Is Gliclazide Associated with a Lower Obesity-Related Cancer Risk Compared to Other Sulfonylureas? A Long-term Prospective Cohort Study

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ABSTRACT

Background: Gliclazide has been suspected to be associated with a lower obesity-related cancer risk; however, current evidence is limited by important methodologic shortcomings. This study aimed to evaluate whether gliclazide is preferred over other sulfonylureas regarding obesity-related cancer risk.

Methods: In this prospective cohort study, an annual benchmarking database in Dutch primary care (Zwolle Outpatient Diabetes project Integrating Available CareZODIAC, 1998–2014) was linked to the Netherlands Cancer Registry and the Dutch Personal Record Database. Of the 71,648 patients with type 2 diabetes, we included 26,207 who used sulfonylureas and had no history of cancer or insulin use at baseline. Obesity-related cancer was defined using the latest definition of the World Cancer Research Fund. Cox regression analyses were used to estimate HRs, with both baseline sulfonylurea and cumulative exposure modeled and corrected for baseline covariates.

Results: During follow-up for 167,692 person-years, there were 1,111 obesity-related cancer events. For males, the adjusted HRs [95% confidence interval (CI)] for baseline sulfonylurea compared with gliclazide were as follows: glibenclamide, 1.10 (0.92–2.69); glimepiride, 1.13 (0.68–1.84); and tolbutamide, 0.93 (0.59–1.48). For females, these were as follows: glibenclamide, 1.49 (0.72–3.13); glimepiride, 0.96 (0.59–1.54); and tolbutamide, 0.84 (0.54–1.28). The adjusted HRs (95% CI) for one more year of cumulative exposure compared with gliclazide were as follows: glibenclamide, 0.90 (0.71–1.14); glimepiride, 0.96 (0.87–1.06); and tolbutamide, 1.00 (0.92–1.09). For females, these were as follows: glibenclamide, 0.93 (0.77–1.13); glimepiride, 0.99 (0.90–1.10); and tolbutamide, 1.04 (0.96–1.13).

Conclusions: Obesity-related cancer risk was comparable between gliclazide and other sulfonylureas.

Impact: Gliclazide is not preferred over other sulfonylureas regarding obesity-related cancer risk.

Introduction

Patients with type 2 diabetes mellitus are at increased risk of cancer (1), especially obesity-related cancer (2). Obesity-related cancers are cancers that are known to be affected by being overweight or obese, as listed by the World Cancer Research Fund (3). More than 80% of patients with type 2 diabetes in the Dutch primary care are overweight or obese (4, 5), with 804,100 incident cancers attributable to diabetes and high body mass index worldwide in 2012 (6). Given that the obesity and type 2 diabetes pandemic is expected to progress, the incidence of obesity-related cancers among patients with type 2 diabetes can also be expected to increase (7).

To decrease the growing risks, the effects of glucose-lowering agents on cancer risk have been widely studied (8). However, within-class differences for sulfonylureas tend to have been ignored. These are the most widely prescribed oral blood glucose–lowering drugs in patients for whom metformin has proved insufficient (9), but importantly, they are a heterogeneous class with many drug-specific side effects (10, 11). In two guidelines of type 2 diabetes management, gliclazide is the preferred sulfonylurea (12, 13) based on evidence that is it associated with the lowest incidence of hypoglycemic events (14, 15), no need for dose adjustment if renal impairment develops (16), and a putatively favorable cardiovascular safety profile (17). In contrast to other sulfonylureas, severe hypoglycaemia cases have not been reported among gliclazide users (11). Apart from within-class differences in hypoglycemia risk and safety in patients with renal failure, gliclazide might also be preferred over other sulfonylureas regarding cancer risk (11). The lower hypoglycemia risk of gliclazide may be partly explained by its affinity for the sulfonylurea receptor on the β-cell in the pancreas (18), leading to a more glucose-dependent insulin response and possibly lower average insulin levels than other drugs in the class (14, 15). An average lower hyperinsulinemia with gliclazide might result in a lower risk of obesity-related cancer as both hyperinsulinemia and hyperglycemia are potential biological mechanisms linking diabetes and cancer (19). Next to clinical evidence, preclinical results that gliclazide is endowed with antioxidant effects and can protect DNA from damage induced by reactive oxygen species further supports this claim (20, 21). Although a few studies have investigated this possible decreased risk of cancer among gliclazide users, the resulting data have often been limited by important methodologic shortcomings, such as small sample sizes, time-related bias, indication

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bias of drug exposure, retrospective designs, and failure to account for the cumulative duration of use (22–24).

In this study, we aimed to evaluate whether users of gliclazide had a lower overall and site-specific obesity-related cancer risk overcoming the methodologic shortcomings of previous studies.

