine records. Exclusion of inpatient laboratory test results reduced the potential impact of a severe acute illness on eGFR values. Minor misclassification of eGFR cannot be ruled out after the implementation of standardised creatinine measurement in some laboratories during the later years of the study period. Missing data on race may have led us to underestimate eGFR in the expected few non-Caucasian patients included. A further limitation was the need to restrict the study population to persons with a baseline creatinine value, since availability of baseline creatinine values may correlate with frequency of medical contacts. According to the guidelines, however, diabetes patients should have their creatinine measured at least once yearly, independent of antidiabetic treatment, and we therefore expect that most patients with diabetes were included. Finally, we used dispensations of antidiabetic drugs in the Danish data as a proxy for a diabetes diagnosis since there are no GP diabetes diagnoses in the Danish data. However, some patients may have been diagnosed with type 2 diabetes earlier than the dispensation date and thus we may have underestimated diabetes duration in some patients. In addition, using a single prescription for an antidiabetic drug may have led inadvertent inclusion into the study population of patients with pre-diabetes, metformin-treated PCOS, and in Denmark, even some with type 1 diabetes. However, this contamination is unlikely to be severe given that 95.8% of patients in the UK data had a diagnosis of type 2 or unspecified diabetes before or at cohort entry. The prevalence of PCOS without diabetes at metformin initiation

was low (1.6% in Denmark and 0.9% in the UK), and contraindications for metformin use are expected to be similar in patients with PCOS as in patients with type 2 diabetes. Based on the available data, duration of diabetes was estimated differently in the CPRD, where outpatient diagnoses enable identification of both date of the first diabetes diagnosis and date of the first diabetes treatment. This may explain the longer observed mean diabetes duration among the UK patients.

Our finding that a considerable proportion of metformin initiators had some renal impairment confirms result from previous smaller studies and suggests that our findings are applicable to other European countries. A Scottish study of 11,297 metformin users from a diabetes register, found that as many as 25% of the users had an eGFR of <60 ml/min/1.73m^2, including 14% with eGFR 50-59 ml/min/m^2, 8.5% with eGFR 40-49 ml/min/1.73m^2, and 2.8% with an eGFR of 30-39 ml/min/1.73m^2.[15] In other smaller studies, the proportion of metformin users with eGFR <60 ml/min/1.73m^2 was consistent across geographic regions, study designs, and types of diabetic population: 17% among 558 hospitalised patients with poorly regulated diabetes in Poland;[12] 18% among women and 13% among men in a randomised trial of glycaemic optimisation of 4,838 metformin users;[16] 19% among 308 hospitalised metformin users in Germany;[17] and 18% among 425 general-population diabetes patients in Australia. The latter study even found that the proportion of metformin users with renal impairment increased during follow-up.[14] Our finding that a large proportion of patients continue taking metformin despite renal impairment is also consistent with a US study of 234 patients, reporting that 44% of patients with eGFR <60 ml/min/1.73m^2 continued metformin.[13]

Conclusions

Metformin is widely prescribed in patients with mild, but not severe renal impairment. We observed no dose reduction with decreasing eGFR level at metformin initiation. Among the few metformin initiators with a decline in eGFR to below 30 ml/min/1.73m^2, a large proportion continued metformin use.

Acknowledgments

Acknowledgements

The authors would like to thank the Pharmacovigilance Working Party (PhVWP) at the European Medicines Agency for helpful comments during the project. They are grateful to Hanne Kjeldahl Schlosser, Helle Vester and Kathleen Jick for outstanding administrative support.

Competing interests

The Department of Clinical Epidemiology is a member of the Danish Center for Strategic Research in Type 2 Diabetes (Danish Research Council, Grants no. 09-075724 and 10-079102). C.F. Christiansen, H.T. Sørensen, S. Skovbo, U. Heide-Jørgensen, V. Ehrenstein, H. Nørrelund, S. Jick, and L. Li did not report receiving fees, honoraria, grants or consultancies. Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study.

Funding

This work was commissioned and funded by the European Medicines Agency (Procurement Procedure No. EMA/2013/08/PV). The study received the ENCePP Study Seal.

Disclaimer

This document expresses the opinion of the authors of the paper, and may not be understood or quoted as being made on behalf or of reflecting the position of the European Medicines Agency or one of its committees or working parties. The EMA had no direct role in preparation of this manuscript.

Contributors

CFC participated in study conception and design, contributed to data analysis and interpretation, and led the writing. VE and SJ participated in the conception and design of the study, and contributed to data analysis. LL and SS contributed to the design of study and conducted data analyses in CPRD and Denmark, respectively. UHJ conducted data analyses and interpreted the data. HN contributed to study design and provided clinical expertise. HTS oversaw the study, provided clinical expertise,

and is responsible for the access to Danish databases. All authors participated in revisions of the manuscript draft for intellectual content. VE and SJ are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

In Denmark, the study was approved by the Danish Data Protection Agency (record numbers: 2012-41-0793 and 2013-41-1924). It did not require ethical committee approval due to lack of direct patient contact. In the UK, we obtained ethical approval from the CPRD's Independent Scientific Advisory Committee.

