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Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: open cohort study in primary care

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ABSTRACT

OBJECTIVE

To assess the risks of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia in patients with type 2 diabetes associated with prescribed diabetes drugs, particularly newer agents including gliptins or glitazones (thiazolidinediones).

DESIGN

Open cohort study in primary care.

SETTING

1243 practices contributing data to the QResearch database in England.

PARTICIPANTS

469 688 patients with type 2 diabetes aged 25-84 years between 1 April 2007 and 31 January 2015.

EXPOSURES

Hypoglycaemic agents (glitazones, gliptins, metformin, sulphonylureas, insulin, and other) alone and in combination.

MAIN OUTCOME MEASURES

First recorded diagnoses of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia recorded on patients' primary care, mortality, or hospital records. Cox models estimated hazard ratios for diabetes treatments adjusting for potential confounders.

RESULTS

21 308 (4.5%) and 32 533 (6.9%) patients received prescriptions for glitazones and gliptins during follow-up, respectively. Compared with non-use, glitazones were associated with a decreased risk of blindness (adjusted hazard ratio 0.71, 95% confidence interval 0.57 to 0.89; rate 14.4 per 10 000 person years of exposure) and an increased risk of hypoglycaemia (1.22, 1.10 to 1.37; 65.1); gliptins were associated with a decreased risk of hypoglycaemia (0.86, 0.77 to 0.96; 45.8). Although the numbers of patients prescribed gliptin monotherapy or glitazones monotherapy were relatively low, there were significantly increased risks of severe kidney failure compared with metformin monotherapy (adjusted hazard ratio 2.55, 95% confidence interval 1.13 to 5.74). We found significantly lower risks of hyperglycaemia among patients prescribed dual therapy involving metformin with either gliptins (0.78, 0.62 to 0.97) or glitazones (0.60, 0.45 to 0.80) compared with metformin monotherapy. Patients prescribed triple therapy with metformin, sulphonylureas, and either gliptins (adjusted hazard ratio 5.07, 95% confidence interval 4.28 to 6.00) or glitazones (6.32, 5.35 to 7.45) had significantly higher risks of hypoglycaemia than those prescribed metformin monotherapy, but these risks were similar to those involving dual therapy with metformin and sulphonylureas (6.03, 5.47 to 6.63). Patients prescribed triple therapy with metformin, sulphonylureas, and glitazones had a significantly reduced risk of blindness compared with metformin monotherapy (0.67, 0.48 to 0.94).

CONCLUSIONS

We have found lower risks of hyperglycaemia among patients prescribed dual therapy involving metformin with either gliptins or glitazones compared with metformin alone. Compared with metformin monotherapy, triple therapy with metformin, sulphonylureas, and either gliptins or glitazones was associated with an increased risk of hypoglycaemia, which was similar to the risk for dual therapy with metformin and sulphonylureas. Compared with metformin monotherapy, triple therapy with metformin, sulphonylureas, and glitazones was associated with a reduced risk of blindness. These results, while subject to residual confounding, could have implications for the prescribing of hypoglycaemic drugs.

WHAT IS ALREADY KNOWN

Type 2 diabetes is associated with increased risks of microvascular complications (including lower limb amputation, blindness, kidney failure) and hypoglycaemic and hyperglycaemic attacks

Clinical trial evidence for glitazones and gliptins is largely based on surrogate endpoints (such as reduction of HbA_{1c}) rather than hard clinical endpoints (such as reduced incidence of complications)

There is a need to quantify risks of clinical outcomes in large representative populations of patients with type 2 diabetes prescribed these drugs over longer periods of time

WHAT THIS STUDY ADDS

Although the numbers of patients prescribed gliptin monotherapy or glitazone monotherapy were relatively low, we found an increased risk of severe kidney failure compared with metformin monotherapy despite adjustments for serum creatinine and other risk factors at baseline

We found reduced risks of hyperglycaemia among patients prescribed dual therapy of metformin with either gliptins or glitazones, compared with metformin monotherapy

Compared with metformin monotherapy, triple therapy with metformin, sulphonylureas, and either gliptins or glitazones was associated with an increased risk of hypoglycaemia; compared with metformin monotherapy, triple therapy with metformin, sulphonylureas, and glitazones was associated with a reduced risk of blindness

Introduction

Type 2 diabetes is associated with increased risks of macrovascular complications (such as heart failure and

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cardiovascular disease), microvascular complications (including lower limb amputation, blindness, kidney failure), and hypoglycaemic and hyperglycaemic attacks. Higher levels of glycated haemoglobin (HbA_{1c}) are associated with higher risks of both microvascular and microvascular complications.[1] The UK Prospective Diabetes Study (UKPDS) showed a reduced risk of microvascular complications with intensive hypoglycaemic treatment, particularly with metformin, but no conclusive benefit for cardiovascular outcomes.[2 3] Additional observational analyses of the UKPDS cohort suggested that any lowering of HbA_{1c} is likely to reduce risk of microvascular complications as well as cardiovascular outcomes.[1]

Apart from the original UKPDS studies, clinical trial evidence for newer hypoglycaemic agents—such as glitazones (thiazolidinediones) and gliptins—has been largely based on surrogate endpoints such as reduction of HbA_{1c} rather than hard clinical endpoints such as increased survival rates or reduced incidence of complications. While the assumption that lowering HbA_{1c} will result in a net clinical benefit seems plausible, evidence suggests that it is not always reliable. Phenformin, a biguanide, was withdrawn from the market in 1978 because of concerns about increased risk of cardiovascular events and lactic acidosis.[4] In the United Kingdom, troglitazone (an insulin sensitising glitazone) was withdrawn from the market in 1997 a few months after its launch because of hepatotoxicity.[5] The drug was withdrawn from the United States three years later.

Other newer hypoglycaemic agents have subsequently shown unexpected increases in cardiovascular endpoints.[6-9] For example, rosiglitazone, another glitazone, was associated with an increased incidence of heart failure.[6] This resulted in the drug's withdrawal from Europe, India, New Zealand, and South Africa in 2010-11, although it continues to be available in the USA, albeit with limitations. Uncertainty therefore remains over the longer term comparative clinical risks and benefits among patients prescribed diabetes drugs, particularly gliptins and glitazones alone and in combination with other treatments.[10 11] Regulatory agencies have responded to this uncertainty, not by requiring evidence of direct clinical benefit but by requiring evidence that new hypoglycaemic drugs are not associated with harmful increases in cardiovascular events.[12 13] This has led to industry funded, controversial non-inferiority trials such as the RECORD study, in which rosiglitazone was assumed to be non-inferior so long as the upper limit of the 95% confidence interval of the hazard ratio for cardiovascular disease was less than 1.20.[14 15] While the RECORD study confirmed an increased risk of heart failure with rosiglitazone, it was unable to rule out an increased risk of myocardial infarction.[14]

The lifelong nature of diabetes, together with the marked increase in its prevalence and the inclusion of prescribing recommendations in guidelines,[16] are likely to lead to increases in the numbers of patients prescribed different diabetes drugs. Given the impracticability and ethical difficulties of head to head trials, there is a need to quantify risks of clinical outcomes in large representative populations of patients with type 2 diabetes prescribed these drugs over longer periods. This information can complement information from meta-analyses of clinical trials where available, although these sources can have publication bias, lack sufficient reporting of outcomes, and have insufficient duration of follow-up or power to make relevant comparisons for effects on clinical endpoints.[11 17] Although the focus of attention for new diabetes drugs has shifted from HbA_{1c} alone to include cardiovascular outcomes, relatively little clinical trial evidence has accrued as to whether the newer diabetes drugs increase or decrease risk of other diabetes complications including lower limb amputation, blindness, kidney failure, serious hyperglycaemic or hypoglycaemic episodes, although these are the complications of particular importance to patients.[18] There is also a lack of evidence on how these drugs are used, alone and in combination, in real world populations. This is important given that there are now a plethora of individual hypoglycaemic agents available from at least six different drug classes.

We therefore carried out a cohort study using a large UK primary care database with linked general practice, mortality, and hospital admissions data. This study aimed to investigate the associations between different classes of diabetes drugs and the risks of microvascular complications (severe kidney failure, blindness, and amputation), and serious hyperglycaemic or hypoglycaemic events. We were particularly interested in the risks associated with the newer agents, including glitazones and gliptins. In a separate analysis not included in this paper, we have compared the risks of heart failure, cardiovascular disease, and all cause mortality between different classes of diabetes drugs in patients with type 2 diabetes.