Materials and Methods

Study design

This is a prospective cohort study of the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC), an annual benchmarking database for 731 general practitioners (GP) in Dutch primary care, for the period 1998 to 2014. Data were linked to the Netherlands Cancer Registry (NCR) and the Dutch Personal Record Database (BRP) for cancer and mortality data. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology recommendations (25). Patients included in the ZODIAC database consented to the anonymous collection and use of their data for study purposes. The medical ethics committee of Isala evaluated the linkage procedures and exempted this study from formal medical ethics committee review, according to the Dutch Medical Research with Human Subjects Law (*Wet Medisch-wetenschappelijk Onderzoek met mensen*, WMO; METC reference numbers 16.12216 and 16.12214).

Data sources

We linked three databases in this study, as shown in **Fig. 1:** (i) clinically collected annual data for patients with type 2 diabetes from the ZODIAC database, (ii) cancer-related data from the Dutch NCR, and (iii) mortality data from the national Dutch BRP.

The ZODIAC project started in 1998 as part of a study into the effects of structured shared care provided by specialized diabetes nurses and GPs together for patients with type 2 diabetes (26). After showing an improvement in quality of care, shared care became the standard of treatment for patients with diabetes in the Zwolle region and this approach gradually expanded to other regions of the Netherlands, as did the data collection (5, 26). There were 53 GPs participated the project in 1998, which increased to 459 in 2008 (4) and 731 in 2013 (27).Only patients with type 2 diabetes, either known or with a new diagnosis, and exclusively treated in primary care, were included in this cohort. Patients with a short life expectancy or with poor cognitive abilities were excluded. The following data were collected annually by participating nurses and GPs: demographic data, vital signs, medical diagnoses, prescriptions (the use of drugs was evaluated in the check-up), lifestyle characteristics (e.g., smoking and body mass index), and laboratory results (e.g., hemoglobin A1c and serum creatinine).

The NCR was founded in 1989 and has since contained data of most newly diagnosed cases of cancer in the Netherlands (28). New diagnoses are reported to the registry by the Dutch Pathology Network based on histologic, cytologic, and autopsy reports submitted by pathology departments. Additional information on patient and tumor characteristics, diagnostics, and therapy is collected from hospital records by trained registry personnel who use international coding rules (29). Topography and morphology are coded according to *the International Classification of Diseases for Oncology, Third Edition* (30), and staging is recorded using the tumor–node–metastasis (TNM) classification (31). Potential underregistration of cancer cases has been estimated to be below 2% (32).

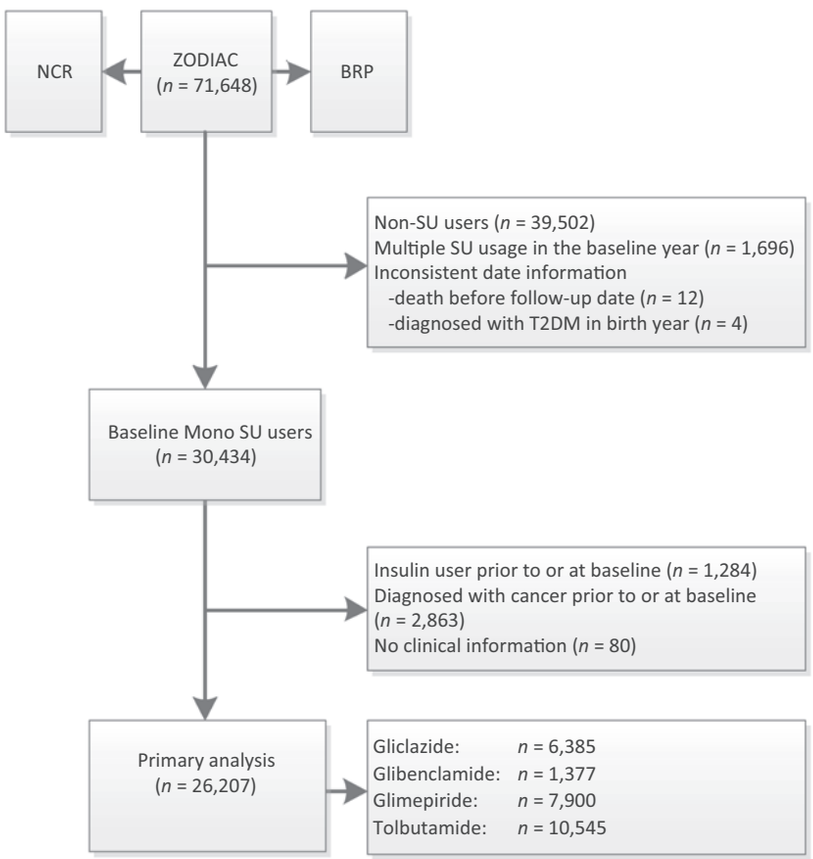

Figure 1.
Study flow chart including the database linkage and known sulfonylurea users. The ZODIAC cohort contains clinical data from January 1998 to December 2014. A linkage procedure for the three databases was last performed in March 2017, with cancer and death events observable to December 31, 2016. SU, sulfonylurea; T2DM, type 2 diabetes mellitus.

The BRP is a municipal personal records database for all residents in the Netherlands and was used to obtain information on the date of death for all patients. It contains information on all dates of death for all Dutch inhabitants (100% coverage; ref. 33).