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

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

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

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

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

BMJ Open

Metformin Initiation and Renal Impairment: A cohort study in Denmark and the United Kingdom

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008531.R2
Article Type:	Research
Date Submitted by the Author:	06-Aug-2015
Complete List of Authors:	Christiansen, Christian; Aarhus University Hospital, Department of Clinical Epidemiology Ehrenstein, Vera; Aarhus University Hospital, Department of Clinical Epidemiology Heide-Jørgensen, Uffe; Aarhus University Hospital, Department of Clinical Epidemiology Skovbo, Stine; Aarhus University Hospital, Department of Clinical Epidemiology Nørrelund, Helene; Aarhus University Hospital, Department of Clinical Epidemiology Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology Li, Lin; Boston University School of Public Health, Boston Collaborative Drug Surveillance Program Jick, Susan; Boston University,
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Renal medicine, Epidemiology, Health services research
Keywords:	Chronic renal failure < NEPHROLOGY, DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Diabetes & endocrinology < INTERNAL MEDICINE

Metformin Initiation and Renal Impairment: A cohort study in Denmark and the United Kingdom

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Key words: Chronic Kidney Disease, Diabetes Mellitus, Drug Utilization, Glomerular Filtration Rate, Metformin

Word count: 2,958

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Abstract

Objectives: To estimate prevalence of renal impairment, rate of decline in kidney function, and changes in metformin use after decline in kidney function, in metformin initiators.

Design, setting and participants: We conducted this two-country cohort study using routine data from northern Denmark and the United Kingdom (UK) during 2000-2011. We included metformin initiators among patients aged ≥30 years with medically treated diabetes.

Main outcome measures: We described patients' demographics, comorbidity, co-medications, and their estimated glomerular filtration rates (eGFR). Furthermore, we described the patients´ characteristics according to eGFR level. Finally, we examined rate of any decline in eGFR and changes in metformin use within 90 days after first decline in eGFR during follow-up.

Results: We included 124,720 metformin initiators in the two countries. Prevalence of eGFR <60 ml/min/1.73m^2 among metformin initiators was 9.0% in Denmark and 25.2% in the UK. In contrast, prevalence of eGFR values <30 ml/min/1.73m^2 among metformin initiators was 0.3% in Denmark and 0.4% in the UK. Patients with renal impairment were older and more likely to have received cardiovascular drugs. Incidence rate of decline in renal function was 4.92 per 100 person-years (95% CI 4.76-5.09) in Denmark and 7.48 (95%CI: 7.39-7.57) in the UK. The proportion of patients continuing metformin use even after a first decline brought the eGFR below 30 ml/min/1.73m^2 was 44% in Denmark and 62% in the UK. There was no clinically significant dose reduction with decreasing baseline eGFR level discernible from the data.

Conclusions: Mild to moderate renal impairment was common among metformin initiators, while severe renal impairment was uncommon. Patients with severe renal impairment frequently continued receiving/redeeming metformin prescriptions even 90 days after eGFR decline.

Article summary

Strengths and limitations of the study:

- The study describes metformin initiators in a large population of patients with medically treated diabetes
- The study includes comparable and complementary data from electronic databases in two European Union member states: Denmark and the United Kingdom
- The data include comprehensive individual-level prescription data, laboratory data, and data on medical history, all linked at the individual level
- Some misclassification may arise from the use of automated prescription and dispensation data to assess initiation and continuation of metformin

Introduction

Metformin was approved in Europe in the 1950s for treatment of type 2 diabetes.[1,2] While metformin is a first-line treatment, it is contraindicated in patients with certain acute and chronic conditions – such as severe infections, cardiac or respiratory failure, shock, or chronic renal or hepatic dysfunction – because of the feared, although not convincingly demonstrated, risk of lactic acidosis.[3-7]

Because metformin is eliminated through renal excretion,[8] patients with renal impairment may be vulnerable to its side effects. Current guidelines recommend cautious use of metformin in patients with renal impairment, and metformin is contraindicated in patients with severe renal impairment.[4] Guidelines recommend discontinuation of metformin in patients with an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73m^2, but recommended eGFR thresholds that should trigger cautious use and dose reduction, but not discontinuation, vary between 60 and 45 ml/min/1.73m^2.[2,4,9-11] Reported prevalence of eGFR below 60 ml/min/1.73m^2 among metformin users ranges from 4.5% to 25%,[12-17] with most evidence originating from studies that were small,[12-14,17] hospital-based,[12,17] or restricted to patients with poorly controlled diabetes.[12] Given the lack of clear-cut recommendations, the observed utilisation patterns, and the limitations of previous studies, the use and safety of metformin in patients with renal impairment should be further examined in a population-based setting among a broad range of diabetes patients.

This study was commissioned by the European Medicines Agency (EMA) with the goal of assessing the utilization of metformin in patients with and without renal insufficiency in current clinical practice in at least two European Union Member States. The study was undertaken to inform potential reassessment and unified recommendations' by the regulator of guidelines for metformin use in patients with renal impairment. In a series of epidemiologic analyses among pharmacologically-treated diabetes patients, we examined 1) prevalence of renal impairment and other contraindications among metformin initiators, 2) characteristics of metformin initiators by stage of

renal impairment, 3) rate of decline in renal function, and 4) utilisation of metformin after worsening of renal impairment.