Methods

Setting and data source

We did a population based open cohort study of patients in England aged 25-84 years with a diagnosis of type 2 diabetes. We used a large population of primary care patients derived from version 40 of the QResearch database (www.qresearch.org). QResearch is a continually updated, patient level, pseudonymised database with event level data extending back to 1989. QResearch currently includes clinical and demographic data from 1243 general practices in England and two practices in Scotland covering a population of over 24 million patients, collected in the course of routine healthcare by general practitioners and associated staff.

The primary care data includes demographic information, diagnoses, prescriptions, referrals, laboratory results, and clinical values. Diagnoses are recorded using the Read code classification.[19] QResearch has been used for a wide range of clinical research including the assessment of unintended effects of commonly prescribed medicines.[20-25] The primary care data are linked at individual patient level to Hospital Episode Statistics, and mortality records from the Office for National Statistics (ONS). Hospital Episode Statistics provides details of all inpatient admissions in the UK's health service since 1997, including primary and

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secondary causes coded by ICD-10 (international classification of diseases, 10th revision) and operations and interventions coded by OPCS-4 (OPCS classification of interventions and procedures version 4). ONS provides details of all deaths in England with primary and underlying causes, also coded using ICD-10. Patient records are linked using a project specific pseudonymised NHS number, which is valid and complete for 99.8% of primary care patients, 99.9% for ONS mortality records, and 98% for hospital admissions records.[1]

Inclusion and exclusion criteria

We included all QResearch practices in England who had been using the Egton Medical Information Systems (EMIS) computer system for at least a year. We initially identified an open cohort of patients aged 25-84 years registered with eligible practices between 1 April 2007 and 31 January 2015. We chose this study period because both pioglitazone and gliptins were available in the UK for the full study period. We then selected patients with diabetes if they had a Read code for diabetes or more than one prescription for a hypoglycaemic drug.

We excluded patients as having type 1 diabetes if they had been diagnosed under the age of 35 years and prescribed insulin.[26] We also excluded patients without a postcode related deprivation score. We determined an entry date to the cohort for each patient, which was the latest of the following: date of diagnosis of diabetes, 25th birthday, date of registration with the practice plus one year, date on which the practice computer system was installed plus one year, and the beginning of the study period. We excluded patients with an existing diagnosis of an outcome of interest at the study entry date from the analysis of that outcome.

We used an incident user design for patients prescribed glitazones, gliptins (our main exposures of interest), or insulin to reduce bias.[27] We defined incident users as patients without a prescription for these drugs in the 12 months before the study entry date as in other studies,[28] and we excluded people who had received any of these drugs in the previous 12 months. We included prevalent users of metformin or sulphonylureas in the study cohort, because glitazones and gliptins are usually prescribed after monotherapy with metformin or sulphonylureas. Exclusion of prevalent users of metformin or sulphonylureas would have substantially reduced the numbers of new users of glitazones and gliptins, which were our main exposures of interest.

Outcomes

We had five primary outcomes based on diagnoses and procedures recorded either in the patient's primary care record or in their linked hospital record or mortality record during follow-up:

- Lower limb amputation—including hindquarter, above knee, or below knee amputation
- Blindness—including blindness in one or both eyes, registered blindness, and severe visual impairment
- Severe kidney failure—including kidney dialysis, kidney transplant, chronic kidney disease stage 5
- Hyperglycaemia—including hyperosmolar hyperglycaemic coma, diabetic ketoacidosis
- Hypoglycaemia—including spontaneous, reactive, drug induced hypoglycaemia events requiring paramedic or hospital admission or resulting in death

We used Read codes to identify recorded diagnoses from the primary care records. We used ICD-10 clinical codes and OPCS-4 procedure codes to identify incident cases from hospital and ONS mortality records. Web appendix 1 lists the clinical codes used to identify each outcome. We used the earliest recorded date from any of the three data sources as the index date for the diagnosis for each outcome. Patients were censored at the earliest date of the first recorded diagnosis of the outcome of interest, death, deregistration with the practice, last upload of computerised data, or the study end date (31 January 2015).

Exposure data

Our primary exposures of interest were new use of gliptins and new use of glitazones during the study period. We extracted details of all individual prescriptions for all types of hypoglycaemics for each patient including the prescription date and the type. We partitioned the follow-up time into different treatment periods, where each period corresponded to treatment with a particular type or combination of hypoglycaemic drugs, or could be a period of no treatment with any hypoglycaemic drugs. If the patient changed to a different type of treatment or to a different combination of treatments, we classified that as a separate treatment period. For example, consider a patient who was prescribed metformin alone on cohort entry for 12 months, then was prescribed both glitazones and metformin for another 24 months, and then had a treatment free period for six months until they were censored. This patient would have three treatment periods (metformin only for 12 months, metformin and glitazones for 24 months, and no treatment for six months).

We determined the duration of each treatment period by calculating the number of days between the earliest issue date and the latest issue date for the type of treatment prescribed. If another treatment was added before the initial treatment was stopped, the treatment period on the initial treatment alone was the number of days between the earliest issue date for the initial treatment and the earliest issue date for the next treatment. We added 90 days to the last prescription date as an estimate of the date on which the patient stopped treatment (the stop date). We made this assumption to allow for events that occur during a withdrawal period to be attributed to the medication rather than counting as unexposed time.

For the analysis, we used six binary exposure variables for each treatment period to indicate treatment with any of the diabetes drugs grouped into six drug classes: glitazones, gliptins, metformin, sulphonylureas, insulin, and other oral hypoglycaemic drugs (including α-glucosidase inhibitors, glinides, sodium-glucose cotransporter 2 inhibitors, guar). These

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drug classes were not split into individual drugs in the analyses. This exposure classification allowed for patients to be on different combinations of these drugs during a treatment period. To further assess associations for different specific treatment combinations (such as dual therapy with metformin and glitazones), we also categorised treatments during each treatment period into one categorical variable with 21 mutually exclusive categories. These mutually exclusive categories included a no current treatment group and 20 categories for mono, dual, and triple combinations of drugs.

Confounding variables

We considered confounding variables that were likely to be associated with the risk of the diabetes complications according to the established literature[28-32] or with the likelihood of receiving treatment for different hypoglycaemic drugs. These included:

- Age at study entry
- Sex
- Number of years since diagnosis of diabetes (categorised as <1, 1-3, 4-6, 7-10, ≥11)[32]
- Calendar year
- Smoking status (non-smoker, ex-smoker, light smoker (1-9 cigarettes/day), moderate smoker (10-19 cigarettes/day), heavy smoker (≥20 cigarettes/day), not recorded)
- Ethnic group (categorised as white/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed)[29]
- Townsend deprivation score
- Complications (severe kidney failure,[32] one or more episodes of hyperglycaemia, one or more episodes of hypoglycaemia, amputation, blindness—other than where the complication was the outcome of interest in which case patients with an existing diagnosis of the outcome of interest at the study entry date were excluded)
- Comorbidities (cardiovascular disease,[32] heart failure, peripheral vascular disease, valvular heart disease, chronic kidney disease, atrial fibrillation,[29] hypertension,[29] rheumatoid arthritis[29])
- Prescription drugs (statins, aspirin, anticoagulants, thiazides, angiotensin converting enzyme (ACE) inhibitors/angiotensin blockers, calcium channel blockers)
- Clinical values (body mass index,[32] cholesterol:high density lipoprotein (HDL) ratio,[29] systolic blood pressure,[29] serum creatinine, HbA_{1c}[1 32]).

We evaluated confounders at the start of each treatment period for comorbidities, other complications, other prescribed medications, smoking status, and clinical values. For comorbidities and other complications, we identified whether patients had a diagnosis recorded before the relevant treatment period. For prescribed medications, we defined patients as treated at the start of the relevant period of diabetes drug treatment if they had at least two prescriptions for the other type of drug, including one in the 28 days before the treatment period and one after the start date. For smoking status and continuous variables (systolic blood pressure, body mass index, creatinine, cholesterol:HDL ratio, and HbA_{1c}), we used the most recent recorded value immediately before the relevant treatment period. We categorised duration of diabetes as this had a highly skewed distribution, with a substantial proportion of newly diagnosed patients due to the open cohort design.

