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Determinants of treatment modification before and after implementation of the updated 2015 NICE guideline on type 2 diabetes: A retrospective cohort study

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ABSTRACT

Aims: To identify patient-specific factors associated with early metformin treatment modification among type 2 diabetes patients before and after implementation of the updated 2015 NICE (National Institute for Health and Care Excellence) guideline.

Methods: We conducted a population-based cohort study using data from the Clinical Practice Research Datalink GOLD database (2009–2016). Patients ≥ 18 years, newly treated with metformin only, during the period of valid data collection were included. The first prescription defined start of follow-up. Determinants of treatment modification in two cohorts (before and after implementation of the updated guideline) were studied by time-dependent Cox proportional hazards regression.

Results: After implementation of the updated guideline, patients were less likely to receive sulphonylureas (62.3% vs 41.3%) or thiazolidediones (4.7% vs 2.2%) and more likely to receive dipeptidyl peptidase-4 inhibitors (15.8% vs 27.1%) or sodium-glucose cotransporter-2 inhibitors (0.8% vs 9.9%). Some determinants influenced general practitioners' prescribing differently after implementation of the updated guideline compared to before, including a high body mass index and heart failure.

Conclusions: Our results indicate that a first step towards tailored prescribing has been made. However, not all determinants that are important to consider when prescribing

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second-line glucose-lowering agents were of influence on general practitioners' prescribing.

1. Introduction

For decades, metformin has been the recommended first-line treatment for patients with type 2 diabetes as it lowers fasting blood glucose levels by 20 percent and glycated haemoglobin (HbA1c) levels by 1.5 percent points [1]. However, not all patients achieve adequate glucose control with metformin alone and therefore require stepped-up therapy.

Although sulphonylureas have been the second-line therapy for many years, the arrival of several new therapies (e.g. dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose cotransporter-2 [SGLT-2] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonists) has enabled tailoring of treatment to individual patient characteristics. This has led to substantial changes in type 2 diabetes management guidelines in many countries, including the UK NICE (National Institute for Health and Care Excellence) guideline in 2015. While sulphonylureas were the preferred second-line therapy in the 2009 guideline [2], the new guideline (published in December 2015) recommends to choose the second-line treatment based on patient characteristics, risk factors, treatment efficacy, safety and tolerability, costs and patient preferences [3].

Recent studies have shown that patient characteristics and risk factors are associated with treatment choices [4,5]. In particular, body mass index (BMI), HbA1c, age, cardiovascular risk and renal function have been identified as significant determinants of general practitioners' prescribing [4,5]. However, these studies were performed with British data prior to 2015, with sulphonylureas as the recommended second-line therapy. Importantly, these studies did not account for important risk factors such as ethnicity, drug-related side-effects, contraindications or complications. Moreover, it is of great interest to investigate whether the implementation of the updated guideline has resulted in more individualised prescribing.

Therefore, the objective of this study was to identify patient-specific determinants of early treatment modification (addition of or switching to second-line therapy within one year) in patients with type 2 diabetes before and after implementation of the updated NICE guideline in the UK.

2. Subjects, materials and methods

2.1. Data sources

A cohort study was conducted using the Clinical Practice Research Datalink (CPRD) GOLD. The CPRD GOLD contains prospectively collected data of 674 primary care practices in the UK including approximately 7% of the British population. It comprises a wide range of information including demographics, ethnicity, diagnoses, referrals to secondary care, test results, prescription details and health-related behaviours. Data in CPRD GOLD have been shown to be valid and of high quality for a wide range of diseases [6].

2.2. Study population

Patients who received a first ever prescription of metformin (no other glucose-lowering agent) and aged $\geq$ 18 years during the period of valid CPRD GOLD data collection were included. All patients were required to have at least 1-year of eligible data collection to meet eligibility for our study. Therefore, we can ensure that all patients in our study had a minimum of a 1-year period of non-use of glucose-lowering agents prior to their first metformin prescription. For this study, two cohorts were created: one cohort with data from May 2009 (introduction of the old NICE guideline) - December 2014 and one cohort with data from January 2016 - December 2016. New users of metformin in the period January 2015 - December 2015 were not included in cohort 1 to exclude influence of the upcoming updated guideline (December 2015). Cohort entry (index date) was defined as the date of the first ever metformin prescription after start of valid data collection.

2.3. Study outcomes

To investigate determinants of prescribing of second-line therapies, the main outcome of interest was a prescription of a glucose-lowering agent other than metformin, i.e. second-line therapy. This was defined as a prescription of sulphonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, insulin and/or other glucose-lowering agents (e.g. α-glucosidase inhibitors and repaglinide) after metformin only therapy. As a secondary outcome of interest we studied the potential determinants of a prescription of sulphonylureas only (and no other second-line therapies) after metformin only therapy. Sulphonylureas were chosen as we hypothesized that the greatest change would be observed in this group since sulphonylureas would no longer be the only second-line option after the implementation of the updated guideline.

All patients were followed for a maximum of one year after cohort entry, or until patients received a prescription of a second-line therapy, the date of transfer out of the practice area, the date on which the practice stopped delivering data, or the date of death in the CPRD; whichever came first. All patients with a history of a glucose-lowering drug prescriptions, including insulin, were excluded.

2.4. Determinants

Determinants of treatment modification were largely based on diabetes-related complications, side-effects and contraindications of the different glucose-lowering agents and

Table 1 – Baseline characteristics of all metformin users before and after implementation of the updated guideline (December 2015).