Patients and methods

Study design and inclusion period

We undertook a cohort study including metformin initiators in northern Denmark and in the UK. The inclusion period was defined, based on data availability in northern Denmark (including 2000-2010 in the former counties of Aarhus and North Jutland, 2007-2010 in the former county of Ringkjobing, 2009-2012 in the former county of Viborg), and in the United Kingdom (UK) (including 2000-June 2011).

Source population and data sources

The source population for the study was residents of northern Denmark and the UK – the two EU Member States with relevant routine databases. In Denmark, we individually linked data from four registries using the unique personal identification number, assigned at birth or upon immigration by the Danish Central Personal Registry.[18,19] This registry, covering the entire Danish population, has recorded vital status and migrations of Danish residents since 1968. We obtained data from the Aarhus University Prescription Database (AUPD) on reimbursed prescriptions for antidiabetic and other drugs dispensed in the community outpatient pharmacies of northern Denmark.[20] Data on creatinine, blood glucose and glycated haemoglobin were obtained from the Danish Laboratory Information System for the North and Central Denmark (LABKA) database,[21] which tracks all hospital-based laboratory tests in the study region, including those sent to hospital laboratories by general practitioners (GPs). The Danish National Registry of Patients[22] provided data on comorbidities and prevalence of contraindications. This registry covers the entire Danish population and has registered hospitalizations since 1977 and outpatient visits since 1995. Up to 20 discharge diagnoses are recorded for each hospital contact, using the *International Classification of Diseases,* 8th revision (ICD-8) until 1994 and the ICD-10 thereafter.

In the UK, the source population was restricted to eligible patients treated by GPs participating in the Clinical Practice Research Datalink (CPRD).[23,24] The CPRD is an ongoing longitudinal database that has collected data from over 500 general practices in the UK since 1987. It covers approximately 8 million individuals (~6% of the UK population), whose age and sex distribution is representative of the UK population. We accessed the database through the Boston Collaborative Drug Surveillance Program (BCDSP). The BCDSP has received anonymised raw data generated by the GPs since the CPRD was first established. Validation studies have shown greater than 90% concordance between information from the original paper records and information recorded on the computer file. Further, the indication for newly prescribed drugs is recorded more than 95% of the time.[23] The CPRD data housed at the BCDSP are updated annually, so that the most recent data available are never more than 15 months out-of-date. The data are recorded using multiple data screens or files, including registration, drug, and laboratory data, event files, and files containing additional clinical details.

Study population

The study population of metformin initiators was derived from a cohort of persons aged 30 years or older at study start, with medically treated diabetes, as defined by at least one prescription for an antidiabetic medication during the study period. The study population was restricted to patients aged 30 years or older to avoid, to the extent possible, inclusion of patients with metformin-treated polycystic ovary syndrome (PCOS) or type 1 diabetes, both of which are frequently diagnosed before age 30 years.[25,26] In addition, we excluded patients with a diagnosis of type 1 diabetes in the UK, while the ICD-10 coding in Denmark did not allow clear distinction between diabetes types. The study was also restricted to patients with at least one year of prescription history before cohort entry, in order to allow for an observable washout period to define new users. In addition, we required patients to have at least one measurement of serum creatinine on or before cohort entry in order to assess baseline renal function. Patients were followed from day of first metformin prescription until death, emigration, end of enrolment in a CPRD practice (the UK only), or end of follow-up on 31 December 2011 in Denmark and 30 June 2012 in the UK.

Use of metformin and other antidiabetic agents

Metformin users were identified from records of issued prescriptions provided by GPs in the UK and from outpatient-dispensed prescriptions in Denmark. We identified all patients with at least one prescription for metformin during the study period, but included only metformin initiators in the main analyses.[27] Metformin initiators were defined as patients with no prescriptions for metformin within a washout period of 365 days before the first metformin prescription during the study period.

The cohort entry (start of follow-up) was the date of the first new metformin prescription during the study period. For each patient with at least two prescriptions for metformin, we estimated the mean daily dose at cohort entry as the ratio of the total amount of metformin dispensed at cohort entry to the number of days until the second metformin dispensation. We estimated the mean daily dose during the follow-up using the cumulative prescribed dose dispensed from all prescriptions during the follow-up divided by the number of days of use. To estimate the last day of use in the UK, we calculated the length of the last metformin prescription in the follow-up using the amount dispensed in the last issued prescription divided by the prescribed daily dose whenever available. Otherwise, we assumed that the last filled metformin prescription in the follow-up covered a period corresponding to the mean duration of all metformin prescriptions in the data set, i.e., 43-day in Denmark and 42-day in the UK.

We defined discontinuation after an eGFR decline as presence of a metformin prescription within 90 days before the date of the eGFR decline combined with absence of a metformin prescription within 90 days after the date of the eGFR decline in patients without rebound in eGFR level within this 90 day period. We defined switching as a prescription for a non-metformin antidiabetic drug within 90 days after the date of persistent eGFR decline, with no metformin prescription recorded within this 90-day time window. Patients were considered to have stopped metformin before a persistent eGFR decline if the last prescription prior to the eGFR ended more than 90 days before the date of the decline. Patients with fewer than 90 days of follow-up after the date of persistent eGFR decline were categorised as having incomplete follow-up.

