

BMJ Open Metformin initiation and renal impairment: a cohort study in Denmark and the UK

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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 2-country cohort study using routine data from northern Denmark and the 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 the 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 2 countries. Prevalence of eGFR < 60 mL/min/ 1.73 m² among metformin initiators was 9.0% in Denmark and 25.2% in the UK. In contrast, prevalence of eGFR values < 30 mL/min/ 1.73 m² 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 to 5.09) in Denmark and 7.48 per 100 person-years (95% CI 7.39 to 7.57) in the UK. The proportion of patients continuing metformin use, even after a first decline brought the eGFR below 30 mL/min/ 1.73 m², 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.

INTRODUCTION

Metformin was approved in Europe in the 1950s for treatment of type 2 diabetes.^{1 2}

Strengths and limitations of this 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 UK.
- 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.

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/ 1.73 m²; but recommended eGFR thresholds that should trigger cautious use and dose reduction, but not discontinuation, vary between 60 and 45 mL/min/ 1.73 m².^{2 4 9–11} Reported prevalence of eGFR below 60 mL/min/ 1.73 m² 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 patients with diabetes.

This study was commissioned by the European Medicines Agency (EMA) with the goal of assessing the utilisation 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 epidemiological analyses among patients with pharmacologically treated diabetes, 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 Ringkjøbing, 2009–2012 in the former county of Viborg), and in the 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 on 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 (HbA1c) 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 Patients²² provided data on comorbidities and prevalence of contraindications. This registry covers the entire Danish population and has registered hospitalisations since 1977 and outpatient

visits since 1995. Up to 20 discharge diagnoses are recorded for each hospital contact, using the *International Classification of Diseases*, Eighth 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 eight 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, 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 1 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 (S_{cr}) 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 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, that is, 43 days in Denmark and 42 days 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 S_{cr} laboratory values in the LABKA database in Denmark²¹ 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 eGFR²⁸ at baseline and during follow-up. We used the four-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 the 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/1.73 m² (corresponding to stage 1 and 2 chronic kidney disease or normal renal function); eGFR 45–59 mL/min/1.73 m² (stage 3a chronic kidney disease); eGFR 30–44 mL/min/1.73 m² (stage 3b chronic kidney disease); eGFR 15–29 mL/min/1.73 m² (stage 4 chronic kidney disease) and eGFR <15 mL/min/1.73 m² (stage 5 chronic kidney disease).

Covariates

We identified the following characteristics from the available data sources: age at cohort entry; sex; 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 (categorised as first prescription, <1; 1 to <3; 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), antihypertensives 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).

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 S_{cr} 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 V.9 (Cary, North Carolina, 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

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/1.73 m ²	20 677 (90.98)	76 304 (74.81)
45–59 mL/min/1.73 m ²	1576 (6.93)	20 648 (20.24)
30–44 mL/min/1.73 m ²	410 (1.80)	4620 (4.53)
15–29 mL/min/1.73 m ²	61 (0.27)	408 (0.40)
<15 mL/min/1.73 m ²	4 (0.02)	12 (0.01)
Metformin daily dose (mg) at cohort entry, mean (SD)*	1433.53 (2410.20)	1104.63 (426.64)
Metformin daily dose during follow-up (mg), mean (SD)*	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)
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)
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)
Antihypertensives	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‡	NA	54 100 (53.04)
Smoking		
Current	NA	17 505 (17.16)
Former	NA	41 660 (40.85)
Never	NA	40 957 (40.16)
Missing	NA	1870 (1.83)

*Based on non-missing values.

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

‡Defined as a body mass index ≥30 kg/m².

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NA, not available/applicable; NSAID, non-steroidal anti-inflammatory drug.

(IQR 51–69) in Denmark and 63 years (IQR 54–72) in the UK. There was no clinically important difference in mean HbA1c between countries.

The overall mean daily dose of metformin at cohort entry was 1433 mg in Denmark and 1105 mg in the UK.

The prevalence of diabetic ketoacidosis, liver disease or alcohol-related diseases was 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/1.73m²) 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/1.73m² 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).

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 to 5.09) per 100 person-years in Denmark and 7.48 (7.39 to 7.57) per 100 person-years in the UK.

Most patients continued metformin use within 90 days after a persistent decline in eGFR from ≥ 60 to 45–59 mL/min/1.73 m²: 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/1.73 m², 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/1.73 m² in table 4).

DISCUSSION

Among metformin initiators in Denmark and in the UK, we identified a considerable number of patients with baseline eGFRs below 45 mL/min/1.73 m², in particular in the UK. However, few metformin initiators had eGFRs below the absolute contraindicated eGFR of 30 mL/min/1.73 m². Among the few metformin users whose eGFR dropped below 30 mL/min/1.73 m², 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 S_{cr} 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, patients with diabetes 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 to inadvertent inclusion of patients with prediabetes, those with metformin-treated PCOS and, in Denmark, even some with type 1 diabetes, into the study population. 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 those 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 results 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/1.73 m², including 14% with eGFR 50–59 mL/min/m², 8.5% with eGFR 40–49 mL/min/1.73 m² and 2.8% with an eGFR of 30–39 mL/min/1.73 m².¹⁵ In other smaller studies, the proportion of metformin users with eGFR <60 mL/min/1.73 m² 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 4838 metformin users;¹⁶ 19% among 308 hospitalised metformin users in Germany;¹⁷ and 18% among 425 general

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

eGFR (using last creatinine measurement within a year before cohort entry, mL/min/1.73 m ²)	Northern Denmark eGFR					UK eGFR				
	≥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)*	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)*	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 to >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)
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)
Antihypertensives	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)

*Based on non-missing values.

†In the UK, duration was defined as time since first antidiabetic prescription or first diagnosis of type 2 diabetes, whichever was earlier. eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; NSAID, non-steroidal anti-inflammatory drug.

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

Baseline eGFR	Northern Denmark				UK			
	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 to 5.09)	101 992	27 325	365 208	7.48 (7.39 to 7.57)
≥60	20 677	2695	65 088	4.14 (3.99 to 4.30)	76 304	18 936	275 873	6.86 (6.77 to 6.96)
45–59	1576	583	3857	15.12 (13.94 to 16.40)	20 648	7089	73 832	9.60 (9.38 to 9.83)
30–44	410	143	761	18.80 (15.96 to 22.15)	4620	1266	14 637	8.65 (8.18 to 9.14)
15–29	61	13	82	15.79 (9.17 to 27.19)	408	34	866	3.93 (2.76 to 5.42)
<15	4	.	4	–	12	0	11	NA

eGFR, estimated glomerular filtration rate; NA, not available/applicable.

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

Baseline eGFR, mL/min/1.73 m ²	First eGFR decline, mL/min/1.73 m ²	Northern Denmark, N (%)							UK, N (%)						
		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: outcome 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

population patients with diabetes 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/1.73 m² 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/1.73 m², a large proportion continued metformin use.

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Ethics approval In Denmark, the study was approved by the Danish Data Protection Agency (record numbers: 2012-41-0793 and 2013-41-1924). In the UK, ethical approval was obtained from the CPRD's Independent Scientific Advisory Committee.

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