Impact of oral hypoglycemic agents on mortality among diabetic patients with non-muscle-invasive bladder cancer: A population-based analysis

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Abstract

Introduction: Non-muscle-invasive bladder cancer (NMIBC) accounts for 75–85% of all urothelial bladder cancers (UBC). Many UBC patients are also afflicted by diabetes mellitus (DM). It has been postulated that several oral hypoglycemic agents could impact disease-specific survival (DSS), but the data are sparse among NMIBC patients. Our primary objective was to evaluate the impact of metformin on DSS and overall survival (OS) in NMIBC patients.
Methods: This is a retrospective, population-based study that used linked administrative databases to identify diabetic patients ≥66 years who were subsequently diagnosed with NMIBC in Ontario between 1992 and 2012. Cumulative use of metformin and other hypoglycemic agent were calculated before and after NMIBC diagnosis. DSS and OS were estimated using multivariable competing risk and Cox proportional hazards models, respectively.
Results: A total of 1742 subjects were included in the study. After a median followup of 5.2 years, 1122 (64%) had died, including 247 (15%) deaths as a result of UBC. On multivariable analysis, cumulative duration of metformin use after NMIBC diagnosis did not appear to impact DSS (hazard ratio [HR] 1.1; 95% confidence interval [CI] 0.92–1.2), whereas glyburide use appeared to have a detrimental effect (HR 1.17; 95% CI 1.02–1.3). None of the other hypoglycemic agents had an impact on OS.
Conclusions: In this large, population-based study, we have provided further evidence that metformin use does not significantly impact DSS among diabetic patients diagnosed with NMIBC. However, our findings demonstrate that glyburide use inversely affects DSS. The detrimental effect of glyburide on DSS will require further validation.

Introduction

Urothelial bladder cancer (UBC) is the fifth most common solid organ cancer in North America, with over 74 000 new cases diagnosed every year in the U.S. alone.[1] UBC is especially prevalent among the elderly, with an average age at diagnosis of 73 years.[1] Fortunately, approximately 75% of cases are non-muscle-invasive bladder cancer (NMIBC).[2] Although associated with high recurrence rates, these cancers have lower progression and metastatic rates than muscle-invasive tumours (MIBC).[3,4]

Many NMIBC patients are also afflicted by diabetes mellitus (DM), which affects over 25% of individuals aged 65 and older.[5] Metformin, a member of the biguanide medication class, is considered to be the first-line therapy in the management of DM.[6] Interestingly, metformin has recently gained interest for its antineoplastic properties against a number of non-genitourinary and genitourinary cancers.[7-9] More specifically, there have been in vitro and animals studies demonstrating putative antineoplastic effects of metformin on UBC.[10] However, there are limited clinical data evaluating the role of metformin in UBC patients and results, thus far, have been equivocal.[11-13] Furthermore, many of these studies were underpowered and only one of them assessed NMIBC.[12] It has also been proposed that other oral hypoglycemic agents may have a potential impact on cancer outcome.[14,15]

Our primary objective was to assess the impact of cumulative use (after NMIBC diagnosis) of metformin on the disease-specific survival (DSS) and the overall survival (OS). The secondary objectives were to assess the impact of metformin (before NMIBC diagnosis) and other hypoglycemic agents (before and after NMBIC diagnosis) on both the DSS and OS. We hypothesized that metformin after NMIBC diagnosis is associated with improved DSS and OS, while the other studied hypoglycemic agents have no impact.

Methods

Study population

This was an institutional review board-approved, population-based, retrospective study. Individuals diagnosed with incident UBC in Ontario and concomitant DM between January 1, 1992 and December 31, 2012 were identified using administrative databases. Individuals with other concomitant neoplasms (other than non-melanoma skin cancer) were excluded. The cohort was also restricted to subjects ≥66 years of age at the time of DM and UBC diagnosis. Since staging and pathological data were unavailable or incompletely captured with the available administrative databases, NMIBC patients were identified as individuals with UBC who had not undergone a cystectomy and/or radiotherapy and/or systemic chemotherapy treatments (i.e., radical or systemic therapy) within six months of the diagnosis of UBC, as these treatments are usually reserved for MIBC and/or advanced UBC (Supplementary Table 1). Similarly, individuals who were lost to followup or who died within six months of diagnosis were excluded, as the anti-diabetic medications were unlikely to have affected their outcomes and because those who died of UBC during that period were more likely to have been diagnosed with MIBC or advanced disease. Lastly, individuals diagnosed with DM after UBC diagnosis were also excluded.