Analysis

We used Cox proportional hazards models to assess the associations between the six different classes of hypoglycaemic drugs and risk of each of our outcomes, adjusting for potential confounding variables. We used the Cox model for analysis rather than a competing risks analysis, because it is considered more appropriate for aetiological analyses such as this study whereas competing risks analyses tend to be most useful for prediction modelling or estimating absolute risks.[33-35] To account for patients starting and stopping different treatments and changing between treatments, we treated hypoglycaemic exposures as time varying exposures.

In the analysis, we calculated unadjusted and adjusted hazard ratios for the six different diabetes drug classes (each as a binary variable indicating use or no use) with adjustment for the confounding variables and the other classes of hypoglycaemic drugs. We also calculated unadjusted and adjusted hazard ratios for the mutually exclusive treatment combinations comparing each treatment category with no current treatment and also with metformin alone. To determine whether significant differences existed between classes or individual drugs, we carried out Wald's tests. We tested for interactions between the six different drug classes and age, sex, HbA_{1c}, and body mass index.

We used multiple imputation with chained equations to replace missing values for continuous values and smoking status, and used these values in our main analyses.[36-38] We did this for each study outcome and included the censoring indicator for the outcome, the log of survival time, all the confounding variables, and the diabetes drug treatment variables in the imputation model. We log-transformed body mass index, HbA_{1c}, creatinine, cholesterol, and HDL cholesterol before imputation, because they had skewed distributions. We carried out five imputations and combined results using Rubin's rules.

To evaluate the robustness of our results and assess the effect of confounding variables, we added the confounding variables to our model in blocks and compared the adjusted hazard ratios. We assessed four models:

- Model A: diabetes drug classes adjusted for age, sex, ethnicity, deprivation, calendar year, duration of diabetes plus other diabetes drugs
- Model B: model A plus comorbidities (hypertension, cardiovascular disease, atrial fibrillation, chronic renal disease, rheumatoid arthritis, valvular heart

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disease, peripheral vascular disease) plus existing complications (history of hypoglycaemia, hyperglycaemia, amputation, severe kidney failure, blindness) plus use of other drugs (statins, aspirin, anticoagulants, diuretics, ACE inhibitors/angiotensin blockers, β blockers, calcium channel blockers)
- Model C (primary analysis model): model B plus clinical values (body mass index, cholesterol:HDL ratio, systolic blood pressure, serum creatinine, HbA_{1c})
- Model D: model C plus interaction terms

We also carried out a sensitivity analysis (model E) by excluding prevalent users of sulphonylureas from the study cohort so that the hazard ratios for sulphonylureas are based on incident users, and we refitted the primary analysis model (model C).

We included all the eligible patients in the database to maximise the power and also generalisability of the results. We used a P value less than 0.01 (two tailed) to determine statistical significance. Hazard ratios calculated as at least 1.10 or calculated as 0.90 or lower were considered as clinically important. We used Stata (version 13.1) for all analyses.

Patient involvement

Patients were not involved in setting the research question, the outcome measures, the design, or implementation of the study. Patient representatives from the QResearch Advisory Board have written the information for patients on the QResearch website about the use of the database for research. They have also advised on dissemination including the use of lay summaries describing the research and its results.

Results

Overall study population

Overall, 1243 QResearch practices in England met the inclusion criteria. We identified a cohort of 601 405 patients aged 25-84 years with diabetes (fig 1). We sequentially excluded 31 224 (5.2%) patients with type 1 diabetes, 748 (0.1%) without a Townsend deprivation score, and 99 745 (16.6%) prescribed glitazones, gliptins, or insulin in the 12 months before the study entry date. These exclusions left 469 688 patients with type 2 diabetes in the study cohort. Figure 1 also shows the numbers of patients with each outcome at baseline who were excluded from the analysis of that outcome as well as the numbers of incident outcomes observed during follow-up.

Baseline characteristics

In total, 274 324 (58.4%) of the patients in the study cohort received prescriptions for one or more diabetes drugs during follow-up. 21 308 (4.5%) were prescribed glitazones, 32 533 (6.9%) prescribed gliptins, 256 024 (54.5%) prescribed metformin, 134 570 (28.7%) prescribed sulphonylureas, 19 791 (4.2%) prescribed insulin, and 12 062 (2.6%) prescribed other oral hypoglycaemic agents. Of those patients receiving prescriptions for glitazones, 19 051 (89.4%) received pioglitazone with the remainder receiving rosiglitazone.

Table 1 shows the characteristics of patients prescribed each of the six classes of diabetes drugs during follow-up based on the last recorded value before the medication was first prescribed (or at study entry for patients already prescribed sulphonylureas, metformin, or other hypoglycaemics at baseline). The groups were similar for most characteristics except for increased levels of comorbidities other than hypertension in patients prescribed insulin, and reduced levels of prescriptions for statins and aspirin in patients prescribed metformin compared with the other drugs.

Table 2 shows levels of recording and mean values for HbA_{1c}, body mass index, cholesterol:HDL ratio, systolic blood pressure, and serum creatinine before the start of treatment (or at study entry for patients already prescribed sulphonylureas, metformin, or other hypoglycaemics at baseline). Highest levels of recording were for HbA_{1c}, which were in excess of 97% for all six drug groups. Lowest levels of recording were for cholesterol:HDL

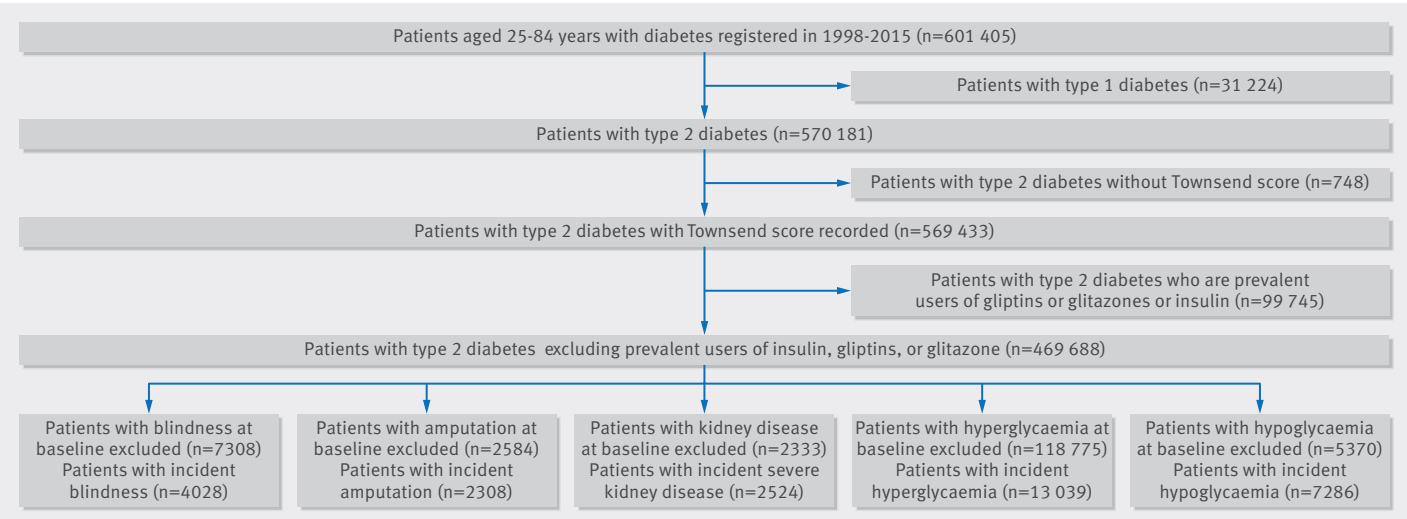

Fig 1 | Flow of patients through study

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Table 1 | Characteristics of patients with type 2 diabetes