	Before the updated guideline (May 2009 – December 2014)		After the updated guideline (2016)	
	N = 100,313	%	N = 11,476	%
Follow-up, years (mean [SD])	0.96	(0.2)	0.96	(0.2)
Number of females	47,962	(47.8)	5,606	(48.8)
Age, years (mean [SD])	58.5	(15.8)	58.0	(16.0)
Median (IQR)	60.0	(22.0)	59.0	(23.0)
Age Category				
18 – 29 years	5,025	(5.0)	587	(5.1)
30 – 39 years	8,284	(8.3)	1,087	(9.5)
40 – 49 years	14,405	(14.4)	1,606	(14.0)
50 – 59 years	21,908	(21.8)	2,652	(23.1)
60 – 69 years	24,647	(24.6)	2,629	(22.9)
70 – 79 years	17,340	(17.3)	1,903	(16.6)
80 + years	8704	(8.7)	1,012	(8.8)
Alcohol use				
Yes	63,468	(63.3)	6,823	(59.5)
No	30,394	(30.3)	3,634	(31.7)
Unknown	6,451	(6.4)	1,019	(8.9)
Ethnicity				
White	48,630	(48.5)	5,360	(46.7)
South Asian	2,555	(2.5)	294	(2.6)
Black	1,641	(1.6)	201	(1.8)
Mixed	1,844	(1.8)	236	(2.1)
Other	2,826	(2.8)	275	(2.4)
Missing	42,817	(42.7)	5,110	(44.5)
Geographic region				
North East	1,314	(1.3)	108	(0.9)
North West	10,888	(10.9)	858	(7.5)
Yorkshire and the Humber	1,983	(2.0)	161	(1.4)
East Midlands	1,653	(1.6)	0	(0.0)
West Midlands	10,377	(10.3)	830	(7.2)
East of England	7,013	(7.0)	402	(3.5)
South West	8,723	(8.7)	757	(6.6)
South Central	11,002	(11.0)	836	(7.3)
London	12,742	(12.7)	1,407	(12.3)
South East Coast	10,318	(10.3)	1,716	(15.0)
Northern Ireland	2,947	(2.9)	565	(4.9)
Scotland	8,338	(8.3)	1,631	(14.2)
Wales	13,015	(13.0)	2,205	(19.2)

Table 1 – Continued.

	Before the updated guideline (May 2009 – December 2014)		After the updated guideline (2016)	
	N = 100,313	%	N = 11,476	%
BMI, kg/m^2 (mean [SD])	32.3	(6.9)	32.6	(7.1)
<20	1,102	(1.1)	118	(1.0)
20–24.9	10,065	(10.0)	1,054	(9.2)
25–29.9	28,326	(28.2)	3,024	(26.4)
30–34.9	28,327	(28.2)	3,091	(26.9)
≥ 35	28,940	(28.8)	3,395	(29.6)
Unknown	3,553	(3.5)	794	(6.9)
Most recent eGFR measurement (mL/min/1.73 m^2) 6 months prior to index date				
<30	106	(0.1)	<6	(0.0)
30–59	7,605	(7.6)	721	(6.3)
≥60	61,727	(61.5)	7,025	(61.2)
Unknown	30,875	(30.8)	3,725	(32.5)
Most recent HbA1c measurement 6 months prior to index date (mean [SD])	8.3	(1.8)	8.2	(1.7)
<6.5% (48 mmol/mol)	4,400	(4.4)	605	(5.3)
6.5–7.4% (48–57 mmol/mol)	18,054	(18.0)	2,757	(24.0)
7.5–8.5% (58–69 mmol/mol)	15,901	(15.9)	1,781	(15.5)
>8.5% (69 mmol/mol)	20,625	(20.6)	2,512	(21.9)
Unknown	41,333	(41.2)	3,821	(33.3)
Most recent fasting plasma glucose level 6 months prior to index date (mean [SD])	9.9	(4.0)	9.6	(4.0)
<6.0 mmol/L	1,855	(1.9)	203	(1.8)
6.0–7.4 mmol/L	6,796	(6.8)	468	(4.1)
7.5–8.9 mmol/L	6,507	(6.5)	372	(3.2)
≥9 mmol/L	12,067	(12.0)	756	(6.6)
Unknown	73,088	(72.9)	9,677	(84.3)
History of disease				
Cardiovascular disease	6,200	(6.2)	652	(5.7)
Heart failure	2,425	(2.4)	289	(2.5)
Ischemic heart disease	12,493	(12.5)	1,192	(10.4)
Cerebrovascular disease	6,167	(6.1)	649	(5.7)
Hypertension	36,848	(36.7)	3,895	(33.9)
Gastro-intestinal complications				
Nausea	5,633	(5.6)	708	(6.2)
Diarrhoea	14,919	(14.9)	1,743	(15.2)
Vomiting	7,573	(7.5)	931	(8.1)
Flatulence	1,196	(1.2)	134	(1.2)

Table 1 – Continued.

	Before the updated guideline (May 2009 – December 2014)		After the updated guideline (2016)	
	N = 100,313	%	N = 11,476	%
(Proxies of) osteoporosis				
Osteoporosis	2,053	(2.0)	270	(2.4)
History of fracture	22,017	(21.9)	2,738	(23.9)
Use of bisphosphonates	2,095	(2.1)	222	(1.9)
Chronic liver disease	1,702	(1.7)	237	(2.1)
History of a hypoglycaemic event	430	(0.4)	51	(0.4)
Oedema	10,760	(10.7)	1,030	(9.0)
Haematuria	5,094	(5.1)	541	(4.7)
Microalbuminuria	2,130	(2.1)	174	(1.5)
Bladder cancer	450	(0.4)	43	(0.4)
Pancreas carcinoma	50	(0.0)	10	(0.1)
Pancreatitis	1,143	(1.1)	165	(1.4)
Schizophrenia/psychosis	1,604	(1.6)	189	(1.6)
Alzheimer/Dementia	1,754	(1.7)	237	(2.1)
Cognitive impairment	328	(0.3)	61	(0.5)
Profession as driver	756	(0.8)	113	(1.0)

Abbreviations: BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

other patient- and prescribing-related factors. All determinants were selected based on a review of literature and reviewed by clinical experts to ensure clinical relevance prior to analysis. Potential determinants of treatment modification were assessed at index date or as time-dependent determinants. Total follow-up was divided into 90-day intervals in order to assess time-dependent determinants.

The following determinants were examined at the index date: age, sex, BMI, alcohol use and ethnicity [7]. Other determinants considered in this study, including drug-related side-effects, contraindications or complications, were identified time-dependently at the start of each new interval. These included the following most recently recorded values in the past 6 months: HbA1c, fasting plasma glucose and estimated glomerular filtration rate (eGFR); chronic liver disease; a history of a hypoglycaemic event; cardiovascular disease; hypertension; heart failure; ischaemic heart disease; cerebrovascular disease; oedema; haematuria; microalbuminuria; bladder cancer; pancreatic cancer; pancreatitis; gastrointestinal complications; (proxy indicators of) osteoporosis, schizophrenia/psychosis; Alzheimer´s diseases/dementia; cognitive impairment; or a profession as a driver.