Data sources

All medical procedures in Ontario are reimbursed by a single payer system (Ontario Health Insurance Plan [OHIP]) that covers over 95% of the population.[16] To identify the management of subjects diagnosed with NMIBC, several validated databases were linked together (Ontario Cancer Registry [OCR], the Registered Persons Database and the Ontario Diabetes Database [ODD]).[17,18] The ODD is a population-based disease registry that uses a validated algorithm based on hospitalizations and physician visits to identify individuals with physician-diagnosed DM.[19] These aforementioned databases were then linked to the Ontario Drug Benefit Database (ODB), which is another reliable and validated database that contains information on all medications dispensed in Ontario to individuals over 65 years of age.[20] Thus, we restricted the cohort to diabetic individuals ≥66 years at the time of diagnosis as a mean to limit uncaptured medication exposure prior to study entry. This provided a minimum look-back window of one year to minimize the risk that included subjects were exposed to the studied drugs prior to being captured in the ODB (i.e., limited the possibility of incomplete drug history). Eligible individuals were observed until they experienced an event or until their last contact with the Ontario health system.

Statistical analysis

Descriptive statistics consisting of medians and interquartile range (IQR) were reported for continuous variables, while proportions were used to report categorical variables. The ODB database was used to identify all prescriptions for hypoglycemic medications between the date of DM diagnosis and the end of followup. The drug identifier numbers used to identify each drug are summarized in Supplementary Table 2. The drugs were categorized into five distinct groups: metformin, glyburide, thiazolidinediones (pioglitazone, rosiglitazone), insulin, and other oral hypoglycemic agents (chlorpropamide, gliclazide, tolbutamide, glimepiride, sitagliptin, saxagliptin, nateglinide, repaglinide).

The cumulative daily duration of exposure was determined by adding the duration of each single prescription. During periods where individuals were deemed to be off the drug, the cumulative duration of exposure remained unchanged. Cumulative exposure to the different medications was divided between exposure before and after UBC diagnosis, with the objective to use post-diagnosis exposure as the main exposure variable while adjusting for exposure before UBC diagnosis in the multivariable models. A cumulative exposure analysis was used as opposed to the more traditional ever vs. never approach, as it offers, according to the literature, less bias estimate of the true effect.[21] OS was calculated from the date of UBC diagnosis to the date where the individual experienced death or the date of censoring (i.e., end of the study followup period [December 31, 2014] or lost to followup [i.e., date of last contact with OHIP]). DSS was calculated in a similar fashion, with non- UBC-related deaths considered competing events.

The effect of cumulative duration of exposure to hypoglycemic medications before and after NMIBC on the risk of OS was assessed using Cox proportional hazards model, whereas a proportional subdistribution hazard model (i.e., competing risks) with time dependent weights was used to assess their impact on the DSS. All models were adjusted for patient's baseline characteristics at the time of UBC diagnosis (sex, age, year of diagnosis, area of residency, Charlson comorbidity score, time since diagnosis of DM, and neighborhood income quintile, which was identified derived from each individual postal code) and for cumulative use of all included hypoglycemic agents, categorized as previously mentioned, into use before and after NMIBC diagnosis. In particular, adjustment for use of thiazolidinediones was made given their known association with UBC.[22] To decrease the risk of bias, all cumulative drug exposures before and after NMIBC diagnosis were modelled as time-dependent covariates and as continuous variables.[23]

Estimates in the multivariable models are reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Because the increment of a single day is

clinically negligible, all HRs are presented as an estimate of the effect of 12 months of use. Two sensitivity analyses were also performed. The first one included all individuals who died within six months of the UBC diagnosis, while the second was restricted to individuals diagnosed with DM after 1996, after which the prescription duration variable in ODB became a mandatory entry field. All statistical analyses were performed using SAS 9.4 and R version 3.1.3 statistical software. All analyses were two sided, with p-values less than 0.05 considered statistically significant.