	Glitazones	Gliptins	Metformin	Sulphonylureas	Insulin	Other hypoglycaemic agents
Total No of patients exposed	21 308	32 533	256 024	134 570	19 791	12 062
Mean age at study entry (SD)	63.0 (11.9)	63.3 (12.1)	64.6 (13.1)	66.2 (12.9)	64.5 (12.7)	60.0 (11.9)
Mean Townsend score (SD)	0.4 (3.5)	0.5 (3.5)	0.6 (3.6)	0.6 (3.6)	0.5 (3.6)	0.8 (3.6)
Male	12 658 (59.4)	18 871 (58.0)	146 690 (57.3)	79 284 (58.9)	11 499 (58.1)	6509 (54.0)
Time since diagnosis of diabetes						
Newly diagnosed	4412 (20.7)	10 166 (31.2)	100 690 (39.3)	33 363 (24.8)	6223 (31.4)	2895 (24.0)
1-3 years ago	5996 (28.1)	8590 (26.4)	62 951 (24.6)	32 604 (24.2)	3999 (20.2)	3115 (25.8)
4-6 years ago	5033 (23.6)	6561 (20.2)	43 477 (17.0)	28 187 (20.9)	3628 (18.3)	2570 (21.3)
7-10 years ago	3389 (15.9)	4288 (13.2)	28 054 (11.0)	21 768 (16.2)	3128 (15.8)	1874 (15.5)
>10 years ago	2478 (11.6)	2928 (9.0)	20 852 (8.1)	18 648 (13.9)	2813 (14.2)	1608 (13.3)
Ethnicity recorded	19 130 (89.8)	29 396 (90.4)	228 962 (89.4)	119 507 (88.8)	17 264 (87.2)	10 947 (90.8)
White or not recorded	17 112 (80.3)	26 104 (80.2)	204 915 (80.0)	107 537 (79.9)	17 001 (85.9)	10 135 (84.0)
Indian	997 (4.7)	1662 (5.1)	11 732 (4.6)	5978 (4.4)	476 (2.4)	420 (3.5)
Pakistani	811 (3.8)	1132 (3.5)	7425 (2.9)	3972 (3.0)	389 (2.0)	290 (2.4)
Bangladeshi	586 (2.8)	713 (2.2)	7282 (2.8)	3980 (3.0)	370 (1.9)	374 (3.1)
Other Asian	476 (2.2)	720 (2.2)	5873 (2.3)	2947 (2.2)	234 (1.2)	164 (1.4)
Caribbean	473 (2.2)	795 (2.4)	6376 (2.5)	3700 (2.7)	549 (2.8)	278 (2.3)
Black African	392 (1.8)	676 (2.1)	5715 (2.2)	2977 (2.2)	350 (1.8)	161 (1.3)
Chinese	84 (0.4)	95 (0.3)	983 (0.4)	513 (0.4)	36 (0.2)	34 (0.3)
Other	377 (1.8)	636 (2.0)	5723 (2.2)	2966 (2.2)	386 (2.0)	206 (1.7)
Smoking status recorded	21 215 (99.6)	32 399 (99.6)	255 186 (99.7)	134 080 (99.6)	19 569 (98.9)	12 003 (99.5)
Non-smoker	11 374 (53.4)	17 116 (52.6)	132 634 (51.8)	69 849 (51.9)	9393 (47.5)	6126 (50.8)
Ex-smoker	6252 (29.3)	9725 (29.9)	78 935 (30.8)	41 438 (30.8)	6142 (31.0)	3726 (30.9)
Light smoker	2170 (10.2)	3358 (10.3)	25 678 (10.0)	13 846 (10.3)	2413 (12.2)	1252 (10.4)
Moderate smoker	730 (3.4)	1121 (3.4)	9395 (3.7)	4661 (3.5)	832 (4.2)	441 (3.7)
Heavy smoker	689 (3.2)	1079 (3.3)	8544 (3.3)	4286 (3.2)	789 (4.0)	458 (3.8)
Comorbidities						
Cardiovascular disease	2962 (13.9)	5325 (16.4)	48 066 (18.8)	28 895 (21.5)	4596 (23.2)	1992 (16.5)
Heart failure	302 (1.4)	737 (2.3)	6943 (2.7)	5069 (3.8)	960 (4.9)	374 (3.1)
Peripheral vascular disease	1008 (4.7)	1576 (4.8)	12 458 (4.9)	8467 (6.3)	1519 (7.7)	544 (4.5)
Valvular heart disease	379 (1.8)	914 (2.8)	7378 (2.9)	4606 (3.4)	765 (3.9)	292 (2.4)
Hypertension	12 520 (58.8)	19 293 (59.3)	150 219 (58.7)	80 776 (60.0)	11 117 (56.2)	7310 (60.6)
Atrial fibrillation	929 (4.4)	1980 (6.1)	17 327 (6.8)	10 574 (7.9)	1890 (9.5)	657 (5.4)
Chronic kidney disease	388 (1.8)	593 (1.8)	3067 (1.2)	4183 (3.1)	1165 (5.9)	224 (1.9)
Rheumatoid arthritis	719 (3.4)	1237 (3.8)	9718 (3.8)	5382 (4.0)	842 (4.3)	460 (3.8)
Prior complications						
Existing severe kidney failure	54 (0.3)	74 (0.2)	509 (0.2)	825 (0.6)	213 (1.1)	36 (0.3)
Existing blindness	260 (1.2)	383 (1.2)	3715 (1.5)	2404 (1.8)	360 (1.8)	170 (1.4)
Existing amputation	85 (0.4)	125 (0.4)	1239 (0.5)	894 (0.7)	161 (0.8)	65 (0.5)
At least one previous episode of hypoglycaemia	288 (1.4)	286 (0.9)	2247 (0.9)	1946 (1.4)	337 (1.7)	215 (1.8)
At least one previous episode of hyperglycaemia	7921 (37.2)	10 054 (30.9)	68 839 (26.9)	46 341 (34.4)	7279 (36.8)	3914 (32.4)
Other medications						
Anticoagulants	642 (3.0)	1419 (4.4)	9409 (3.7)	5989 (4.5)	1344 (6.8)	540 (4.5)
Thiazides	3444 (16.2)	4346 (13.4)	31 291 (12.2)	16 972 (12.6)	2386 (12.1)	1844 (15.3)
ACE inhibitors	9318 (43.7)	12 939 (39.8)	83 847 (32.7)	48 960 (36.4)	7750 (39.2)	5362 (44.5)
Angiotension 2 blockers	3399 (16.0)	4895 (15.0)	28 629 (11.2)	16 976 (12.6)	2633 (13.3)	2088 (17.3)
Calcium channel blockers	5613 (26.3)	8105 (24.9)	55 674 (21.7)	32 141 (23.9)	5034 (25.4)	3328 (27.6)
Statins	15 512 (72.8)	21 383 (65.7)	137 574 (53.7)	77 865 (57.9)	12 640 (63.9)	8451 (70.1)
Aspirin	7890 (37.0)	9684 (29.8)	68 013 (26.6)	41 647 (30.9)	7057 (35.7)	4096 (34.0)

Data are no (%) of patients unless stated otherwise. Values represent those recorded before starting treatment or at study entry for prevalent users. Treatment groups not mutually exclusive.
ACE=angiotension converting enzyme; SD=standard deviation.

ratios, which were above 84% for all drug groups. Overall, at least 82% of patients had complete data for all five clinical values across all drug groups. Apart from higher mean levels of HbA_{1c} in patients before exposure to insulin and the other hypoglycaemic groups, and higher levels of creatinine among those prescribed sulphonylureas or insulin, mean values were similar across the six groups. Web table 1 shows mean values before starting the 20 different treatment combinations. The mean values for HbA_{1c} tended to be higher for patients starting triple therapy (as high values of HbA_{1c} will tend to trigger changes in therapy).