Renal function and renal impairment

For each patient, we identified all recorded serum creatinine (S_{cr}) laboratory values in the LABKA database in Denmark[21] and in the CPRD's laboratory file. We did not include measurements during hospital inpatient admissions, to avoid confounding by acute illness. Creatinine values were used to assess renal function in the calculation of the eGFR[28] at baseline and during follow-up. We used the 4-item Modification of Diet in Renal Disease (MDRD) equation, which estimates eGFR based on S_{cr}, age, race, and sex.[28,29] Because neither study database collects data on race, the eGFR calculation assumed Caucasian race for all persons in the study, as they represent majority of Danish and UK residents. Based on eGFR, kidney function was classified as follows, in accordance with the criteria for chronic kidney disease: eGFR ≥ 60 ml/min/1.73m^2 (corresponding to Stage 1 and 2 chronic kidney disease or normal renal function); eGFR 45-59 ml/min/1.73m^2 (Stage 3a chronic kidney disease); eGFR 30-44 ml/min/1.73m^2 (Stage 3b chronic kidney disease); eGFR 15-29 ml/min/1.73m^2 (Stage 4 chronic kidney disease); and eGFR <15 ml/min/1.73m^2 (Stage 5 chronic kidney disease).

Covariates

We identified the following characteristics from the available data sources: age at cohort entry; sex; glycated haemoglobin A1c (HbA1c) level measurement within 12 months before cohort entry; time from the first recorded antidiabetic drug prescription until the cohort entry date, as a proxy for diabetes duration in Denmark, or time from either the first recorded antidiabetic drug prescription or first recorded diabetes diagnosis, whichever was earlier, until cohort entry in the UK (categorized as first prescription,< 1 year; 1-<3 years; 3+ years); history of potential contraindications for metformin within 5 years before cohort entry, including diagnoses of diabetic ketoacidosis, liver disease, and alcohol-related diseases; history of other chronic diseases within up to 5 years before cohort entry, including each of the conditions in the Charlson Comorbidity Index (except for diabetes and diabetes with organ complications);[30,31] and concomitant use (within 90 days before cohort entry) of other antidiabetic medications, non-steroidal anti-inflammatory drugs (NSAIDs), anti-hypertensives, or aspirin (acetylsalicylic acid).

Statistical analyses

First, we described characteristics, including eGFR level, of the metformin initiators at cohort entry. (See Table 1 for the list of characteristics.)

Table 1. Renal impairment and other characteristics of metformin initiators during the study period.

	Northern Denmark N = 22 728	UK N = 101 992
eGFR (most recent within a year before cohort entry) - n (%)		
>= 60 ml/min/1.73m^2	20 677 (90.98)	76 304 (74.81)
45-59 ml/min/1.73m^2	1576 (6.93)	20 648 (20.24)
30-44 ml/min/1.73m^2	410 (1.80)	4620 (4.53)
15-29 ml/min/1.73m^2	61 (0.27)	408 (0.40)
<15 ml/min/1.73m^2	4 (0.02)	12 (0.01)
Metformin daily dose (mg) at cohort entry, mean (SD)[a]	1433.53 (2410.20)	1104.63 (426.64)
Metformin daily dose during follow-up (mg), mean (SD)[a]	1387.37 (539.86)	1265.86 (634.70)
Demographics at cohort entry		
Age (years) - median (IQR)	61 (51 - 69)	63 (54-72)
Age (years) - n(%)		
30-39	1639 (7.21)	4542 (4.45)
40-49	3186 (14.02)	12 566 (12.32)
50-59	5572 (24.52)	23 228 (22.77)
60-69	6895 (30.34)	29 098 (28.53)
70-79	3971 (17.47)	23 507 (23.05)
>= 80	1465 (6.45)	9051 (8.87)
Female gender – n (%)	10 269 (45.18)	45 361 (44.48)
Male gender – n (%)	12 459 (54.82)	56 631 (55.52)
Duration of type 2 diabetes at cohort entry* - n(%)		
First prescription at cohort entry	21 799 (95.91)	18 766 (18.40)
<1 year	55 (0.24)	32 868 (32.23)
1-3 years	220 (0.97)	19 211 (18.84)
>= 3 years	654 (2.88)	31 147 (30.54)
Glycated haemoglobin A (HbA1c) at cohort entry, %, mean (SD) (a)	8.09 (1.91)	8.67 (1.80)
History of potential contraindications for metformin within 5 years before cohort entry - n(%)		
Diabetic ketoacidosis	10 (0.04)	69 (0.07)
Liver disease	215 (0.95)	1034 (1.01)
Alcohol-related diseases	128 (0.56)	1070 (1.05)

	Northern Denmark N = 22 728	UK N = 101 992
Co-medication within 90 days before cohort entry - n(%)		
Other antidiabetic medications	738 (3.25)	20 141 (19.75)
NSAIDs	3802 (16.73)	11 965 (11.73)
Anti-hypertensives	11 878 (52.26)	64 112 (62.86)
Aspirin	982 (4.32)	28 954 (28.39)
Charlson Comorbidity Index Score at cohort entry- n(%) (a)		
0	16 196 (71.26)	57 993 (56.86)
1	3754 (16.52)	24 592 (24.11)
2	1781 (7.84)	11 870 (11.64)
3	585 (2.57)	4704 (4.61)
≥4	412 (1.81)	2833 (2.78)
Lifestyle factors at cohort entry (where available)		
Obesity [b]	N/A	54 100 (53.04)
Smoking		
Current	N/A	17 505 (17.16)
Former	N/A	41 660 (40.85)
Never	N/A	40 957 (40.16)
Missing	N/A	1870 (1.83)

eGFR: estimated glomerular filtration rate; IQR: interquartile range; N/A: Not available/applicable; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation

In the UK, duration was defined as time since first antidiabetic prescription or first diagnosis of type 2 diabetes, whichever was earlier

[a]Based on non-missing values

[b]Defined as a body mass index ≥ 30 kg/m^2

Second, we described the patient characteristics according to the five categories of chronic renal disease at cohort entry. Third, we assessed the rate of first decline in eGFR level following patients from first new metformin prescription until first decline in eGFR, emigration, or death, whichever came first.

Fourth, we assessed continued use and discontinuation of metformin within 90 days after the first decline in eGFR, from the baseline eGFR (based on last available outpatient serum creatinine measurement within 1 year before or on the cohort entry date) excluding patients with rebound in eGFR level during the 90 day period after first decline. Both study sites used SAS statistical software Version 9 (Cary, NC, USA) for data management and analyses.

Results

Characteristics of metformin initiators

The study included 22 728 metformin initiators in Denmark and 101 992 metformin initiators in the UK. Table 1 provides characteristics of metformin initiators in Denmark and the UK. The median age was 61 years (interquartile range (IQR) 51-69) in Denmark and 63 years (IQR 54-72) in the UK. There was no clinically important difference in mean glycated haemoglobin between countries.

The overall mean daily dose of metformin at cohort entry was 1433 mg in Denmark and 1105 mg in the UK. The prevalences of diabetic ketoacidosis, liver disease, or alcohol-related diseases were low. Most patients had no major comorbidity, as indicated by a Charlson Comorbidity Index Score of 0 (71.3% in Denmark and 56.9% in the UK) (Table 1).

The proportion of patients with chronic kidney disease (eGFR values below 60 ml/min/1.73m^2) was 9.0% in Denmark and 25.2% in the UK (Table 1). The proportion of patients with a baseline eGFR level below 30 ml/min/1.73m^2 was 0.3% in Denmark and 0.4% in the UK (Table 1).

Characteristics of metformin initiators according to eGFR level

The proportion of metformin initiators using other concurrent antidiabetic medication, mainly sulfonylureas, was higher in the UK than in Denmark, and increased with decreasing eGFR levels in both countries. We observed no substantial decrease in mean daily metformin dose with decreasing eGFR at cohort entry. NSAIDs were prescribed in more than 10% of patients within 90 days before cohort entry, even in patients with low baseline eGFR levels (Table 2).

Table 2. Antidiabetic drug use and other characteristics according to level of renal function at cohort entry among metformin initiators.

	Northern Denmark					UK				
	Estimated glomerular filtration rate (eGFR)					Estimated glomerular filtration rate (eGFR)				
eGFR (using last creatinine measurement within a year before cohort entry, ml/min/1.73m^2)	**≥ 60 (N=20 677)**	**45-59 (N=1576)**	**30-44 (N=410)**	**15-29 (N=61)**	**<15 (N=4)**	**≥ 60 (n = 76 304)**	**45-59 (n =20 648)**	**30-44 (n =4620)**	**15-29 (n =408)**	**<15 (n =12)**
Concurrent antidiabetic drug use - n (%) (These are not mutually exclusive categories)										
Metformin	20 677 (100.0)	1576 (100.0)	410 (100.0)	61 (100.0)	4 (100.0)	76 304 (100)	20 648 (100)	4620 (100)	408 (100)	12 (100)
Insulin	183 (0.89)	12 (0.76)	5 (1.22)	3 (4.92)	0	1542 (2.02)	599 (2.90)	195 (4.22)	25 (6.13)	0
Sulfonylureas	455 (2.20)	62 (3.93)	21 (5.12)	3 (4.92)	0	12 649 (16.58)	4813 (23.31)	1423 (30.80)	136 (33.33)	5 (41.67)
Glitazones	7 (0.03)	0	0	0	0	903 (1.18)	276 (1.34)	74 (1.60)	8 (1.96)	0
Other antidiabetic drugs	34 (0.16)	5 (0.32)	1 (0.24)	0	0	449 (0.59)	142 (0.69)	55 (1.19)	1 (0.25)	0
Metformin daily dose (mg) at cohort entry, mean (SD)[a]	1423.24 (2379.07)	1574.50 (2999.11)	1395.60 (1264.01)	2017.26 (2678.15)	793.65 (-)	1118.67 (430.21)	1070.94 (415.64)	1029.79 (402.61)	1046.76 (385.35)	1045.45 (415.60)
Metformin daily dose during follow-up (mg), mean (SD)[a]	1398.75 (543.07)	1282.06 (495.61)	1173.55 (429.39)	1429.44 (548.43)	942.59 (256.33)	1294.23 (659.96)	1202.78 (530.95)	1094.17 (584.86)	1097.94 (615.96)	1253.35 (784.43)
Demographics										
Age (years) - median (IQR)	60 (50 – 67)	72 (65 – 79)	78 (72 – 83)	78 (70 – 86)	65.5 (42.5 – 84)	60 (51, 68)	71 (64, 77)	77 (71, 82)	77 (72, 83)	60.5 (53.5, 77.5)
Age(years) - n(%)										
30-39	1626 (7.86)	11 (0.70)	1 (0.24)	0	1 (25.00)	4436 (5.81)	95 (0.46)	8 (0.17)	3 (0.74)	0
40-49	3149 (15.23)	30 (1.90)	3 (0.73)	3 (4.92)	1 (25.00)	11 963 (15.68)	557 (2.70)	40 (0.87)	4 (0.98)	2 (16.67)
50-59	5413 (26.18)	146 (9.26)	13 (3.17)	0	0	20 593 (26.99)	2435 (11.79)	182 (3.94)	15 (3.68)	3 (25.00)
60-69	6384 (30.87)	439 (27.86)	61 (14.88)	11 (18.03)	0	22 246 (29.15)	6047 (29.29)	752 (16.28)	51 (12.50)	2 (16.67)
70-79	3232 (15.63)	574 (36.42)	147 (35.85)	18 (29.51)	0	13 579 (17.80)	7766 (37.61)	1983 (42.92)	176 (43.14)	3 (25.00)
>= 80	873 (4.22)	376 (23.86)	185 (45.12)	29 (47.54)	2 (50.00)	3487 (4.57)	3748 (18.15)	1655 (35.82)	159 (38.97)	2 (16.67)