2.5. *Data analysis*

We investigated the percentage of patients with a treatment modification during the first year of metformin therapy, before and after implementation of the updated guideline. The proportional contribution of each individual glucose lowering treatment group was calculated.

To evaluate trends of prescribing over time, the proportion of prescriptions for each second-line glucose-lowering agent was calculated annually for the years 2009–2014 and 2016. We used chi-square tests to evaluate differences before and after implementation of the guideline. In addition, we investigated if the treatment modification could be considered as a treatment intensification or a treatment switch. Stop- and start-dates of corresponding therapies were compared to define intensifications or switches. Patients were considered a switcher if they had not received metformin during the 90 days following a prescription of a second-line therapy. Otherwise the treatment modification was considered an intensification.

Cox proportional hazard models were used to identify determinants of early treatment modification. Crude and adjusted Hazard Ratios (HRs) were calculated. HRs were adjusted for all other determinants using multivariate regression. Missing values were included in the models as a separate category. A test of interaction was performed to investigate if HRs before and after the updated guideline were statistically significantly different [8]. In a sensitivity analysis we included only new metformin users in 2014 as the pre-intervention group (instead of 2009–2014). All other methods were identical to the primary analysis. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. *Patients' characteristics before and after implementation of the updated guideline*

A total of 111,789 patients starting metformin therapy during the study period were included, 100,313 (89.7%) before and 11,476 (10.3%) after the implementation of the updated guideline (Table 1). The mean age of metformin users was 58.0 years before and 58.5 years after implementation of the guideline in 2015. The proportion of female users increased slightly after guideline implementation, from 47.8% to 48.8%. No substantial differences were observed for clinical characteristics.

3.2. *Initiation of second-line treatment before and after updated guideline*

Table 2 shows the distribution of the second-line therapies before and after implementation of the updated guideline. In the first year of treatment, 23,334 (23.3%) and 2,523 (22.0%) users of metformin received one treatment modification, before and after implementation of the updated guideline, respectively. Patients who switched to or received $\geq$ 2 new agents are not shown (6.6% and 6.1% of all treatment modifications). Following the new guideline, patients were less likely to receive a prescription of sulphonylureas (62.3% vs 41.3%) or thiazolidinediones (4.7% vs 2.2%) and more likely to receive a prescription of DPP-4 inhibitors (15.8% vs 27.1%) or SGLT-2 inhibitors (0.8% vs 9.9%). Treatment modifications

Table 2 – Switch to or addition of one second-line therapy in the first year of treatment.

	Before the updated guideline†		After the updated guideline†		
Glucose-lowering drug	N	%	N	%	
All second-line therapies	23,334	(23.3)	2,523	(22.0)	
Sulphonylureas	14,536	(62.3)	1,043	(41.3)	↓
DPP-4 inhibitors	3,676	(15.8)	683	(27.1)	↑
Thiazolidinediones	1,103	(4.7)	56	(2.2)	↓
Insulin	3,254	(13.9)	432	(17.1)	↑
GLP-1 receptor agonists	465	(2.0)	53	(2.1)	–
SGLT-2 inhibitors	186	(0.8)	251	(9.9)	↑
other	114	(0.5)	5	(0.2)	↓

Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1 glucagon-like peptide-1; SGLT-2 sodium-glucose co-transporter 2.

† Distribution of second-line therapies is statistically significant different before and after implementation of the updated guideline (Chi-square test, $p < 0.01$).

were the result of a treatment intensification (i.e. second-line therapy was added to metformin) in 83% of the patients, both before and after implementation of the updated guideline (data not shown). In the remaining patients (17%), treatment modification was suggestive of a switch from metformin to another therapy.

Prescribing trends from 2009 to 2014 (supplemental Fig. S1) show that DPP-4 inhibitors were already prescribed more often from 2009 to 2014, regardless of the introduction of the new guideline. However, a substantial shift in the distribution of second-line therapies was observed after implementation of the new guideline, in particular a rapid decline in sulphonylureas.

3.3. *Determinants of initiation of second-line treatment before and after updated guideline*

Overall, initiation of a second-line therapy was associated with a similar set of determinants before and after the guideline change (Table 3). For example, male sex, older age, lower eGFR, higher HbA1c, higher fasting plasma glucose level, history of hypoglycaemic events, pancreas carcinoma and pancreatitis were associated with an increased likelihood of prescribing second-line therapy. Conversely, the presence of gastro-intestinal complications, oedema, haematuria and a profession as driver were negatively associated with the initiation of second-line therapy.

However, we found eight determinants of second-line therapy prescribing with a statistically significant different adjusted HR (aHR) before and after implementation of the updated guideline. The statistically significant, negative association with a BMI $\geq$ 35 kg/m^2 that was observed before the implementation of the updated guideline (aHR 0.84; 95%CI 0.80–0.88), was not observed after implementation (aHR 0.99; 95%CI 0.85–1.14). The association of a mixed ethnicity with the likelihood of a second-line therapy prescription changed after the implementation of the updated guideline, but was not statistically significant at either time interval (aHR 1.13; 95%CI 0.86–1.48 after versus aHR 0.93; 95%CI 0.84–1.02 before). After the guideline change, a positive association with Alzheimer's disease/dementia was observed (aHR 1.29; 95%CI 1.01–1.64), which was not observed before (aHR 0.96; 95%CI 0.88–1.05). In contrast, after the guideline change, a negative association with cognitive impairment was observed (aHR 0.55; 95%CI 0.31–0.97), which was not observed before (aHR 1.10; 95%CI 0.91–1.34). The increased likelihood of prescribing a second-line therapy in patients with heart failure before the implementation of the updated guideline (aHR 1.20; 95%CI 1.11–1.29), was not observed after (aHR 0.90; 95%CI 0.70–1.15). A similar result was observed for a history of fracture (aHR 0.93; 95%CI 0.85–1.02 after versus aHR 1.05; 95%CI 1.02–1.08 before). Schizophrenia/psychosis was associated with an reduced likelihood of a second-line therapy prescription after the updated guideline (aHR 0.64; 95%CI 0.46–0.89), but an increased likelihood before (aHR 1.17; 95%CI 1.07–1.28). Finally, a HbA1c measurement > 8.5% (69 mmol/mol) was less strongly associated with a prescription of a second-line therapy after implementation of the updated guideline (aHR 6.60; 95%CI 5.23–8.33) than before (aHR 9.37; 95%CI 8.63–10.18). Overall, the sensitivity analysis with new metformin users (N = 15,690) in 2014 as the pre-intervention group showed similar results (supplemental Table S1) as compared to our primary analysis with new metformin users in May 2009 through December 2014 as the pre-intervention group (Table 3). However, some determinants no longer showed a statistically significant difference. A BMI $\geq$ 35 kg/m^2, a history of fracture, heart failure, and a HbA1c measurement > 8.5% were no longer statistically significantly different between the pre- and post-intervention periods, although the determinants BMI $\geq$ 35 kg/m^2 and heart failure showed a similar trend as in the primary analysis.