Risks associated with use of each medication group

Table 3 shows the number of incident cases of each outcome for patients during periods of exposure to each of

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Table 2 | Recorded clinical values for patients before starting diabetes medication or at study entry for prevalent users

	Glitazones	Gliptins	Metformin	Sulphonylureas	Insulin	Other hypoglycaemic agents
Total patients exposed	21 308	32 533	256 024	134 570	19 791	12 062
No (%) of patients with values recorded						
HbA_{1c}	21 251 (99.7)	32 474 (99.8)	253 219 (98.9)	133 170 (99.0)	19 255 (97.3)	12 022 (99.7)
Body mass index	21 120 (99.1)	32 224 (99.1)	252 290 (98.5)	132 477 (98.4)	19 436 (98.2)	11 749 (97.4)
Cholesterol:HDL ratio	18 264 (85.7)	29 307 (90.1)	224 504 (87.7)	115 991 (86.2)	16 723 (84.5)	10 619 (88.0)
Systolic blood pressure	21 306 (100.0)	32 529 (100.0)	255 892 (99.9)	134 487 (99.9)	19 765 (99.9)	12 057 (100.0)
Creatinine	21 288 (99.9)	32 509 (99.9)	255 381 (99.7)	134 244 (99.8)	19 655 (99.3)	12 044 (99.9)
All above values recorded	18 097 (84.9)	29 010 (89.2)	220 119 (86.0)	113 843 (84.6)	16 270 (82.2)	10 340 (85.7)
Mean values (SD) recorded						
HbA_{1c} (mmol/mol)	66.8 (18.9)	68.4 (18.4)	61.4 (18.7)	64.9 (19.9)	75.4 (22.7)	70.9 (19.6)
Body mass index	31.7 (6.0)	31.7 (5.9)	30.6 (5.9)	30.1 (5.8)	30.2 (6.1)	34.1 (6.6)
Cholesterol:HDL ratio	3.8 (1.3)	3.9 (1.3)	3.8 (1.3)	3.8 (1.3)	4.0 (1.4)	4.0 (1.3)
Systolic blood pressure (mm Hg)	133.1 (14.8)	132.3 (14.7)	132.5 (15.3)	132.8 (15.9)	131.7 (16.9)	132.5 (14.9)
Creatinine (μmol/L)	87.1 (33.7)	84.9 (33.3)	84.8 (30.1)	92.1 (47.7)	99.3 (62.0)	83.5 (34.6)

Treatment groups not mutually exclusive. HDL=high density lipoprotein; SD=standard deviation.

Table 3 | Number of incident events, person years, rates, and adjusted hazard ratios for each study outcome by use of diabetes drug

Study outcome/ diabetes drug group	No of events	No of person years	Rate per 10 000 person years of exposure	Adjusted hazard ratios (95% CI)*
Blindness				
Glitazones	79	54 981	14.4	0.71 (0.57 to 0.89)
Gliptins	117	70 197	16.7	0.83 (0.69 to 1.01)
Metformin	2021	1 045 943	19.3	0.70 (0.66 to 0.75)
Sulphonylureas	1220	494 418	24.7	0.96 (0.89 to 1.04)
Insulin	202	56 153	36.0	1.48 (1.28 to 1.72)
Other hypoglycaemic agents	52	27 715	18.8	0.86 (0.65 to 1.13)
Hyperglycaemia				
Glitazones	180	32 966	54.6	0.88 (0.76 to 1.02)
Gliptins	265	46 686	56.8	0.93 (0.82 to 1.05)
Metformin	5368	712 777	75.3	0.65 (0.62 to 0.67)
Sulphonylureas	2216	297 347	74.5	0.99 (0.94 to 1.04)
Insulin	415	32 321	128.4	1.69 (1.53 to 1.87)
Other hypoglycaemic agents	130	17 531	74.2	0.95 (0.80 to 1.14)
Hypoglycaemia				
Glitazones	355	54 507	65.1	1.22 (1.10 to 1.37)
Gliptins	319	69 719	45.8	0.86 (0.77 to 0.96)
Metformin	3905	1 047 042	37.3	0.58 (0.55 to 0.61)
Sulphonylureas	4064	491 712	82.7	2.93 (2.78 to 3.09)
Insulin	1133	53 882	210.3	4.57 (4.27 to 4.89)
Other hypoglycaemic agents	176	27 313	64.4	1.07 (0.92 to 1.25)
Amputation				
Glitazones	62	55 551	11.2	0.77 (0.60 to 1.00)
Gliptins	99	71 007	13.9	0.88 (0.71 to 1.08)
Metformin	1195	1 059 266	11.3	0.70 (0.64 to 0.77)
Sulphonylureas	819	502 028	16.3	1.05 (0.95 to 1.15)
Insulin	199	56 798	35.0	1.64 (1.41 to 1.91)
Other hypoglycaemic agents	45	28 028	16.1	0.93 (0.69 to 1.25)
Kidney failure				
Glitazones	54	55 677	9.7	1.05 (0.80 to 1.38)
Gliptins	64	71 251	9.0	0.99 (0.77 to 1.27)
Metformin	562	1 064 018	5.3	0.41 (0.37 to 0.46)
Sulphonylureas	881	502 691	17.5	1.21 (1.10 to 1.33)
Insulin	235	56 573	41.5	1.45 (1.25 to 1.68)
Other hypoglycaemic agents	35	28 166	12.4	0.80 (0.56 to 1.14)

Hazard ratio for each diabetes drug group is compared with patients not prescribed that particular medication.
*Hazard ratios adjusted for: sex; age; calendar year; duration since diagnosis of diabetes (five levels); ethnicity (nine levels); Townsend deprivation score; smoking status (five levels); use of anticoagulants, thiazides, ACE inhibitors, angiotensin 2 blockers; calcium channel blockers; statins; aspirin; existing complications (blindness, hyperglycaemia, hypoglycaemia, amputation, severe kidney failure); hypertension; cardiovascular disease; atrial fibrillation; chronic renal disease; rheumatoid arthritis; valvular heart disease; peripheral vascular disease; body mass index; systolic blood pressure; HbA_{1c}; serum creatinine; cholesterol:high density lipoprotein ratio. Hazard ratios also mutually adjusted for use of each of the other diabetes drug classes.

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the six treatment classes during follow-up. The treatment classes in table 3 are not mutually exclusive—for example, the row for glitazones includes any use of glitazones, whether as monotherapy, dual therapy, or triple therapy. Similarly, the adjusted hazard ratios for model C shown in table 3 give an overall risk for the use of each drug group compared with non-use of that drug group, having adjusted for use of other diabetes drugs and the potential confounders listed in the footnote.

For our main exposures of interest, we found:

- Compared with non-use, glitazones were significantly associated with a 29% decreased risk of blindness; and a 22% increased risk of hypoglycaemia.
- Compared with non-use, gliptins were significantly associated with a 14% decreased risk of hypoglycaemia.

In addition for the other diabetes drug groups, we found:

- Compared with non-use, metformin was associated with a significantly decreased risk of all five outcomes: reductions in risk of 30% for blindness, 35% for hyperglycaemia, 42% for hypoglycaemia, 30% for amputation, and 59% for severe kidney failure.
- Compared with non-use, sulphonylureas were significantly associated with a 193% increased risk of hypoglycaemia and a 21% increased risk of severe kidney failure.
- Compared with non-use, insulin was associated with significantly increased risks of all outcomes: increases of 48% for blindness, 69% for hyperglycaemia, 357% for hypoglycaemia, 64% for amputation, and 45% for severe kidney failure.
- Compared with non-use, the other hypoglycaemic group was not associated with a significant increase or decrease in risk of any complication though the person years of exposure for this group were lower than the other groups in the analysis.

The only significant interaction involving glitazones or gliptins was between glitazones and age for hypoglycaemia (web table 2; model D), where the increased risk of hypoglycaemia associated with glitazone use became more marked with increasing age.

Web table 2 also shows the results from analyses adding confounders in separate blocks (models A and B). Generally, inclusion of comorbidities and existing complications in the model (model B) tended to slightly reduce hazard ratios (compared with model A), which was most marked for sulphonylureas and insulin. Further inclusion of clinical values (table 3; model C) only resulted in small changes to the hazard ratios with the exception of severe kidney failure which had some larger increases, for example, from 0.74 (95% confidence interval 0.56 to 0.97) to 1.05 (0.80 to 1.38) for glitazones.

The sensitivity analysis excluding the 73 445 prevalent users of sulphonylureas at study entry showed some increases in adjusted hazard ratios for sulphonylureas compared with model C (web table 2; model E), with the largest increase for hypoglycaemia (increase from 2.93 to 3.99).

Risks associated with different treatment combinations

Table 4 shows a more detailed breakdown of 21 mutually exclusive treatment categories, including a "no current treatment group" that included 0.7 million person years free of any hypoglycaemic medication. The table shows the number of events for each clinical outcome for each of the treatment categories.