Study population

The combined dataset contained 71,648 patients, among which 6,811 primary obesity-related cancer events (936 advanced prostate cancer; 2,411 breast cancer; 2,251 colorectal cancer), and 5,224 deaths occurred before the end of the study. To achieve a representative study population, we included data for all patients from the ZODIAC database who were prescribed with a sulfonylurea between January 1998 and December 2014. Patients were excluded if they had a record of using multiple sulfonylureas in the same year, had been diagnosed with cancer, had been treated with insulin, or had no clinical data prior to or at baseline. See **Fig. 1** for more details.

Definitions

The World Cancer Research Fund has listed 13 obesity-related cancers, including cancer of the liver, kidney, stomach cardia, colorectum, prostate (advanced), breast, gallbladder, pancreas, ovarian, endometrium, and esophagus, as well as cancer of the cervix and of the mouth, pharynx, and larynx, which were only recently added (3). We used this updated list, as summarized in **Table 1**. Advanced prostate cancer was defined as stage III or IV on the TNM tumor classification, Gleason grade ≥7, or metastatic cancer (34).

Baseline was defined as either the first year of use for those who started a sulfonylurea after cohort entry or as the year of entry for those already using a sulfonylurea. New users were defined as patients who started a sulfonylurea after cohort entry or as those already using a sulfonylurea at cohort entry if they had been diagnosed with diabetes for less than one year. The predefined end date of follow-up was the earliest among the following events: first switch to a different sulfonylurea, first cancer incident, death, or December 31, 2016. The latter date was the last date on which survival and cancer statuses were verified. Once a patient switched between sulfonylureas, patients were censored; as a consequence, the person-time and events after the switch were not included in the analysis. If a cancer event occurred in the same year as a patient switched to another sulfonylurea, data were censored at the time of cancer diagnosis.

In this analysis, only patients who used a certain type of sulfonylurea (gliclazide, glibenclamide, glimepiride, or tolbutamide) were included. A variable was constructed to indicate which type of sulfonylurea the patient used, where gliclazide was the reference. Cumulative exposure was calculated from baseline until censoring in one single variable. All known years of use were summed up. In case there was a missing year between two known usage years, the previous cumulative exposure was carried forward to the missing year. To account for the time it would take to develop cancer after drug exposure, a lag period of 1 year was allowed to discount cancers diagnosed shortly after starting a sulfonylurea (35).

Study outcomes

The primary outcome was the difference in the incidence of first obesity-related cancer between gliclazide users and other sulfonylurea users. The secondary outcome was the difference in the incidence of three most common cancer types (advanced prostate, breast, and colorectal) between gliclazide users and other sulfonylurea users as a group. Because the prescription of glibenclamide was not recommended due to its relatively higher risk of hypoglycemia, these analyses was repeated by excluding glibenclamide (36).

Baseline confounding variables

The predefined confounding variables were age, sex, metformin use, diabetes duration, hemoglobin A1c, body mass index, serum creatinine, smoking status, and baseline year (1, 19, 37). Evidence suggests that metformin is protective against cancer (38). We therefore adjusted for the potential effects of metformin by adding a continuous variable of known years of metformin use at baseline. To account for the effect of age of type 2 diabetes diagnosis, diabetes duration was calculated as that from diagnosis to baseline. Body mass index, hemoglobin A1c, and serum creatinine were included as continuous variables. Active smoking was categorized into "ever smokers," "never smokers," and "unknown." On the basis of a previous study in the same cohort, no significant or potentially relevant differences on time-varying confounders were observed between the different sulfonylureas (39), therefore all covariates were measured at baseline. Newer drugs such as dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter-2 inhibitors were rarely used in the Dutch primary care during the study period, therefore they were not accounted for in this study.

Table 1. The obesity-related cancers included in the analysis.

Men	Number	Women	Number
Esophageal (adenocarcinoma)	40	Esophageal (adenocarcinoma)	9
Stomach cardia	13	Stomach cardia	3
Kidney	54	Kidney	32
Gallbladder	3	Gallbladder	3
Liver	23	Liver	4
Pancreatic	50	Pancreatic	53
Colorectal	236	Colorectal	202
Mouth, pharynx, and larynx	26	Mouth, pharynx, and larynx	18
Prostate[a]	210	Ovarian	31
		Breast	277
		Endometrial	66
		Cervical	8

[a]Advanced prostate cancer was included, which was defined as stage III or IV on the TNM tumor classification, Gleason grade ≥7, or metastatic cancer.

Table 2. Baseline patient characteristics by sulfonylureas.