Female gender - n(%)	9050 (43.77)	936 (59.39)	238 (58.05)	43 (70.49)	2 (50.00)	29 991 (39.30)	11 882 (57.55)	3218 (69.65)	263 (64.46)	7 (58.33)
Male gender - n(%)	11 627 (56.23)	640 (40.61)	172 (41.95)	18 (29.51)	2 (50.00)	46 313 (60.70)	8766 (42.45)	1402 (30.35)	145 (35.54)	5 (41.67)
Duration of type 2 diabetes at cohort entry* – n (%)										
First prescription at cohort entry	19 855 (96.02)	1505 (95.49)	382 (93.17)	54 (88.52)	3 (75.00)	14 814 (19.41)	3173 (15.37)	701 (15.17)	72 (17.65)	6 (50.00)
<1 year	51 (0.25)	4 (0.25)	0	0	0	25 724 (33.71)	5910 (28.62)	1142 (24.72)	92 (22.55)	0
1->3 years	199 (0.96)	16 (1.02)	3 (0.73)	2 (3.28)	0	14 467 (18.96)	3885 (18.82)	803 (17.38)	54 (13.24)	2 (16.67)
>= 3 years	572 (2.77)	51 (3.24)	25 (6.10)	5 (8.20)	1 (25.00)	21 299 (27.91)	7680 (37.19)	1974 (42.73)	190 (46.57)	4 (33.33)
Glycated haemoglobin A (HbA1c) at cohort entry, %, mean (SD) (a)	8.11 (1.91)	7.90 (1.84)	7.71 (1.62)	7.91 (1.92)	6.68 (1.70)	8.70 (1.81)	8.55 (1.74)	8.63 (1.85)	8.85 (2.11)	9.89 (4.16)
History of potential contraindications for metformin within 5 years before cohort entry – n (%)										
Diabetic ketoacidosis	9 (0.04)	1 (0.06)	0	0	0	54 (0.07)	10 (0.05)	4 (0.09)	1 (0.25)	0
Liver disease	200 (0.97)	10 (0.63)	4 (0.98)	1 (1.64)	0	849 (1.11)	155 (0.75)	26 (0.56)	4 (0.98)	0
Alcohol-related diseases	118 (0.57)	8 (0.51)	2 (0.49)	0	0	950 (1.25)	97 (0.47)	20 (0.43)	3 (0.74)	0
Co-medication within 90 days before cohort entry - n(%)										
Other antidiabetic medications	634 (3.07)	73 (4.63)	26 (6.34)	5 (8.20)	0	13 341 (17.48)	5152 (24.95)	1506 (32.60)	138 (33.82)	4 (33.33)
NSAIDs	3424 (16.56)	288 (18.27)	76 (18.54)	13 (21.31)	1 (25.00)	8855 (11.60)	2474 (11.98)	585 (12.66)	50 (12.25)	1 (8.33)
Anti-hypertensives	10 454 (50.56)	1058 (67.13)	313 (76.34)	50 (81.97)	3 (75.00)	43 595 (57.13)	16 048 (77.72)	4096 (88.66)	362 (88.73)	11 (91.67)
Aspirin	807 (3.90)	124 (7.87)	47 (11.46)	3 (4.92)	1 (25.00)	19 181 (25.14)	7650 (37.05)	1943 (42.06)	174 (42.65)	6 (50.00)

eGFR: estimated glomerular filtration rate; IQR: interquartile range; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation
*In the UK, duration was defined as time since first of fist antidiabetic prescription or first diagnosis of type 2 diabetes, whichever was earlier.
[a]Based on non-missing values

Decline in eGFR and metformin use

Among the 22 728 metformin initiators in Denmark, 3434 had a decline in eGFR level during 69 792 person-years (mean follow-up 3.1 years) (Table 3). Among the 101 992 metformin initiators in the UK, 27 325 had a decline in eGFR within 365 208 person-years (mean follow-up 3.6 years). The corresponding incidence rates were 4.92 (95% CI 4.76-5.09) per 100 person-years in Denmark and 7.48 (7.39-7.57) per 100 person-years in the UK.