Table 5 shows the corresponding adjusted hazard ratios for each treatment group category compared with monotherapy with metformin. For glitazones, we saw a significant increase in the risk of severe kidney failure for monotherapy with glitazones (155% increase), but no significant associations between glitazone monotherapy and risk of any other complications, compared with monotherapy with metformin. However, glitazone monotherapy was relatively uncommon (table 4). Dual therapy with glitazones and metformin was associated with a significantly decreased risk of hyperglycaemia (reduction of 40%). Dual therapy with glitazones and sulphonylureas was associated with a 93% increased risk of hyperglycaemia, a 106% increased risk of amputation, a 114% increased risk of severe kidney failure, and more than a 13-fold increased risk of hypoglycaemia compared with metformin monotherapy. Triple therapy with metformin, sulphonylureas, and glitazones was associated with a decreased risk of blindness (33% reduction) and more than a sixfold increased risk of hypoglycaemia.

Gliptin monotherapy was associated with more than a threefold increased risk of severe kidney failure compared with monotherapy with metformin (adjusted hazard ratio 3.52; 95% confidence interval 2.04 to 6.07), but there were no other significant associations although gliptin monotherapy was relatively uncommon (table 4). Dual therapy with gliptins and metformin was associated with a 22% decreased risk of hyperglycaemia. Dual therapy with gliptins and sulphonylureas was associated with nearly a sixfold increased risk of hypoglycaemia and more than a threefold increased risk of severe kidney failure. Triple therapy with gliptins, metformin and sulphonylureas was associated with a fivefold increased risk of hypoglycaemia (5.07; 4.28 to 6.00). The increased risks of hypoglycaemia in patients prescribed triple therapy with metformin, sulphonylureas, and either gliptins or glitazones were similar to those involving dual therapy with metformin and sulphonylureas (adjusted hazard ratio 6.03, 95% confidence interval 5.47 to 6.63).

Web table 3 shows the results for the different treatment combinations compared with periods of no hypoglycaemic treatment. Web table 4 shows the results for the different treatment combinations compared with no treatment having dropped prevalent users of sulphonylureas at study entry. Overall, the adjusted hazard ratios for glitazones and gliptins were similar to those in web table 3 except confidence intervals were wider due to

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Table 4 | Number of incident events for each outcome, person years of exposure, and rates per 10 000 person years of exposure for mutually exclusive diabetes treatment groups

	Blindness		Hyperglycaemia		Hypoglycaemia		Amputation		Kidney failure	
	No of events; PY	Rate	No of events; PY	Rate	No of events; PY	Rate	No of events; PY	Rate*	No of events; PY	Rate
Periods with no current treatment	1541; 692 694	22.2	6905; 497 577	138.8	1850; 695 332	26.6	800; 702 512	11.4	1124; 701 350	16.0
Monotherapy										
Metformin alone	1053; 578 632	18.2	3407; 428 157	79.6	546; 583 302	9.4	504; 586 234	8.6	299; 588 181	5.1
Sulphonylureas alone	334; 87 687	38.1	499; 54 551	91.5	817; 87 839	93.0	182; 89 826	20.3	546; 88 327	61.8
Insulin alone	61; 16 247	37.5	156; 9572	163.0	383; 15 307	250.2	74; 16 463	44.9	147; 16 025	91.7
Glitazones alone	3; 1651	18.2	9; 1149	78.3	3; 1668	18.0	3; 1690	17.8	6; 1675	35.8
Gliptins alone	7; 2487	28.1	14; 1929	72.6	2; 2468	8.1	3; 2536	11.8	14; 2524	55.5
Other hypoglycaemic agents alone	3; 1591	18.9	3; 1056	28.4	12; 1516	79.2	0; 1601	0.0	13; 1572	82.7
Dual therapy										
Metformin and sulphonylureas	676; 309 595	21.8	1315; 186 517	70.5	2251; 308 091	73.1	450; 313 843	14.3	184; 315 690	5.8
Metformin and insulin	57; 18 124	31.5	123; 10 463	117.6	291; 17 393	167.3	54; 18 182	29.7	13; 18 422	7.1
Metformin and glitazones	25; 17 805	14.0	45; 12 082	37.2	23; 17 727	13.0	10; 17 942	5.6	7; 17 990	3.9
Metformin and gliptins	28; 23 879	11.7	81; 17 503	46.3	28; 23 831	11.7	22; 24 092	9.1	7; 24 172	2.9
Metformin and other hypoglycaemic agents	15; 9187	16.3	46; 6314	72.9	30; 9099	33.0	11; 9306	11.8	3; 9355	3.2
Sulphonylureas and insulin	30; 4364	68.7	37; 2510	147.4	156; 4159	375.1	23; 4497	51.1	55; 4354	126.3
Sulphonylureas and glitazones	7; 3467	20.2	18; 1898	94.8	57; 3401	167.6	11; 3524	31.2	15; 3506	42.8
Sulphonylureas and gliptins	14; 4293	32.6	13; 2688	48.4	31; 4276	72.5	10; 4399	22.7	23; 4375	52.6
Sulphonylureas and other hypoglycaemic agents	2; 1076	18.6	3; 648	46.3	18; 1045	172.2	4; 1072	37.3	7; 1084	64.6
Triple therapy										
Metformin, sulphonylureas, and insulin	37; 11 313	32.7	56; 6072	92.2	194; 11 034	175.8	28; 11 449	24.5	8; 11 545	6.9
Metformin, sulphonylureas, and glitazones	36; 24 733	14.6	74; 13 390	55.3	199; 24 487	81.3	26; 24 994	10.4	18; 25 098	7.2
Metformin, sulphonylureas, and gliptins	53; 31 204	17.0	115; 19 326	59.5	188; 30 881	60.9	49; 31 511	15.6	13; 31 703	4.1
Metformin, sulphonylureas, and other hypoglycaemic agents	20; 9871	20.3	44; 5805	75.8	56; 9744	57.5	14; 9986	14.0	5; 10 057	5.0
All other drug combinations	26; 13 797	18.8	76; 8484	89.6	151; 13 623	110.8	30; 13 990	21.4	17; 14 026	12.1
Total	4028; 1 863 697	21.6	13 039; 1 287 691	101.3	7286; 1 866 223	39.0	2308; 1 889 649	12.2	2524; 189 1031	13.3

Data are number of incident events, number of person years of exposure (PY), and rate per 10 000 person years of exposure.

reduced numbers and there were fewer significant associations.

Discussion

Key findings

This cohort study has found clinically important differences between different hypoglycaemic drugs (alone and in combination) and the risk of five key outcomes (blindness, amputation, severe kidney failure, hyperglycaemia, and hypoglycaemia) in patients with type 2 diabetes. Our study aimed to look at a range of complications in relation to drug treatment whereas many previous studies have either been clinical trials that have had limited sample sizes and durations; or observational studies that have focused on one particular drug or drug combination.

Overall, we found a reduced risk of blindness and an increased risk of hypoglycaemia associated with glitazones, and a reduced risk of hypoglycaemia associated with gliptins. A more detailed analysis according to combinations of treatments showed some differences according to whether glitazones and gliptins were prescribed as monotherapy or dual or triple therapy with other agents. Our results indicate that gliptins and glitazones are associated with an increased risk of kidney failure compared with metformin monotherapy only when used as monotherapy or in combination with sulphonylureas, despite adjustments for serum creatinine and other risk factors at baseline. However, the risks when used in combination with sulphonylureas are similar to the risk with sulphonylureas monotherapy. This suggests either a drug-drug interaction in the dual therapy, where the other drug used has a modifying effect on risk, or indication bias when these drugs are used as monotherapy since this combination is mainly likely to be in patients with contraindications to metformin, as recommended in guidelines. For example, the British National Formulary indicates that metformin should be avoided in patients with significant renal impairment owing to increased risk of lactic acidosis.