	Gliclazide ($n = 6,385$)	Glibenclamide ($n = 1,377$)	Glimepiride ($n = 7,900$)	Tolbutamide ($n = 10,545$)
Age (years)	65.8 ± 11.8	68.3 ± 11.1	64.6 ± 12.0	66.8 ± 12.1
Male sex (%)	53.3	50.8	53.0	50.4
Duration of diabetes (years)	4.7 (2.1–8.0)	7.1 (4.0–10.6)	4.8 (2.3–7.9)	4.6 (2.1–7.8)
Known metformin usage (years)	1 (0–3)	1 (0–1)	1 (1–1)	1 (0–1)
New SU user (%)	58.6	17.7	40.6	44.8
HbA1c (%)[a]	6.9 (6.3–7.5)	7.0 (6.5–7.7)	6.8 (6.3–7.5)	6.8 (6.3–7.4)
BMI (kg/cm^2)[b]	30.0 ± 5.6	29.4 ± 5.2	30.2 ± 5.7	29.5 ± 5.3
Creatinine (μmol/L)[c]	76 (65–89)	76 (64–88)	76 (65–89)	75 (64–88)
Smoking (%)[d]	33.7	22.1	23.9	24.2
History of macrovascular events (%)	13.9	17.5	14.2	15.7
Use of statins (%)	40.6	48.2	61.6	56.4
Duration of follow-up (years)[e]	6 (3–10)	8 (5–10)	7 (5–9)	7 (5–10)

Note: Normally distributed variables presented as mean ± SD. nonnormally distributed data presented as median (IQR). The descriptive analysis was performed before multiple imputation.
Abbreviations: BMI, body mass index; SU, sulfonylureas.
[a]1,639 missing.
[b]2,542 missing.
[c]2,123 missing.
[d]2,546 not known.
[e]The duration between baseline date and end date of the study in years.

Missing data

Missing values for body mass index at baseline were corrected by applying the next observation carried backward principle for body height. The remaining 16% of missing values for body mass index, creatinine, and hemoglobin A1c at baseline were imputed using multiple imputations. All relevant covariates and outcome variables, the follow-up duration, and the baseline cumulative hazard function, $H_0(t)$, were included in the imputation model (40). $H_0(t)$ was estimated using the Nelson–Aalen method (40). The $H_0(t)$ was expected to be different for different study outcomes, so for each outcome, we did multiple imputations (20 times; ref. 41).

Statistical analyses

Descriptive analyses for nonmissing data are reported as proportions, medians with interquartile ranges (IQR), and means with SDs. Incidence rates with 95% confidence intervals (CI) were calculated for the two outcomes as the number of cancer cases divided by 10^5 person-years of follow-up for each sulfonylurea user group.

Cox regression models were used to estimate the relative hazards of study outcomes in each nongliclazide group compared with the gliclazide group as a reference, adjusted for all baseline covariates. Given that cancer risk increases with age, we used age as a timescale for all models to keep patients of similar risk together, thereby ensuring a completely nonparametric age effect (42). As cumulative exposure might influence the outcome (43), we used a joint model of both baseline sulfonylurea and time-updated cumulative exposure (44). To allow for a time-updated variable, the data were organized into a person-period dataset in which each year of follow-up was a discrete interval (45, 46). The joint model was performed with and without adjusting for other confounders, in which both type of sulfonylurea and cumulative exposure were included. For both type of sulfonylurea and cumulative exposure, gliclazide was the reference group. Cancer incidence varies by gender, and among the obesity-related cancers, there are several gender-specific cancers. Therefore, we evaluated the study outcomes separately for men and women except for site-specific analyses for colorectal cancer where gender was used as a covariate (47). The Dutch national guideline recommended gliclazide over alternative sulfonylureas from 2013 onward (12). To account for this, we included baseline year as a stratification variable in all the models.

The proportional hazards assumptions were checked by plotting Schoenfeld residuals and adding the interactions of covariates with time when time-dependent variable was included. Proportionality was met for all Cox models. All statistical tests were two-sided and conducted at the 5% significance level. STATA software (version 15.0, StataCorp) was used for all statistical analyses.

Sensitivity analyses

First, a subgroup analysis was performed for new users only. Second, because we could not be certain of the lag period, the primary analysis was repeated with a lag period of 2 and 5 years. For the latter lag period, the use of gliclazide was compared with the use of other sulfonylureas as a group, including or excluding glibenclamide. Third, to quantify the effect of patients switching within the sulfonylurea class, we performed an intention-to-treat analysis based on the assumption that patients who switched kept using the first sulfonylurea (48). Furthermore, a sensitivity analysis was performed that included only complete cases.

Post hoc analysis

As potential favorable cardiovascular safety profile of gliclazide in the class of sulfonylureas has been shown (49) and macrovascular complications could indirectly influence cancer risk, to account for this potential confounding, apart from the confounders included in the primary analysis, we further adjusted for baseline history of macrovascular events and the use of statins at baseline. History of macrovascular events was defined as a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary

angioplasty, coronary artery bypass grafting, stroke or transient ischemic attack. Moreover, to investigate the effect of duration of diabetes at the time on study regarding obesity-related cancer risk, we also repeated the primary analysis with adjustment for duration of diabetes at baseline plus time on study instead of just baseline adjustment.

Data availability

All data and materials are available upon request.