3.4. *Determinants of initiation of sulphonylureas before and after the updated guideline*

We found five determinants of sulphonylurea prescribing, after metformin therapy, with a statically significant different aHR before and after implementation of the updated guideline (Table 4). Patients with a BMI 30–34.9 kg/m^2 were less likely to receive a sulphonylurea after implementation of the updated guideline (aHR 0.54; 95%CI 0.55–0.68 after versus aHR 0.70; 95%CI 0.66–0.74 before). Similarly, prior to the guideline change, a stronger negative association with flatulence was observed (aHR 0.30; 95%CI 0.11–0.79 after versus aHR 0.83; 95%CI 0.70–0.98 before). In contrast, pancreatitis was more strongly associated with a prescription of a sulphonylurea after (aHR 2.69; 95%CI 1.94–3.73) than before (aHR 1.38; 95%CI 1.21–1.57) implementation of the updated guideline. The increased likelihood of a sulphonylurea prescription in patients with heart failure before the implementation of the updated guideline (aHR 1.27; 95%CI 1.16–1.40), was not observed after (aHR 0.82; 95%CI 0.55–1.23). A similar result was observed for schizophrenia/psychosis (aHR 0.57; 95%CI 0.32–1.01 after versus aHR 1.23; 95%CI 1.10–1.39 before).

4. Discussion

In this large, population-based study we identified patient-specific determinants related to early treatment modification in patients with type 2 diabetes before and after the implementation of the updated NICE guideline in the UK. Results show that after introduction of the updated NICE guideline, DPP-4 inhibitors and SGLT-2 inhibitors were more often prescribed as second-line therapy in the first year of treatment. Prescriptions of sulphonylureas and thiazolidediones decreased. Overall, initiation of a second-line therapy was associated with similar determinants before and after implementation of the updated guideline. However, we identified several patient-specific determinants that were significantly different before and after implementation of the updated guideline.

The changes in treatment patterns, as observed in the present study, are generally consistent with results of studies investigating type 2 diabetes treatment patterns in the UK over time [9,10]. However, in our study sulphonylureas were still preferred as second-line treatment option after implementation of the updated guideline (December 2015). The study by Curtis and colleagues reported DPP-4 inhibitors as preferred second-line therapy since 2016 [10]. This difference

Table 3 – Influence of determinants on GP's prescribing of second line therapy before (May 2009 – December 2014) and after implementation (2016) of the new guideline among new users of metformin only in the first year of therapy.

	Before the updated guideline (May 2009 – December 2014)				After the updated guideline (2016)			
	Crude HR	95% CI	Adj. HR[†]	95% CI	Crude HR	95% CI	Adj. HR[†]	CI
Sex								
Female	Reference				Reference			
Male	1.19	(1.16–1.22)	1.09	(1.07–1.13)	1.18	(1.10–1.27)	1.11	(1.02–1.21)
Age Category								
18 – 29 years	Reference				Reference			
30 – 39 years	2.27	(2.06–2.50)	2.52	(2.29–2.78)	1.91	(1.46–2.49)	2.18	(1.66–2.85)
40 – 49 years	3.21	(2.94–3.52)	4.43	(4.03–4.86)	2.58	(2.00–3.33)	3.65	(2.81–4.73)
50 – 59 years	2.90	(2.65–3.17)	4.46	(4.07–4.90)	2.33	(1.82–2.99)	3.68	(2.85–4.76)
60 – 69 years	2.58	(2.36–2.82)	4.40	(4.01–4.83)	2.25	(1.75–2.88)	3.84	(2.97–4.97)
70 – 79 years	2.54	(2.32–2.78)	4.49	(4.08–4.94)	1.96	(1.52–2.52)	3.42	(2.62–4.47)
80 + years	2.74	(2.49–3.02)	3.90	(3.52–4.32)	2.31	(1.77–3.02)	3.36	(2.52–4.48)
Alcohol Use								
Yes	Reference				Reference			
No	1.29	(1.26–1.33)	1.30	(1.26–1.33)	1.23	(1.13–1.33)	1.25	(1.14–1.36)
Unknown	1.62	(1.54–1.70)	1.38	(1.31–1.46)	1.81	(1.61–2.04)	1.36	(1.19–1.56)
Ethnicity								
White	Reference				Reference			
South Asian	1.19	(1.10–1.27)	1.09	(1.01–1.18)	1.02	(0.80–1.40)	1.05	(0.82–1.34)
Black	1.22	(1.11–1.33)	1.03	(0.94–1.13)	1.09	(0.82–1.44)	0.98	(0.74–1.31)
Mixed	0.97	(0.88–1.06)	0.93	(0.84–1.02)	1.05	(0.80–1.37)	1.13	(0.86–1.48)[#]
Other	1.19	(1.10–1.28)	1.05	(0.98–1.13)	1.10	(0.87–1.29)	0.91	(0.71–1.16)
Missing	0.86	(0.84–0.89)	0.85	(0.82–0.87)	0.97	(0.90–1.05)	0.90	(0.83–0.97)
BMI, kg/m^2								
<20	1.21	(1.07–1.35)	1.18	(1.05–1.33)	1.40	(0.99–1.98)	1.31	(0.92–1.87)
20–24.9	Reference		Reference					
25–29.9	0.86	(0.82–0.89)	0.86	(0.82–0.90)	0.92	(0.80–1.06)	0.95	(0.82–1.10)
30–34.9	0.79	(0.76–0.83)	0.81	(0.77–0.85)	0.86	(0.75–1.00)	0.92	(0.79–1.06)
>= 35	0.79	(0.76–0.83)	0.84	(0.80–0.88)	0.87	(0.75–1.00)	0.99	(0.85–1.14)[#]
Unknown	1.69	(1.58–1.81)	1.19	(1.10–1.28)	1.91	(1.61–2.26)	1.36	(1.13–1.62)
Most recent eGFR (mL/min/1.73 m^2) within 6 months prior to index date								
<30	2.30	(1.77–2.97)	2.61	(2.01–3.38)	3.45	(1.11–10.65)	4.87	(1.55–15.29)
30–59	1.17	(1.11–1.23)	1.28	(1.21–1.36)	1.15	(0.97–1.35)	1.39	(1.15–1.67)
≥60	Reference				Reference			
Unknown	1.66	(1.62–1.71)	1.31	(1.27–1.35)	2.00	(1.85–2.16)	1.30	(1.17–1.45)
Most recent HbA1c within 6 months prior to index date								
<6.5% (48 mmol/mol)	Reference				Reference			
6.5–7.4% (48–57 mmol/mol)	1.79	(1.64–1.96)	1.75	(1.60–1.91)	1.65	(1.29–2.10)	1.63	(1.27–2.08)
7.5–8.5% (58–69 mmol/mol)	4.63	(4.25–5.04)	4.42	(4.06–4.81)	3.43	(2.69–4.37)	3.38	(2.64–4.31)
>8.5% (69 mmol/mol)	10.26	(9.46–11.13)	9.37	(8.63–10.18)	6.87	(5.46–8.65)	6.60	(5.23–8.33)[#]
Unknown	7.39	(6.82–8.01)	6.71	(6.18–7.28)	7.01	(5.61–8.76)	5.99	(4.74–7.57)