Table 3. Incidence rate of first decline in eGFR in metformin new users.

	Northern Denmark				UK			
Baseline eGFR	N (denominator)	Count (first decline in eGFR)	Person-years (to first decline in eGFR)	Incidence rate (95% CI), per 100 person years	N (denominator)	Count (first decline in eGFR)	Person-years (to first decline in eGFR)	Incidence rate (95% CI), per 100 person years
Total	22 728	3434	69 792	4.92 (4.76-5.09)	101 992	27325	365 208	7.48 (7.39 – 7.57)
>=60	20 677	2695	65 088	4.14 (3.99-4.30)	76 304	18936	275 873	6.86 (6.77 – 6.96)
45-59	1576	583	3857	15.12 (13.94-16.40)	20 648	7089	73 832	9.60 (9.38 – 9.83)
30-44	410	143	761	18.80 (15.96-22.15)	4620	1266	14 637	8.65 (8.18 – 9.14)
15-29	61	13	82	15.79 (9.17-27.19)	408	34	866	3.93 (2.76 – 5.42)
<15	4	.	4	. (.-.)	12	0	11	NA

Most patients continued metformin use within 90 days after a persistent decline in eGFR from ≥60 ml/min/1.73m^2 to 45-59 ml/min/1.73m^2: 70.4% in Denmark and 84.7% in the UK (Table 4). Even when the first decline during follow-up was to an eGFR below 30 ml/min/1.73m^2, 44% (45 out of 103) of metformin users in Denmark and 62% (281 out of 450) in the UK had a prescription for metformin within 90 days after the decline date (cumulated proportion across baseline levels ≥ 30 ml/min/1.73m^2 in Table 4).

Table 4. Metformin use after first estimated glomerular filtration rate (eGFR) decline among metformin initiators with first decline that persisted or worsened within 90 days.

		Northern Denmark, N (%)							UK, N (%)						
Base-line eGFR, ml/min /1.73 m^2	First eGFR decline, ml/min /1.73 m^2	Number of patients	Number who continued use (%)	Number who discontinued use (%)	Number who switched use (%)	Metformin users who stopped before eGFR decline (%)	Metformin users who stopped before eGFR decline but restarted after eGFR decline	Incomplete follow-up: outcome unknown	Number of patients	Number who continued use (%)	Number who discontinued use (%)	Number who switched use (%)	Metformin users who stopped before eGFR decline	Metformin users who stopped before eGFR decline but restarted after eGFR decline	Incomplete follow-up: out-come unknown (%)
>=60	45-59	1618	1139 (70.40)	115 (7.11)	20 (1.24)	236 (14.59)	80 (4.94)	28 (1.73)	2460	2083 (84.67)	160 (6.50)	47 (1.91)	103 (4.19)	41 (1.67)	26 (1.06)
>=60	30-44	88	51 (57.95)	7 (7.95)	4 (4.55)	14 (15.91)	3 (3.41)	9 (10.23)	149	107 (71.81)	22 (14.77)	9 (6.04)	6 (4.03)	0	5 (3.36)
>=60	15-29	8	0	1 (12.50)	0	2 (25.00)	0	5 (62.50)	21	6 (28.57)	7 (33.33)	3 (14.29)	0	1 (4.76)	4 (19.05)
>=60	<15	3	1 (33.33)	2 (66.67)	0	0	0	0	2	1 (50.00)	0	0	0	0	1 (50.00)
45-59	30-44	337	239 (70.92)	29 (8.61)	8 (2.37)	39 (11.57)	12 (3.56)	10 (2.97)	1414	1127 (79.70)	144 (10.18)	60 (4.24)	55 (3.89)	19 (1.34)	9 (0.64)
45-59	15-29	14	3 (21.43)	2 (14.29)	1 (7.14)	1 (7.14)	2 (14.29)	5 (35.71)	46	26 (56.52)	12 (26.09)	2 (4.35)	3 (6.52)	0	3 (6.52)
45-59	<15	0	0	0	0	0	0	0	4	1 (25.00)	1 (25.00)	2 (50.00)	0	0	0
30-44	15-29	77	41 (53.25)	10 (12.99)	2 (2.60)	11 (14.29)	5 (6.49)	8 (10.39)	373	246 (65.95)	73 (19.57)	28 (7.51)	14 (3.75)	7 (1.88)	5 (1.34)
30-44	<15	1	0	0	0	0	0	1 (100.0)	4	1 (25.00)	1 (25.00)	0	0	0	2 (50.00)
15-29	<15	8	3 (37.50)	0	0	4 (50.00)	0	1 (12.50)	9	1 (11.11)	4 (44.44)	2 (22.22)	2 (22.22)	0	0

Discussion

Among metformin initiators in Denmark and in the UK, we identified a considerable number of patients with baseline eGFRs below 45 ml/min/1.73m^2, in particular in the UK. However, only few metformin initiators had eGFRs below the absolute contraindicated eGFR of 30 ml/min/1.73m^2. Among the few metformin users whose eGFR dropped below 30 ml/min/1.73m^2, 44% in Denmark and 62% in the UK continued metformin within 90 days after the decline.