Results

Of the 26,207 patients included for analysis, 11,911 (45.4%) were new users (**Fig. 1**). Among the 4,147 patients excluded because of a history of cancer, insulin use, or no clinical data, 1,003 (13.6%) were gliclazide users, 215 (13.5%) were glibenclamide users, 1,371 (14.8%) were glimepiride users, and 1,638 (13.4%) were tobutamide users. The median follow-up was 7 years (IQR: 5–9), equating to a total of 167,692 person-years. Overall, there were 1,111 obesity-related cancer events (incidence rate: 663 per 10^5 person-years; 95% CI, 625–703) and 167 advanced prostate cancer, 231 breast cancer, and 362 colorectal cancer events (incidence rates: 195, 282, 216 per 10^5 person-years; 95% CI, 167–227, 248–321, 195–239). There were 1,569 (6.0%) patients censored because of a switch of their initial sulfonylurea, of which 212 (3.3%) were gliclazide users, 282 (20.5%) were glibenclamide users, 489 (6.2%) were glimepiride users, and 586 (5.6%) were tolbutamide users.

Table 2 presents the baseline patient characteristics by sulfonylurea. The proportion of new users was highest for gliclazide (58.6%) compared with the other sulfonylureas, and there was a high proportion of active smokers (33.7%). Glibenclamide users had the highest mean age of 68.3 years, the lowest mean body mass index of 29.4 kg/cm^2, the longest median baseline diabetes duration of 7.1 years, and the longest median follow-up duration of 8 years; however, this group contained the smallest proportion of new users (17.7%) and smokers (22.1%).

There were no within-class differences in the risk of overall and site-specific obesity-related cancer (**Table 3**). Both the HRs for baseline sulfonylurea and cumulative exposure were reported, with gliclazide as

Table 3. Incidence rates and relative risk of obesity–related cancer in sulfonylurea users.

				Unadjusted		Adjusted[a]	
SUs	Cancers (*n*)	PYS	IR (95% CI; per 100,000 PYS)	Baseline SU HR (95% CI)	Cumulative exposure HR (95% CI)	Baseline SU HR (95% CI)	Cumulative exposure HR (95% CI)
Male							
Gliclazide[b]	132	20,939.0	630.4 (531.8–747.3)	1.00	1.00	1.00	1.00
Glibenclamide	23	4,766.1	482.6 (321.0–725.5)	0.84 (0.38–1.87)	0.96 (0.79–1.17)	1.10 (0.92–2.69)	0.90 (0.71–1.14)
Glimepiride	160	25,984.0	615.8 (527.6–718.6)	1.10 (0.71–1.70)	0.97 (0.89–1.06)	1.13 (0.68–1.84)	0.96 (0.87–1.06)
Tolbutamide	221	34,061.1	648.8 (568.9–740.0)	0.83 (0.55–1.25)	1.03 (0.96–1.11)	0.93 (0.59–1.48)	1.00 (0.92–1.09)
Female							
Gliclazide[b]	130	18,748.0	693.4 (584.2–823.0)	1.00	1.00	1.00	1.00
Glibenclamide	46	4,995.5	920.8 (690.6–1227.7)	1.44 (0.80–2.58)	0.97 (0.84–1.13)	1.49 (0.72–3.13)	0.93 (0.77–1.13)
Glimepiride	149	23,760.9	627.1 (534.3–735.9)	0.88 (0.57–1.35)	1.01 (0.92–1.11)	0.96 (0.59–1.54)	0.99 (0.90–1.10)
Tolbutamide	250	34,437.6	726.0 (641.6–821.4)	0.87 (0.59–1.27)	1.04 (0.97–1.13)	0.84 (0.54–1.28)	1.04 (0.96–1.13)
Site-specific cancers							
Advanced prostate cancer							
Gliclazide[b]	47	20,939.0	224.5 (222.4–226.5)	1.00	1.00	1.00	1.00
Other sulfonylureas	120	64,811.2	185.2 (184.1–186.2)	0.74 (0.39–1.41)	1.01 (0.90–1.13)	0.91 (0.43–1.92)	0.98 (0.86–1.12)
Other sulfonylureas (glibenclamide excluded)	114	60,045.1	189.9 (188.8–191.0)	0.75 (0.39–1.45)	1.01 (0.90–1.14)	0.90 (0.42–1.90)	0.99 (0.87–1.13)
Breast cancer							
Gliclazide[b]	50	18,748.0	266.7 (264.3–269.1)	1.00	1.00	1.00	1.00
Other sulfonylureas	181	63,194.0	286.4 (285.1–287.8)	1.12 (0.63–1.99)	1.00 (0.89–1.13)	1.20 (0.61–2.36)	0.98 (0.86–1.13)
Other sulfonylureas (glibenclamide excluded)	161	58,198.5	276.6 (275.3–278.0)	1.02 (0.57–1.83)	1.02 (0.90–1.14)	1.15 (0.58–2.27)	0.99 (0.87–1.13)
Colorectal cancer							
Gliclazide[b]	77	39,687.0	194.0 (155.2–242.5)	1.00	1.00	1.00	1.00
Other sulfonylureas	285	128,005.1	222.6 (198.2–249.9)	0.92 (0.58–1.45)	1.04 (0.95–1.14)	0.98 (0.59–1.63)	1.02 (0.92–1.12)
Other sulfonylureas (glibenclamide excluded)	264	118,243.5	223.2 (197.9–251.8)	0.93 (0.59–1.48)	1.04 (0.95–1.14)	0.99 (0.59–1.67)	1.02 (0.92–1.12)

Note: For all the models, age was used as the timescale and baseline year was used as a stratification variable.
Abbreviations: IR, incidence rate; PYS, person-years; SU, sulfonylurea.
[a]Adjusted for baseline covariates: smoking (yes/no, not known), diabetes duration, hemoglobin A1c level, body mass index, creatinine, known metformin usage years, and new or existing users. Site-specific analysis for colorectal cancer was also adjusted by gender.
[b]Reference.