Table 3 – Continued.

	Before the updated guideline (May 2009 – December 2014)				After the updated guideline (2016)			
	Crude HR	95% CI	Adj. HR[†]	95% CI	Crude HR	95% CI	Adj. HR[†]	CI
Most recent fasting plasma glucose within 6 months prior to index date								
<6.0 mmol/L	Reference				Reference			
6.0–7.4 mmol/L	1.18	(0.99–1.40)	1.06	(0.89–1.27)	1.37	(0.74–2.56)	1.51	(0.81–2.82)
7.5–8.9 mmol/L	1.89	(1.60–2.24)	1.33	(1.12–1.57)	1.47	(0.78–2.80)	1.22	(0.64–2.34)
≥9 mmol/L	5.85	(5.02–6.83)	2.36	(2.02–2.75)	4.16	(2.41–7.20)	1.98	(1.14–3.45)
Unknown	3.85	(3.31–4.47)	2.13	(1.84–2.48)	4.40	(2.60–7.44)	2.54	(1.50–4.31)
History of Disease								
Cardiovascular disease	1.13	(1.08–1.19)	1.04	(0.84–1.30)	1.18	(1.01–1.37)	1.16	(0.73–1.85)
Heart failure	1.24	(1.15–1.33)	1.20	(1.11–1.29)	0.90	(0.71–1.14)	0.90	(0.70–1.15)[#]
Ischemic heart disease	1.06	(1.02–1.09)	1.10	(1.06–1.15)	0.95	(0.84–1.07)	1.01	(0.89–1.15)
Cerebrovascular disease	1.13	(1.08–1.19)	1.04	(0.84–1.30)	1.16	(1.00–1.35)	1.02	(0.64–1.63)
Hypertension	0.91	(0.89–0.94)	0.97	(0.94–0.99)	0.90	(0.83–0.97)	0.97	(0.89–1.05)
Gastro-intestinal complications								
Nausea	0.75	(0.71–0.80)	0.95	(0.89–1.01)	0.71	(0.60–0.84)	1.00	(0.84–1.19)
Diarrhoea	0.74	(0.71–0.77)	0.87	(0.84–0.90)	0.63	(0.56–0.70)	0.81	(0.71–0.91)
Vomiting	0.74	(0.70–0.78)	0.91	(0.86–0.96)	0.69	(0.60–0.81)	0.92	(0.79–1.09)
Flatulence	0.68	(0.59–0.77)	0.84	(0.74–0.96)	0.37	(0.22–0.62)	0.50	(0.30–0.83)
(Proxies) of osteoporosis								
Osteoporosis	0.93	(0.85–1.02)	1.03	(0.93–1.14)	0.89	(0.70–1.14)	1.03	(0.79–1.36)
History of fracture	1.02	(0.99–1.06)	1.05	(1.02–1.08)	0.89	(0.81–0.97)	0.93	(0.85–1.02)[#]
Use of bisphosphonates	0.78	(0.71–0.85)	0.82	(0.74–0.91)	0.76	(0.57–1.01)	0.83	(0.61–1.13)
Chronic liver disease	1.01	(0.92–1.11)	1.07	(0.97–1.17)	0.98	(0.77–1.25)	1.07	(0.84–1.37)
History of a hypoglycaemic event	2.03	(1.77–2.33)	1.82	(1.59–2.09)	2.43	(1.70–3.46)	2.27	(1.58–3.26)
Oedema	0.67	(0.64–0.70)	0.75	(0.71–0.78)	0.57	(0.49–0.66)	0.68	(0.58–0.80)
Haematuria	0.80	(0.76–0.85)	0.87	(0.82–0.93)	0.63	(0.51–0.77)	0.77	(0.63–0.95)
Microalbuminuria	0.88	(0.81–0.95)	0.91	(0.84–0.99)	0.92	(0.70–1.22)	1.04	(0.78–1.38)
Bladder cancer	1.00	(0.83–1.20)	1.12	(0.93–1.34)	1.09	(0.62–1.91)	1.07	(0.60–1.90)
Pancreas carcinoma	2.83	(1.93–4.16)	2.12	(1.44–3.12)	3.31	(1.49–7.36)	3.84	(1.71–8.60)
Pancreatitis	1.58	(1.43–1.74)	1.48	(1.35–1.64)	2.01	(1.59–2.55)	1.89	(1.48–2.40)
Schizophrenia/psychosis	1.30	(1.19–1.42)	1.17	(1.07–1.28)	0.72	(0.52–1.00)	0.64	(0.46–0.89)[#]
Alzheimer/Dementia	1.41	(1.30–1.54)	0.96	(0.88–1.05)	1.60	(1.29–2.00)	1.29	(1.01–1.64)[#]
Cognitive impairment	1.34	(1.11–1.62)	1.10	(0.91–1.34)	0.79	(0.46–1.36)	0.55	(0.31–0.97)[#]
Profession as driver	0.67	(0.58–0.78)	0.64	(0.55–0.75)	0.55	(0.36–0.86)	0.61	(0.39–0.94)