Results

During the study period, 38 383 individuals were diagnosed with UBC in Ontario, of which 10 144 were known diabetics. Of these, 7011 individuals were excluded because of prior malignancy (n=1917), because of the age criterion (n=3971), because they were deemed to have MIBC (n=775), and because they died within six months of the diagnosis (n=348). An additional 1391 individuals were also excluded because they were diagnosed with DM after the UBC diagnosis. Therefore, the final cohort comprised of 1742 individuals with underlying DM diagnosed prior to NMIBC and who were ≥66 years of age at the time of diagnosis (Fig. 1).

The median age at NMIBC diagnosis was 78 years (IQR 75–83) while the median time between diagnosis of DM and NMIBC diagnosis was 3.5 years (IQR1.3–6.9). Overall, 523 (30%) and 813 (47%) individuals were exposed to metformin before and after NMIBC diagnosis, respectively. The median exposure before and after diagnosis was 1.5 years (IQR 0.6–3.2) and 1.9 years (IQR 0.6–3.7), respectively. The second most commonly used anti-diabetic agent was glyburide, with 419 (24%) and 545 (31%) individuals exposed to the drug before and after NMIBC diagnosis, respectively. The median exposure to glyburide before and after diagnosis was 1.6 years (IQR 0.5–3.7) and 1.5 years (IQR 0.5–3.4), respectively. Summaries of the cohort baseline characteristics (categorized according to previous use of metformin) and hypoglycemic agents exposure are presented in Tables 1 and 2.

During a median followup of 5.2 years (IQR 3.4–7.8) after NMIBC diagnosis, 1122 (64%) died overall and 247 (15%) died of UBC. On multivariable analysis, the cumulative use of metformin (HR 0.96; 95% CI 0.92–1.01) and other hypoglycemic agents after NMIBC diagnosis was not associated with OS (Table 3). Similarly, on the competing risk model, the use of metformin after NMIBC diagnosis had no impact on the DSS (HR 1.1; 95% CI 0.92–1.2) (Table 4).

However, the use of glyburide was associated with a 17% increase in the risk of death due to NMIBC for every year of use (HR 1.17; 95% CI 1.02–1.3). The remaining hypoglycemic agents had no association with DSS. The absence of a statistically significant association with metformin and the presence of a detrimental effect of glyburide on DSS were corroborated by the first sensitivity analysis that included patients who died within six months of UBC diagnosis. However, in the second sensitivity analysis that restricted the cohort to individuals diagnosed with DM after 1996, the association between glyburide and DSS was no longer statistically significant, possibly due to an underpowered analysis (Supplementary Table 3).