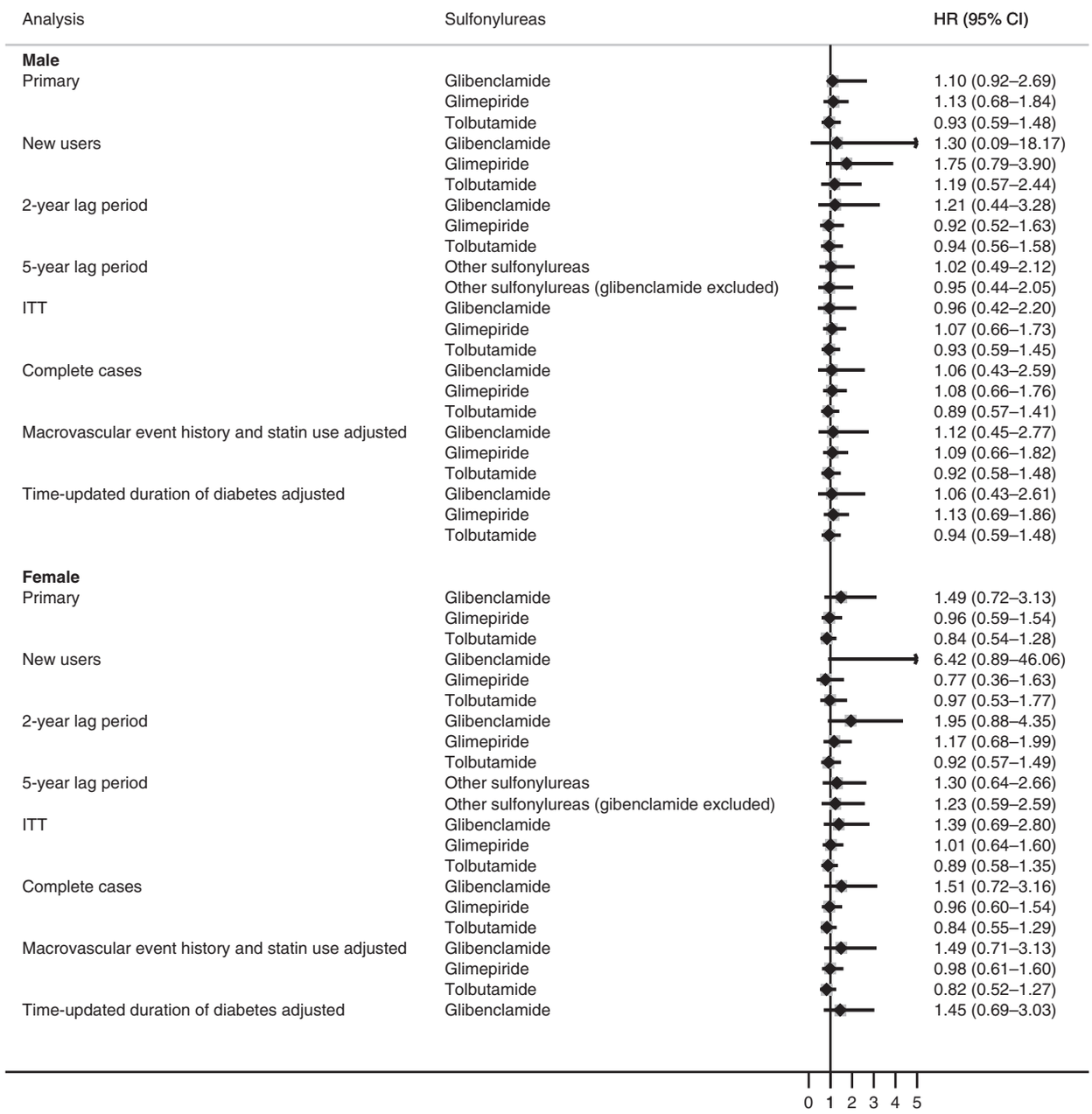

Figure 2.