Abbreviations: BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

[†] Results were corrected for all other determinants.

[#] Test of interaction showed a statistically significant difference before and after implementation of the new guideline [8].

Table 4 – Influence of determinants on GP's prescribing of sulphonylureas before (May 2009 – December 2014) and after implementation (2016) of the new guideline among new users of metformin only in the first year of therapy.

	Before the updated guideline (May 2009 – December 2014)				After the updated guideline (2016)			
	Crude HR	95% CI	Adj. HR[†]	95% CI	Crude HR	95% CI	Adj. HR[†]	CI
Sex								
Female	Reference				Reference			
Male	1.24	(1.20–1.28)	1.09	(1.05–1.13)	1.38	(1.22–1.56)	1.18	(1.03–1.35)
Age Category								
18 – 29 years	Reference				Reference			
30 – 39 years	3.19	(2.69–3.77)	3.46	(2.92–4.09)	2.55	(1.33–4.90)	2.74	(1.43–5.28)
40 – 49 years	5.62	(4.79–6.58)	7.40	(6.30–8.69)	6.23	(3.39–11.45)	7.96	(4.29–14.78)
50 – 59 years	5.27	(4.51–6.17)	7.74	(6.60–9.08)	5.39	(2.95–9.86)	7.69	(4.16–14.23)
60 – 69 years	4.92	(4.20–5.75)	7.95	(6.77–9.33)	5.11	(2.79–9.34)	7.95	(4.29–14.73)
70 – 79 years	5.15	(4.40–6.03)	8.49	(7.22–9.98)	4.85	(2.62–8.91)	7.57	(4.06–14.14)
80 + years	6.19	(5.27–7.27)	8.04	(6.79–9.51)	6.91	(3.73–12.81)	8.96	(4.72–17.00)
Alcohol Use								
Yes	Reference				Reference			
No	1.26	(1.21–1.30)	1.25	(1.20–1.29)	1.15	(1.01–1.31)	1.15	(1.00–1.33)
Unknown	1.51	(1.42–1.62)	1.33	(1.24–1.43)	1.45	(1.17–1.79)	1.18	(0.93–1.50)
Ethnicity								
White	Reference				Reference			
South Asian	1.10	(0.99–1.22)	1.06	(0.95–1.17)	0.92	(0.61–1.39)	1.05	(0.69–1.60)
Black	1.26	(1.12–1.42)	1.13	(1.00–1.28)	1.34	(0.87–2.05)	1.22	(0.79–1.88)
Mixed	1.03	(0.91–1.16)	1.02	(0.90–1.16)	1.20	(0.79–1.82)	1.30	(0.85–1.99)
Other	1.28	(1.17–1.40)	1.17	(1.07–1.28)	1.01	(0.67–1.54)	0.82	(0.54–1.26)
Missing	0.93	(0.90–0.96)	0.89	(0.86–0.93)	1.00	(0.88–1.14)	0.92	(0.81–1.05)
BMI, kg/m^2								
<20	1.26	(1.10–1.44)	1.25	(1.08–1.43)	1.01	(0.58–1.74)	0.92	(0.53–1.61)
20–24.9	Reference				Reference			
25–29.9	0.80	(0.76–0.85)	0.80	(0.75–0.84)	0.75	(0.62–0.92)	0.75	(0.61–0.91)
30–34.9	0.69	(0.65–0.73)	0.70	(0.66–0.74)	0.53	(0.43–0.65)	0.54	(0.44–0.68)[#]
>= 35	0.58	(0.55–0.62)	0.63	(0.59–0.67)	0.48	(0.39–0.60)	0.55	(0.44–0.69)
Unknown	1.41	(1.28–1.54)	1.00	(0.91–1.11)	1.09	(0.83–1.42)	0.80	(0.60–1.06)
Most recent eGFR (mL/min/1.73 m^2) within 6 months prior to index date								
<30	2.69	(1.99–3.64)	2.72	(2.00–3.70)	n.a. [‡]		n.a.[‡]	
30–59	1.23	(1.16–1.31)	1.22	(1.14–1.31)	1.30	(1.02–1.66)	1.49	(1.13–1.98)
≥60	Reference				Reference			
Unknown	1.41	(1.36–1.46)	1.16	(1.11–1.21)	1.59	(1.40–1.81)	1.03	(0.86–1.23)

Table 4 – Continued.