Although the numbers prescribed gliptin monotherapy or glitazones monotherapy were relatively low, the findings appear consistent with other reports of safety of the renally excreted gliptins.[39] But other data in relation to this outcome are limited. Our finding for glitazones is consistent with increased risks of incident chronic kidney disease reported in a observational study of almost 4000 users of pioglitazone followed between 2003 and 2009 in Taiwan.[40] Although pioglitazone is extensively metabolised in the liver,[41] pioglitazone is also known to increase fluid and sodium retention particularly in patents with renal impairment.[42] This, together with the concerns regarding possible increased risk of bladder cancer, has led to the withdrawal of pioglitazone use in France and Germany and caution regarding its use in Switzerland.[43]

Dual treatment combinations for glitazones or gliptins with metformin showed reduced risks of hyperglycaemia compared with metformin monotherapy and no significant increases in risk for the other outcomes. Triple therapy involving metformin, sulphonylureas,

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Table 5 | Adjusted hazard ratios (95% CI) for each study outcome* compared with metformin monotherapy

	Study outcome				
	Blindness	Hyperglycaemia	Hypoglycaemia	Amputation	Kidney failure
Monotherapy					
Metformin alone	1.00	1.00	1.00	1.00	1.00
Sulphonylureas alone	1.42 (1.25 to 1.62)	1.38 (1.25 to 1.52)	7.32 (6.55 to 8.18)	1.44 (1.20 to 1.71)	2.63 (2.25 to 3.06)
Insulin alone	1.96 (1.50 to 2.55)	2.48 (2.11 to 2.92)	21.17 (18.48 to 24.25)	2.68 (2.08 to 3.46)	2.88 (2.32 to 3.57)
Glitazones alone	0.98 (0.31 to 3.03)	1.50 (0.78 to 2.89)	1.83 (0.59 to 5.70)	1.88 (0.60 to 5.84)	2.55 (1.13 to 5.74)
Gliptins alone	1.39 (0.66 to 2.93)	1.44 (0.85 to 2.43)	0.83 (0.21 to 3.33)	1.03 (0.33 to 3.20)	3.52 (2.04 to 6.07)
Other hypoglycaemic agents alone	0.82 (0.26 to 2.55)	0.32 (0.08 to 1.29)	6.44 (3.63 to 11.42)	—	1.17 (0.63 to 2.18)
Dual therapy					
Metformin and sulphonylureas	0.94 (0.85 to 1.04)	1.02 (0.95 to 1.09)	6.03 (5.47 to 6.63)	1.08 (0.95 to 1.23)	0.76 (0.62 to 0.92)
Metformin and insulin	1.58 (1.21 to 2.07)	1.95 (1.63 to 2.34)	14.34 (12.40 to 16.59)	1.78 (1.34 to 2.37)	1.13 (0.65 to 1.98)
Metformin and glitazones	0.87 (0.58 to 1.29)	0.60 (0.45 to 0.80)	1.35 (0.89 to 2.05)	0.57 (0.30 to 1.06)	0.71 (0.33 to 1.50)
Metformin and gliptins	0.72 (0.49 to 1.04)	0.78 (0.62 to 0.97)	1.23 (0.84 to 1.80)	0.84 (0.55 to 1.30)	0.59 (0.28 to 1.25)
Metformin and other hypoglycaemic agents	0.83 (0.50 to 1.38)	1.06 (0.79 to 1.41)	2.77 (1.92 to 4.01)	0.93 (0.51 to 1.70)	0.57 (0.18 to 1.79)
Sulphonylureas and insulin	2.13 (1.47 to 3.09)	2.62 (1.89 to 3.63)	23.91 (19.89 to 28.75)	2.15 (1.40 to 3.29)	3.56 (2.64 to 4.82)
Sulphonylureas and glitazones	0.80 (0.38 to 1.69)	1.93 (1.21 to 3.07)	13.22 (10.04 to 17.39)	2.06 (1.13 to 3.76)	2.14 (1.27 to 3.61)
Sulphonylureas and gliptins	1.32 (0.78 to 2.25)	0.98 (0.57 to 1.69)	5.93 (4.12 to 8.53)	1.30 (0.69 to 2.45)	3.21 (2.08 to 4.93)
Sulphonylureas and other hypoglycaemic agents	0.69 (0.17 to 2.76)	0.73 (0.24 to 2.27)	12.12 (7.57 to 19.41)	2.02 (0.75 to 5.43)	2.38 (1.11 to 5.09)
Triple therapy					
Metformin, sulphonylureas, and insulin	1.36 (0.97 to 1.89)	1.46 (1.12 to 1.91)	13.17 (11.14 to 15.57)	1.30 (0.88 to 1.91)	1.06 (0.53 to 2.16)
Metformin, sulphonylureas, and glitazones	0.67 (0.48 to 0.94)	0.99 (0.79 to 1.25)	6.32 (5.35 to 7.45)	0.70 (0.47 to 1.05)	1.21 (0.75 to 1.96)
Metformin, sulphonylureas and gliptins	0.82 (0.62 to 1.08)	1.09 (0.91 to 1.32)	5.07 (4.28 to 6.00)	0.99 (0.73 to 1.33)	0.68 (0.39 to 1.20)
Metformin, sulphonylureas and other hypoglycaemic agents	0.91 (0.59 to 1.43)	1.03 (0.76 to 1.38)	4.31 (3.26 to 5.68)	0.85 (0.50 to 1.45)	0.93 (0.38 to 2.26)
All other drug combinations	0.94 (0.64 to 1.39)	1.43 (1.14 to 1.80)	9.02 (7.50 to 10.83)	1.25 (0.86 to 1.82)	1.60 (0.98 to 2.62)
No medication	1.40 (1.29 to 1.52)	1.58 (1.51 to 1.65)	3.06 (2.77 to 3.37)	1.44 (1.28 to 1.62)	1.85 (1.61 to 2.12)

Treatment categories are mutually exclusive.
*Hazard ratios adjusted for sex; age; duration since diagnosis of diabetes (five levels); ethnicity (nine levels); Townsend deprivation score; smoking status (five levels); use of anticoagulants, thiazides, ACE inhibitors, angiotensin 2 blockers, calcium channel blockers, statins, aspirin; existing complications (blindness, hyperglycaemic coma, hypoglycaemia, amputation, severe kidney failure); hypertension; cardiovascular disease; atrial fibrillation; chronic renal disease; rheumatoid arthritis; valvular heart disease; peripheral vascular disease; body mass index; systolic blood pressure; HbA_{1c}; serum creatinine; and cholesterol:high density lipoprotein ratio.

and glitazones was associated with a significantly decreased risk of blindness, and an increased risk of hypoglycaemia. Similarly, triple therapy of metformin, sulphonylureas, and gliptins was associated with a significantly increased risk of hypoglycaemia.

Overall, triple therapy involving gliptins or glitazones does not appear to have consistent measurable advantages compared with dual therapy or monotherapy with metformin for these five clinical outcomes. This triple combination also showed substantially increased risks of hypoglycaemia when compared against metformin monotherapy although risks were similar to those involving dual therapy with metformin and sulphonylureas.

Comparison with previous studies

Clinical trial evidence for newer hypoglycaemic agencies, such as glitazones and gliptins, has been largely based on surrogate endpoints such as reduction of HbA_{1c} rather than hard clinical endpoints such as reduced incidence of complications as in our study. The UKPDS-34 study[3] provided the original clinical trial evidence for the use of metformin as first line treatment of choice for patients with type 2 diabetes since it was associated with a greater reduction in diabetes related endpoints and fewer hypoglycaemic attacks than sulphonylureas. Designed in the 1970s and running over a 20 year period, part of the UKPDS cohort was randomised with 342 patients randomised to metformin and 411 patients to diet alone. The researchers reported a 32% reduction (95% confidence interval 13% to 47%) for any diabetes related endpoint.[3] Although the numbers randomised to each arm were small and the numbers of clinical endpoints even smaller (there were only six events of amputation in the metformin group and nine in the diet alone group), the results are comparable with the reduction in risk reported in our study for metformin monotherapy compared with diet only.

Strengths and limitations

Ideally we would now have ongoing published meta-analyses of randomised trials comparing clinical outcomes among patients prescribed different diabetes drugs alone and in combination compared with no medication. These meta-analyses would form the basis of national guidelines and robust systems would be in place to routinely monitor the use of these drugs for unintended or adverse outcomes. However, nearly all clinical trials of diabetes drugs have been designed using intermediate or surrogate outcomes such as changes in HbA_{1c} rather than relevant clinical outcomes. The criteria set by regulators regarding new diabetes agents[12 13] and the impracticability of undertaking adequately powered head to head trials of clinical outcomes for existing drugs means that we need to use alternative methods for establishing the necessary evidence base for clinical outcomes. Therefore, the question becomes how best to assemble the evidence for

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clinical outcomes using observational linked data sources, how to minimise attendant biases, and how to interpret the findings with due caution.