Forest plot with HRs for baseline sulfonylurea of overall obesity-related cancer among nongliclazide sulfonylureas compared with gliclazide in the primary and sensitivity analyses. ITT, intention to treat.

a reference. The HR for baseline sulfonylurea represents the difference of the constant effect of exposing to a nongliclazide sulfonylurea compared with gliclazide, while the HR for cumulative exposure represents the difference of the additional effect of one more year exposure of a nonglclazide sulfonylurea compared with gliclazide. Sensitivity analyses showed similar results (**Figs. 2** and **3** for overall and Supplementary Fig. S1 and S2 for site-specific obesity-related cancer). In addition, the analysis of only new users showed similar results with wider CIs (Supplementary Table S1). However, when we changed the lag time to 2 years (Supplementary Table S2), female glibenclamide users showed a higher risk of obesity-related cancer (HR, 1.93; 95% CI, 1.02–3.65) compared with gliclazide users in a crude model; when we adjusted for baseline covariates, this effect did not persist (HR, 1.95; 95% CI, 0.88–4.35). When the lag period was lengthened to 5 years (Supplementary Table S3), the result was consistent with the primary analysis. Intention-to-treat analysis, assuming that there was no switch between sulfonylureas, did not produce relevant effects on the results (Supplementary Table S4), and

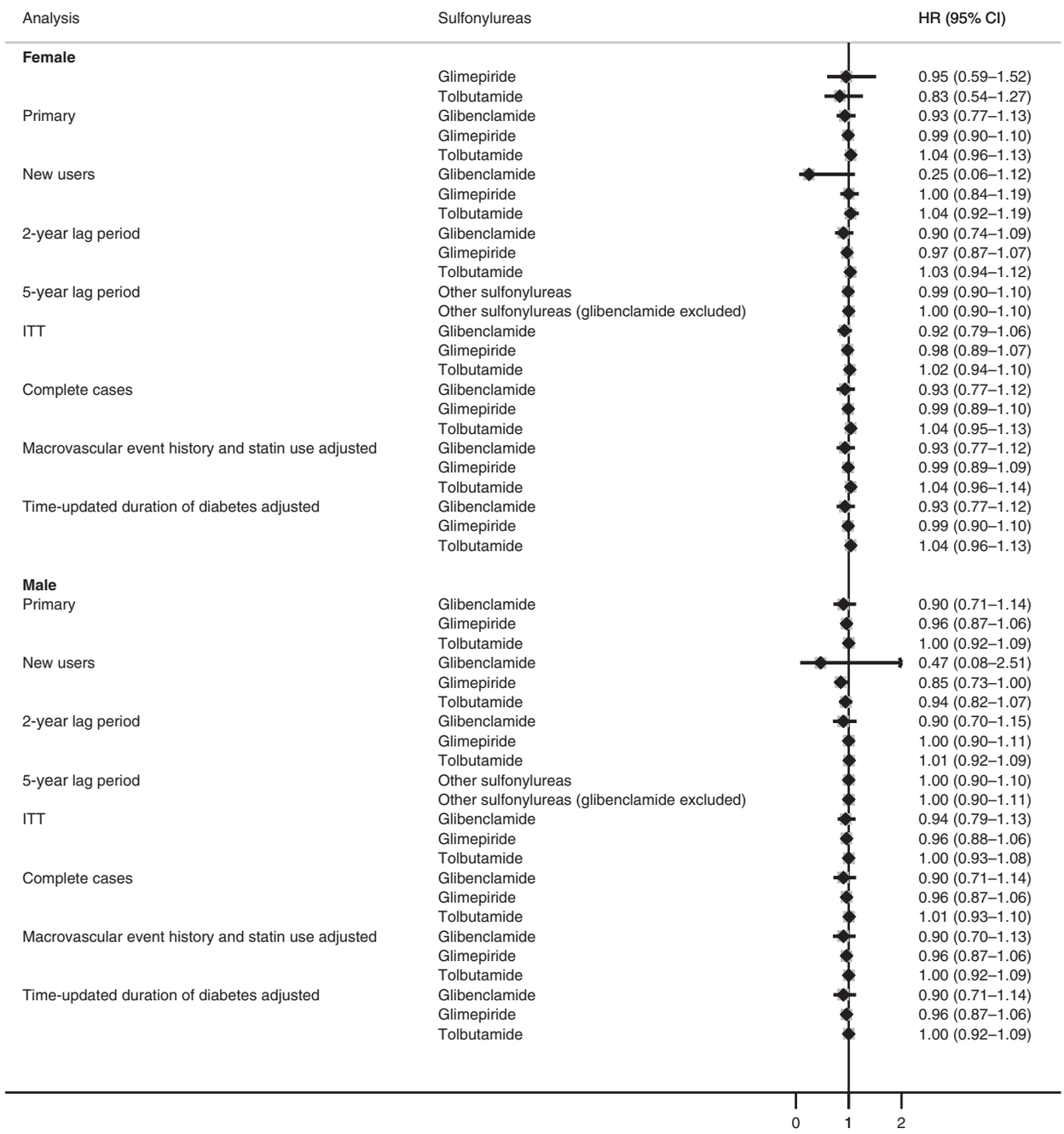

Figure 3.
Forest plot with HRs for cumulative exposure of overall obesity-related cancer among nongliclazide sulfonylureas compared with gliclazide in the secondary and sensitivity analyses. ITT, intention to treat.

analysis of patients with complete clinical data (n = 21,939, 84%) showed no differences by sulfonylurea (Supplementary Table S5). The results of the *post hoc* analyses, further adjusting for baseline history of cardiovascular events and statin use at baseline, and adjusting for duration of diabetes at baseline plus time on study, were both consistent with the primary analysis (Supplementary Tables S6 and S7).