	Before the updated guideline (May 2009 – December 2014)				After the updated guideline (2016)			
	Crude HR	95% CI	Adj. HR[†]	95% CI	Crude HR	95% CI	Adj. HR[†]	CI
Most recent HbA1c within 6 months prior to index date								
<6.5% (48 mmol/mol)	Reference				Reference			
6.5–7.4% (48–57 mmol/mol)	1.88	(1.67–2.11)	1.80	(1.60–2.02)	1.86	(1.18–2.93)	1.74	(1.11–2.75)
7.5–8.5% (58–69 mmol/mol)	5.13	(4.57–5.75)	4.77	(4.25–5.35)	4.15	(2.64–6.50)	3.87	(2.74–6.08)
>8.5% (69 mmol/mol)	11.81	(10.59–13.18)	10.54	(9.43–11.77)	10.56	(6.91–16.15)	9.53	(6.21–14.62)[#]
Unknown	7.35	(6.60–8.19)	7.37	(6.60–8.23)	8.33	(5.48–12.67)	8.62	(5.58–13.32)
Most recent fasting plasma glucose within 6 months prior to index date								
<6.0 mmol/L	Reference				Reference			
6.0–7.4 mmol/L	1.67	(1.28–2.17)	1.35	(1.04–1.76)	1.84	(0.51–6.69)	1.63	(0.45–5.95)
7.5–8.9 mmol/L	2.83	(2.19–3.65)	1.77	(1.37–2.29)	2.39	(0.66–8.66)	1.59	(0.44–5.83)
≥9 mmol/L	9.64	(7.59–12.23)	3.43	(2.70–4.37)	9.56	(3.02–30.23)	3.25	(1.02–10.38)
Unknown	5.37	(4.24–6.79)	2.82	(2.23–3.57)	7.44	(2.40–23.07)	3.49	(1.12–10.90)
History of Disease								
Cardiovascular disease	1.21	(1.14–1.29)	0.90	(0.68–1.19)	1.35	(1.07–1.70)	0.85	(0.40–1.77)
Heart failure	1.41	(1.29–1.55)	1.27	(1.16–1.40)	0.89	(0.61–1.32)	0.82	(0.55–1.23)[#]
Ischemic heart disease	1.06	(1.01–1.11)	1.02	(0.97–1.07)	0.86	(0.70–1.06)	0.83	(0.67–1.03)
Cerebrovascular disease	1.22	(1.14–1.30)	1.20	(0.90–1.59)	1.38	(1.09–1.74)	1.48	(0.71–3.08)
Hypertension	0.93	(0.90–0.97)	0.94	(0.91–0.98)	0.94	(0.83–1.07)	0.96	(0.84–1.10)
Gastro-intestinal complications								
Nausea	0.83	(0.77–0.89)	1.02	(0.94–1.10)	0.81	(0.62–1.06)	1.20	(0.91–1.59)
Diarrhoea	0.83	(0.79–0.87)	0.95	(0.91–1.00)	0.67	(0.56–0.81)	0.87	(0.72–1.07)
Vomiting	0.79	(0.74–0.84)	0.94	(0.87–1.00)	0.68	(0.53–0.88)	0.92	(0.70–1.20)
Flatulence	0.74	(0.62–0.87)	0.83	(0.70–0.98)	0.27	(0.10–0.72)	0.30	(0.11–0.79)[#]
(Proxies of) osteoporosis								
Osteoporosis	1.10	(0.99–1.23)	1.02	(0.90–1.15)	1.03	(0.71–1.50)	0.94	(0.62–1.44)
History of fracture	1.06	(1.02–1.10)	1.08	(1.03–1.12)	0.94	(0.82–1.09)	0.98	(0.84–1.13)
Use of bisphosphonates	1.00	(0.90–1.11)	0.91	(0.81–1.03)	1.15	(0.78–1.70)	1.14	(0.74–1.76)
Chronic liver disease	1.03	(0.92–1.16)	1.09	(0.97–1.23)	1.09	(0.75–1.60)	1.27	(0.86–1.87)
History of a hypoglycaemic event	1.46	(1.18–1.81)	1.25	(1.01–1.55)	1.70	(0.85–3.42)	1.47	(0.73–3.00)
Oedema	0.77	(0.73–0.82)	0.82	(0.78–0.87)	0.55	(0.43–0.72)	0.65	(0.50–0.84)
Haematuria	0.90	(0.83–0.97)	0.92	(0.85–0.99)	0.72	(0.52–0.98)	0.78	(0.57–1.09)
Microalbuminuria	0.88	(0.80–0.98)	0.88	(0.79–0.97)	0.80	(0.49–1.31)	0.79	(0.48–1.31)
Bladder cancer	1.17	(0.94–1.45)	1.17	(0.93–1.46)	2.25	(1.17–4.33)	1.83	(0.93–3.60)
Pancreas carcinoma	2.47	(1.43–4.24)	1.56	(0.91–2.70)	2.97	(0.74–11.89)	2.43	(0.60–9.85)
Pancreatitis	1.56	(1.37–1.77)	1.38	(1.21–1.57)	3.06	(2.22–4.21)	2.69	(1.94–3.73)[#]
Schizophrenia/psychosis	1.33	(1.18–1.50)	1.23	(1.10–1.39)	0.65	(0.37–1.14)	0.57	(0.32–1.01)[#]
Alzheimer/Dementia	1.61	(1.45–1.79)	0.98	(0.87–1.09)	1.78	(1.26–2.52)	1.29	(0.88–1.89)
Cognitive impairment	1.27	(0.98–1.65)	0.93	(0.71–1.20)	1.00	(0.45–2.22)	0.61	(0.26–1.42)
Profession as driver	0.64	(0.52–0.78)	0.61	(0.50–0.75)	0.30	(0.11–0.81)	0.32	(0.12–0.85)

Abbreviations: BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

[†] Results were corrected for all other determinants.

[‡] No patients with a renal function < 30 ml/min/1.73 m^2 received a sulphonylurea after implementation of the updated guideline.

[#] Test of interaction showed a statistically significant difference before and after implementation of the new guideline [8].

might be explained by different methods used, e.g. other definitions of first line therapy and treatment cessation. Of note, the prescribing trends from 2009 to 2014 showed that the prescription of DDP-4 inhibitors already changed proportionally before the introduction of the new guideline. In contrast, the introduction of the new guideline appeared to accelerate the decline in the prescription of sulphonylureas. These results should, however be interpreted with caution, since the observational nature of this study hampers causal inference. For instance, the continuing increase in prescribing SGLT-2 inhibitors after the implementation of the new guideline could also be explained by the publication of landmark studies on SGLT-2 inhibition that appeared in the same period [11]. Nonetheless, while sulfonylureas continue to play an important role in the management of type 2 diabetes, it is clear that DPP-4 inhibitors have become a cornerstone of second-line therapy in the UK.