Generalisability

To our knowledge, this is the largest study based on an ethnically diverse contemporaneous, representative population of patients with type 2 diabetes. We included all eligible patients to minimise selection bias. Therefore, we think the results are likely to be generalisable to similar populations of patients with type 2 diabetes.

Clinical outcomes

Strengths of our analysis were the inclusion of hard clinical endpoints based on clinical diagnoses or procedural codes recorded on at least one of three linked electronic data sources. Use of all three linked data sources was designed to minimise under-ascertainment of outcomes, which would otherwise lead to under-estimation of absolute risks. The clinical outcomes were based on clinical diagnoses made by the treating clinician or hospital procedural codes rather than formally adjudicated events as would occur in a clinical trial. Although some patients may have been incorrectly recorded as having a particular outcome, UK general practices have good levels of accuracy and completeness in recording clinical diagnoses.[44] Also, the diagnostic validity of such diagnoses in general practice has been shown to be high.[45] Possible ascertainment bias of outcomes is unlikely to vary according to the type of hypoglycaemic prescribed so would not explain the associations we have found.

Exposure to medication

We had detailed exposure information on hypoglycaemic agents prescribed throughout the follow-up period, enabling us to develop a detailed categorisation of drug exposure time with 20 different treatment groups including combinations of treatments. This categorisation enabled us to account for switching between different treatments or treatment combinations, and we were able to account for real world prescribing patterns over a long period, allowing multiple comparisons not only between drugs but also between different drug combinations. The recording of prescriptions issued in UK general practices has very high levels of completeness.[46] Our study analysed prescribed medication rather than medication actually taken by the patients, although renewal of prescriptions is likely to indicate drug use because patients need to initiate repeat prescriptions. This could result in misclassification of exposure if patients were prescribed medication that they did not actually take and could underestimate associations between diabetes drug use and clinical outcomes. Unlike previous studies, we have included comparisons of risk against periods of no treatment[6] as well as against metformin monotherapy. The first comparison is important because about 40% of patients with type 2 diabetes are managed without hypoglycaemic treatments throughout follow-up.

Our study included over 55 000 person years of exposure to glitazones. The predominant glitazone was pioglitazone, which was prescribed to 90% of the glitazone users. Our study included over 70 000 person years of exposure to gliptins, which represents one of the largest studies to date. The predominant gliptin prescribed in our dataset was sitagliptin, which was prescribed to 80% of those gliptin users. There are currently too few patients prescribed linagliptin, saxagliptin, and vildagliptin to support separate analyses by individual drug; this was a limitation of the study because there may be differences between individual gliptins and their effect on HbA_{1c}.[47] However, the numbers of patients on different types of gliptin is likely to increase over time and further analyses can be undertaken once more data has accrued. We did not split the other drug classes such as sulphonylureas into different drug subtypes because they were not the main focus of the study, but potential heterogeneity could exist in risk of the outcomes across different subtypes for each drug class in the analyses.

Assessment of other types of bias

Other types of bias that can affect observational studies include recall bias, indication bias, and channelling bias. Recall bias will not have occurred because data on prescriptions for hypoglycaemia and confounding variables were recorded before the clinical outcomes. We restricted the study population to patients with type 2 diabetes to limit indication bias (which occurs when patients are prescribed drugs for a condition associated with the risk of the adverse event under consideration). We used an incident user design to reduce confounding and biases that can otherwise arise from adjustment for intermediate characteristics in the causal path.[27] We saw some differences at baseline between patients prescribed different treatment groups (tables 1 and 2), although these were predominantly increased levels of comorbidities for insulin and lower levels of concurrent use of medication (such as statins and aspirin) for metformin.

To reduce channelling bias (where the choice of a particular drug is influenced by patient characteristics), we adjusted for a wide range of potential confounding variables including demographic characteristics, different comorbidities, clinical values, and concurrent medication. We decided to use the most recent clinical values before changes in treatment since these are the values most likely to be used to inform those decisions. We did not use repeated values or changes in values over long periods because these data are not necessarily recorded consistently and would tend to increase proportions of missing data. However, we are unable to exclude the possibility of residual confounding since there may be other unmeasured patient characteristics that affected selection of hypoglycaemic agents.

As in other similar studies,[28] we excluded prevalent users of insulin at baseline but left patients subsequently prescribed insulin in for the rest of the analysis because it is part of the treatment ladder and some of these patients will also have had other medications of interest during follow-up. Although insulin was not the

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primary exposure of interest, patients prescribed insulin had higher risks of all complications (tables 3 and 5) despite adjustment for higher levels of comorbidity. It is unlikely that this increased risk was a direct result of treatment with insulin. Instead, residual confounding and reverse causality could have occurred—that is, the insulin treated group was at much higher risk of complications than the groups treated with diet or oral medication, and it is this that results in their apparently worse outcomes and not their treatment with insulin. For example, in table 2, the insulin treated group had the highest HbA_{1c} and creatinine values before treatment, although both factors were adjusted for in the analyses. An alternative explanation could be that patients have symptoms that lead to an amputation or sight problems before being diagnosed with these conditions and that the symptoms are associated with subsequent use of insulin rather than glitazones or gliptins.

Although randomised controlled trials of hypoglycaemic treatments are not influenced by residual confounding, they tend to be small, of short duration, and might not report on relevant clinical outcomes. An alternative design would an observational study of a cohort of patients specifically assembled for the purpose rather than routinely collected data as in our study. Studies using routinely collected data are susceptible to missing data, but in our study, over 99% of patients had smoking status recorded, 87% had ethnic group recorded, and over 82% had of patients had complete data for all five clinical values (table 2). We also used multiple imputation to impute missing data. Other problems with routine data include coding errors and variable timing between measurements of risk factors in patients because of differences in when patients present to their general practitioner. Advantages of using routinely collected data rather than a purposeful cohort include size, efficiency, better generalisability, and less susceptibility to selection bias or attrition bias.

We fitted several different models and carried out sensitivity analyses that showed some heterogeneity of results. The results are therefore sensitive to the assumptions made in the study design and modelling and have uncertainty; however, our findings were generally consistent across the different analyses for glitazones and gliptins.

Conclusions

We have found lower risks of hyperglycaemia among patients prescribed dual therapy involving metformin with either gliptins or glitazones compared with metformin alone. Compared with metformin monotherapy, triple therapy with metformin, sulphonylureas, and either gliptins or glitazones was associated with an increased risk of hypoglycaemia, which was similar in magnitude to the risk for dual therapy with metformin and sulphonylureas. Compared with metformin monotherapy, triple therapy with metformin, sulphonylureas, and glitazones was associated with a reduced risk of blindness. These results, while subject to residual confounding, could have implications for prescribing of hypoglycaemic drugs.

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Contributorship: JHC initiated the study, undertook the literature review, data extraction, data manipulation and primary data analysis, and wrote the first draft of the paper. CC contributed to the design, analysis, data manipulation, interpretation, and drafting of the paper. Both authors had access to all the data for this project. JHC is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: JHC is professor of clinical epidemiology at the University of Nottingham and codirector of QResearch—a not for profit organisation that is a joint partnership between the University of Nottingham and EMIS (leading commercial supplier of IT for 60% of general practices in the UK); JHC is a paid director of ClinRisk, which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care; CC is professor of medical statistics in primary care at the University of Nottingham and a paid consultant statistician for ClinRisk.

Ethical approval: The project was reviewed in accordance with the QResearch agreement with Trent multicentre ethics committee (reference 03/4/021).

Data sharing: The patient level data from the QResearch database are specifically licensed according to its governance framework. See www.qresearch.org for further details.

The lead author, Julia Hippisley-Cox, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as have been explained.

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Web appendix 1: Clinical codes used to identify severe kidney failure
Web appendix 2: Clinical codes used to identify blindness
Web appendix 3: Clinical codes used to identify amputation
Web appendix 4: Clinical codes used to identify hyperglycaemia
Web appendix 5: Clinical codes used to identify hypoglycaemia
Web appendix 6: Web tables

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