Discussion

In this prospective study of more than 26,000 patients using sulfonylureas, no significant within-class differences were found in the risk of overall or site-specific obesity-related cancer between the various sulfonylureas after accounting for the cumulative duration of use and a wide range of covariates. The results also remained consistent in various sensitivity and subgroup analyses.

In the available literature, gliclazide users have been reported to have a 40% to 60% decreased risk of cancer incidence compared with nongliclazide users (22, 23). However, these studies were limited by small sample sizes and very low cancer incidence rates, suggesting incomplete cancer events. Another major limitation, which might not attract enough attention, was indication bias. For example, exposure to gliclazide was compared with exposure of any other glucose-lowering drug, which included not only other sulfonylureas but also other drugs classes, such as metformin and insulin. This is problematic because the use of other drug classes may imply a difference in type 2 diabetes disease stage (50). Two studies have compared within-class differences, with one limited by its retrospective design and both failing to account for cumulative duration of use in the within-class comparison (24, 51). This inaccurate representation of drug exposure was considered as important as the presence of bias, limited sample size, and invalid data sources when assessing drug exposure and cancer risk (52). This is also the first study evaluating within-class difference on site-specific obesity-related cancer types, where no within-class difference was observed, although we could not exclude the possibility of a relevant difference being present.

Our study has several strengths. More than 90% of patients in the Netherlands are treated in primary car, and nearly all those in the ZODIAC region were included in our study (53). This produced a large and highly unselected cohort. Data were also collected on an annual basis for benchmarking purposes; that is, the participation rate and the achievement rate of treatment targets (e.g., hemoglobin A1c < 7%) were assessed at the GP level (26). This benchmarking resulted in good data accuracy and completeness (4). We also prospectively collected a wide range of relevant confounders and we independently linked the clinical data with a nearly complete cancer dataset and a complete mortality dataset, resulting in a unique data linkage of good quality (28, 33, 54). In the Netherlands, except for glibenclamide, no specific prescription of sulfonylureas is advised in the Dutch guideline before October 2013 and mostly the choice of a specific sulfonylurea is based on the preference of GPs (36). The design of the within-class comparison therefore generated patient groups that were at comparable disease stages, which mimicked a randomized trial at a GP level in the real world. Equally, although drug data were only collected annually, both baseline and time-updated cumulative exposure were both accounted in the model (52). Time-related biases were avoided, as much as possible, by using age as a timescale and by formulating extensive sensitivity analyses a priori. These sensitivity analyses allowed us to account for different lag periods and to investigate cancer risk in a large subset of new users. Cox regression modeling, using age as a timescale, ensures that patients with similar risks are kept together in a given risk set (55). In this way, age effects were absorbed into unspecified baseline hazards with the potential to adjust for duration of diabetes and baseline year, thereby avoiding potential collinearity.

This study has several weaknesses that should be considered when interpreting the results. First, around 45% of patients in our study were new users at baseline. Although a sensitivity analysis including new users only showed results similar to the primary analysis, the unknown years of exposure limits us to perform an analysis accounting time since first use. Second, clinical data were collected annually and whether the patients adhered to the prescription on a daily basis is unknown, whereas it would have been optimal to have obtained actual drug usage data on a monthly or even a weekly or daily basis. Third, dosage was not accounted for, limiting us to study the cumulative time of drug use. Fourth, the use of a lag period prevents detection bias of cancer events that developed before drug exposure and allows a latency time for cancer development. A lag time of 1, 2, and 5 years and a median follow-up of 7 years might be insufficient to allow for tumor growth of certain tumor types. It would be beneficial for future studies to define the lag period and follow-up time based on tumor volume doubling time for site-specific cancer types. Fourth, given that when a switch occurred, the patient was censored resulting in a shorter follow-up and a possible underestimation of obesity-related cancer risk, the switch rates was higher among nongliclazide users than that of gliclazide users, especially for glibenclamide users, which might have led to an underestimation of the HRs. Fifth, the observational design meant that there were some unmeasured confounders, for example menopausal status, diabetes complications severity. However, we do not believe this will have affected the results significantly because the sulfonylurea choice was mostly random before 2013.

Conclusion

In this primary care cohort of patients with type 2 diabetes, no significant within-class differences among the various sulfonylureas with respect to the risk of overall and site-specific obesity-related cancer were observed. Given that there are many other within-class benefits that support the use of gliclazide over other sulfonylureas, these results indicated that there is no need to change prescribing practices.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J. Du, N. Kleefstra, D. Schrijnders, G.H. de Bock, G.W.D. Landman
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Kleefstra, D. Schrijnders, G.W.D. Landman
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Du, K.H. Groenier, G.H. de Bock, G.W.D. Landman
Writing, review, and/or revision of the manuscript: J. Du, N. Kleefstra, D. Schrijnders, K.H. Groenier, G.H. de Bock, G.W.D. Landman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Schrijnders, G.W.D. Landman
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