Several other studies identified clinical features associated with prescribing of second-line glucose-lowering agents. Elevated HbA1c levels, BMI, age, cardiovascular comorbidities, eGFR, duration of diabetes and diabetes related comorbidities are known factors associated with prescribing of second-line therapies [4,5,12–17]. We also found that a higher fasting plasma glucose, history of a hypoglycaemic event, pancreas carcinoma and pancreatitis were positively associated with a prescription of a second-line glucose-lowering agent both before and after implementation of the updated guideline. Most of the patients with one of the above clinical features are probably in need of more intensive therapy. However, with regard to a history of a hypoglycaemic event, we did not expect to find a positive association as hypoglycaemia is not related to metformin use, yet is for sulphonylureas [18]. In contrast, gastro-intestinal complications, oedema, haematuria and a report of being a driver as a profession were negatively associated with prescribing second-line therapies. We can partially explain these results as thiazolidinediones are associated with oedema [19] and sulphonylureas/insulin are not optimal treatment options for patients with a profession as driver due to the risk of hypoglycaemia. However, we cannot explain why gastro-intestinal complications, a common side effect of metformin, and haematuria were negatively associated with prescribing second-line therapies.

In our primary analysis examining all second-line therapies, we identified eight determinants with statistically different aHRs. Since the determinants of a treatment modification to all second-line therapies combined are difficult to interpret, e.g. we cannot explain why Alzheimer was positively and cognitive impairment negatively associated with the prescription of second-line therapies, it is of great interest to study the differences in prescribing individual second-line therapies, i.e. sulphonylureas. In the analysis examining the prescribing of sulphonylureas only, we identified five key determinants that had a statistically significant different aHR before and after implementation of the updated guideline. Most of the changes are likely a result of more options to consider as second-line therapy after the 2015 guideline. First, patients with a high BMI are more likely to receive GLP-1 receptor agonists as they are known to have more favourable effects on body weight than sulphonylureas [3,20]. Surprisingly, we did not find a statistically significant different aHR in patients with a BMI $\geq$ 35 kg/m^2. Second, patients with heart failure are more likely to receive SGLT-2 inhibitors, as more evidence has become available regarding the beneficial effects of SGLT-2 inhibitors on heart failure [11,21]. Third, metformin users with gastrointestinal side-effects are more likely to switch to second-line therapies [22]. A stronger negative association after implementation of the new guideline with a sulphonylurea prescription was probably the result of the availability of more second-line therapies. Similarly, schizophrenia/psychosis was negatively associated with a sulphonylurea prescription after implementation of the updated guideline. Due to the risk of hypoglycaemia and severe consequences when not taken correctly/overdosed, sulphonylureas are not the best option for patients with schizophrenia/psychosis. In contrast, pancreatitis was more strongly associated with a sulphonylurea prescription after implementation of the updated guideline, as compared to the period before. With the on-going debate regarding the risk of pancreatitis in patients using incretin-based agents [23], this is not surprising.

Although we found some statistically significant differences following the implementation of the updated guideline, we did expect to identify more shifts in determinants. For instance, we expected that a history of hypoglycaemia, alcohol use and older age would have been negatively associated with a sulphonylurea prescription after the implementation of the updated guideline as the new therapies are not associated with hypoglycaemia. However, it is possible that we did not find such results as use of metformin, the starting point in our study, is not contraindicated in patients with these determinants.

A key strength of this study is the availability of detailed information for various potentially relevant determinants in the CPRD. Second, prescriptions for glucose-lowering agents are most of the time issued by a GP. Therefore, our prescribing data can be considered accurate and representative. Third, most of the results of our primary analysis remained consistent in a sensitivity analysis. The loss of power might explain the loss of significance for some determinants, e.g. heart failure. Finally, the separate analysis of data before and after implementation of the updated guideline provides important data regarding the uptake of the guideline.

Our study also has some potential limitations. With limited data after implementation of the updated guideline, we could only investigate treatment modifications in the first year of therapy. It is possible that implementation of the updated guideline requires more time than investigated. Second, the CPRD contains information on prescription and not dispensed data, which might result in misclassification of exposure. However, it is unlikely that this misclassification would be differential before and after implementation of the updated guideline. Third, the patients' electronic records are not collected for research purposes. This can result in missing or incomplete information regarding patients' characteristics, risk factors and lifestyle factors, e.g. profession as a driver, schizophrenia and diet. Fourth, the shift in GP's prescribing can also be the result of sales marketing by pharmaceutical companies for new medications, the influence of (social) media, policies and/or new clinical evidence. Fifth, there is geographical variation in the prescribing of second-

line therapy in the UK [10]. The geographical shift in patients registered in the database (shown in Table 1) may, therefore, have affected our results. Sixth, as previously mentioned, due to the design of our study we could only investigate associations and not causality. Seventh, although the CPRD contains information of a wide range of determinants, the influence of possible important determinants, as well as patient and provider preferences, could not be investigated as this information is not captured in the CPRD GOLD database. Moreover, our analysis did not correct for the potential influence of patients' current non-diabetes medication. Finally, all treatment modifications (switch and intensification) were included in our primary analyses. We showed that treatment modifications were mainly the result of a treatment intensification.

In conclusion, our results show increased diversity in the prescribing of second-line glucose-lowering agents after the implementation of the updated NICE guideline. While many of the patient characteristics associated with prescribing a second-line therapy remained stable before and after implementation of the new guideline, we recognise that more time may be needed to observe the optimal implementation of the updated guideline. We believe our results suggest that a first step towards individually tailoring prescribing to patient-specific characteristics has already been made. However, not all determinants that are important to consider when prescribing second-line glucose-lowering agents, e.g. older age and a history of hypoglycaemia, were of influence on GP's prescribing.

5. Contribution Statement

JvD, initiated the study, did the literature review and wrote the first draft of the paper. JD analysed the data. JvD, MB, FV, AMB and JD and were responsible for the study concept and design and participated in the interpretation of the data. All authors had full access to all of the data in the study, critically revised the paper for intellectual content, approved the final version to be published and can take responsibility for the integrity of the data and accuracy of the data analyses.

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7. Scientific approval

This protocol was approved by the Interdisciplinary Scientific Advisory Committee (ISAC) for Medicines and. Healthcare products Regulatory Agency. (MHRA) database research, protocol no. 18_126R.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.108828.

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