The study included virtually complete unselected population-based data from a well-defined geographical area in Denmark and a representative sample of general practices in the UK. At the same time, although the laboratory data were virtually complete, estimation of eGFR depends on steady-state serum creatinine level, which is difficult to assess from routine records. Exclusion of inpatient laboratory test results reduced the potential impact of a severe acute illness on eGFR values. Minor misclassification of eGFR cannot be ruled out after the implementation of standardised creatinine measurement in some laboratories during the later years of the study period. Missing data on race may have led us to underestimate eGFR in the expected few non-Caucasian patients included. A further limitation was the need to restrict the study population to persons with a baseline creatinine value, since availability of baseline creatinine values may correlate with frequency of medical contacts. According to the guidelines, however, diabetes patients should have their creatinine measured at least once yearly, independent of antidiabetic treatment, and we therefore expect that most patients with diabetes were included. Finally, we used dispensations of antidiabetic drugs in the Danish data as a proxy for a diabetes diagnosis since there are no GP diabetes diagnoses in the Danish data. However, some patients may have been diagnosed with type 2 diabetes earlier than the dispensation date and thus we may have underestimated diabetes duration in some patients. In addition, using a single prescription for an antidiabetic drug may have led inadvertent inclusion into the study population of patients with pre-diabetes, metformin-treated PCOS, and in Denmark, even some with type 1 diabetes. However, this contamination is unlikely to be severe given that 95.8% of patients in the UK data had a diagnosis of type 2 or unspecified diabetes before or at cohort entry. The prevalence of PCOS without diabetes at metformin initiation

was low (1.6% in Denmark and 0.9% in the UK), and contraindications for metformin use are expected to be similar in patients with PCOS as in patients with type 2 diabetes. Based on the available data, duration of diabetes was estimated differently in the CPRD, where outpatient diagnoses enable identification of both date of the first diabetes diagnosis and date of the first diabetes treatment. This may explain the longer observed mean diabetes duration among the UK patients.

Our finding that a considerable proportion of metformin initiators had some renal impairment confirms result from previous smaller studies and suggests that our findings are applicable to other European countries. A Scottish study of 11,297 metformin users from a diabetes register, found that as many as 25% of the users had an eGFR of <60 ml/min/1.73m^2, including 14% with eGFR 50-59 ml/min/m^2, 8.5% with eGFR 40-49 ml/min/1.73m^2, and 2.8% with an eGFR of 30-39 ml/min/1.73m^2.[15] In other smaller studies, the proportion of metformin users with eGFR <60 ml/min/1.73m^2 was consistent across geographic regions, study designs, and types of diabetic population: 17% among 558 hospitalised patients with poorly regulated diabetes in Poland;[12] 18% among women and 13% among men in a randomised trial of glycaemic optimisation of 4,838 metformin users;[16] 19% among 308 hospitalised metformin users in Germany;[17] and 18% among 425 general-population diabetes patients in Australia. The latter study even found that the proportion of metformin users with renal impairment increased during follow-up.[14] Our finding that a large proportion of patients continue taking metformin despite renal impairment is also consistent with a US study of 234 patients, reporting that 44% of patients with eGFR <60 ml/min/1.73m^2 continued metformin.[13]

Conclusions

Metformin is widely prescribed in patients with mild, but not severe renal impairment. We observed no dose reduction with decreasing eGFR level at metformin initiation. Among the few metformin initiators with a decline in eGFR to below 30 ml/min/1.73m^2, a large proportion continued metformin use.

Acknowledgments

Acknowledgements

The authors would like to thank the Pharmacovigilance Working Party (PhVWP) at the European Medicines Agency for helpful comments during the project. They are grateful to Hanne Kjeldahl Schlosser, Helle Vester and Kathleen Jick for outstanding administrative support.

Competing interests

The Department of Clinical Epidemiology is a member of the Danish Center for Strategic Research in Type 2 Diabetes (Danish Research Council, Grants no. 09-075724 and 10-079102). C.F. Christiansen, H.T. Sørensen, S. Skovbo, U. Heide-Jørgensen, V. Ehrenstein, H. Nørrelund, S. Jick, and L. Li did not report receiving fees, honoraria, grants or consultancies. Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies have relation to the present study.

Funding

This work was commissioned and funded by the European Medicines Agency (Procurement Procedure No. EMA/2013/08/PV). The study received the ENCePP Study Seal.

Disclaimer

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Contributors

CFC participated in study conception and design, contributed to data analysis and interpretation, and led the writing. VE and SJ participated in the conception and design of the study, and contributed to data analysis. LL and SS contributed to the design of study and conducted data analyses in CPRD and Denmark, respectively. UHJ conducted data analyses and interpreted the data. HN contributed to study design and provided clinical expertise. HTS oversaw the study, provided clinical expertise,

and is responsible for the access to Danish databases. All authors participated in revisions of the manuscript draft for intellectual content. VE and SJ are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

In Denmark, the study was approved by the Danish Data Protection Agency (record numbers: 2012-41-0793 and 2013-41-1924). It did not require ethical committee approval due to lack of direct patient contact. In the UK, we obtained ethical approval from the CPRD's Independent Scientific Advisory Committee.

Data sharing statement

No additional data are available.

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

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

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

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

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