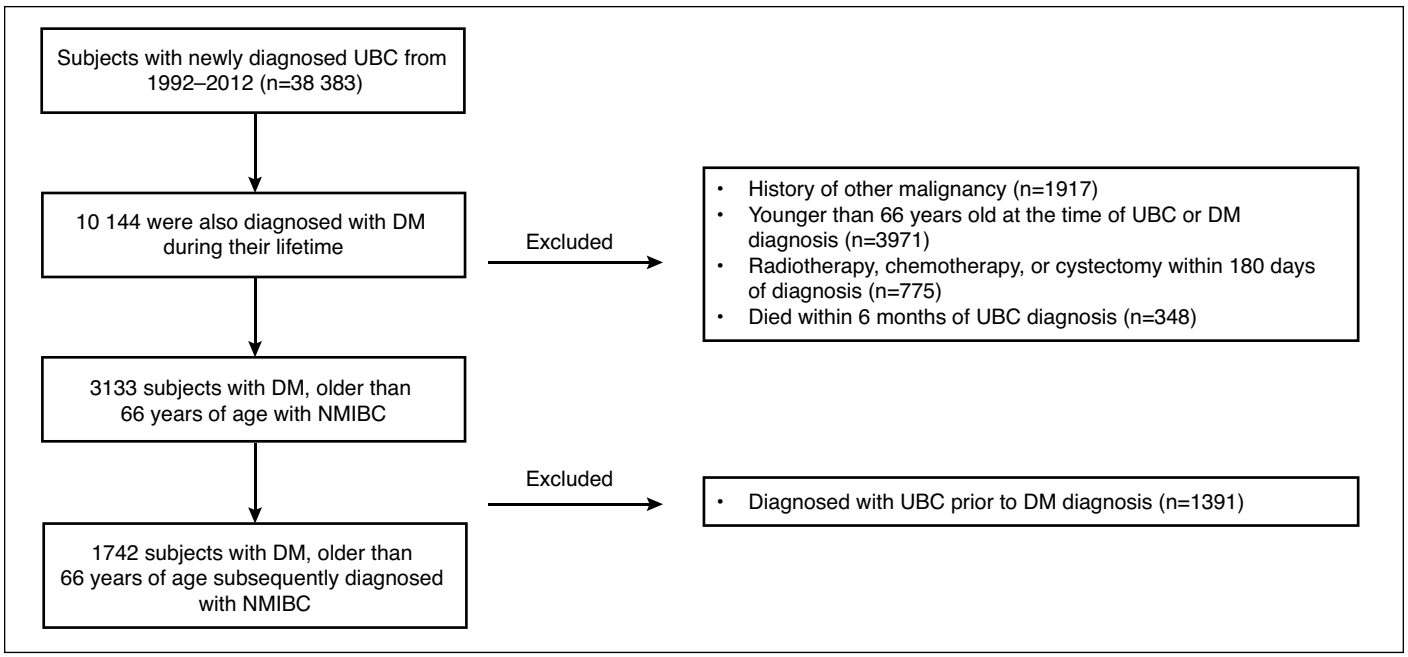

Fig. 1. Study flow chart. DM: diabetes mellitus; NMIBC: non-muscle-invasive bladder cancer; UBC: urothelial bladder cancer.

Table 1. Baseline individuals characteristics of the total cohort and according to use of metformin

Characteristics	Total (n=1742)	Ever* (n=813)	Never (n=929)	p
Age at NMIBC diagnosis in years, n (%)				
66–69	63 (4)	38 (5)	25 (3)	<0.001
70–74	330 (19)	172 (21)	158 (17)	
75–79	554 (32)	285 (35)	269 (29)	
80–84	465 (27)	105 (13)	252 (27)	
85–High	330 (19)	213 (26)	225 (24)	
Time between DM and NMIBC diagnosis, years				
Median, IQR	3.5 (1.3–6.9)	3.9 (1.5–7.1)	3.2 (1.2–6.6)	0.045
Followup after NMIBC diagnosis, years				
Median, IQR	5.2 (3.4–7.8)	5.9 (4.1–8.9)	4.3 (2.9–6.9)	<0.001
Gender, n (%)				
Male	1377 (79)	658 (81)	719 (77)	0.07
Female	365 (21)	155 (19)	210 (23)	
Area of residency, n (%)				
Urban	1508 (87)	701 (86)	807 (87)	0.6
Rural	234 (13)	112 (14)	122 (13)	
Charlson comorbidity score, n (%)				
0	682 (39)	296 (36)	386 (42)	0.03
1	137 (8)	67 (8)	70 (8)	
2	621 (36)	290 (36)	331 (36)	
3+	283 (16)	152 (19)	131 (14)	
Unknown	19 (1)	8 (1)	11 (1)	
Neighborhood income quintile, n (%)†				
First	383 (22)	190 (23)	193 (21)	0.4
Second	343 (20)	150 (19)	193 (21)	
Third	356 (20)	158 (19)	198 (21)	
Fourth	330 (19)	163 (20)	167 (18)	
Fifth	321 (18)	148 (18)	173 (19)	
Unknown	9 (1)	4 (1)	5 (1)	
Mortality, n (%)				
All-cause mortality	1122 (64)	487 (60)	635 (68)	<0.001
Cancer-specific mortality	247 (15)	90 (11)	157 (17)	

*Defined as use of metformin before or after NMIBC diagnosis during the study period. †First denotes the lowest quintile; fifth, the highest. DM: diabetes mellitus; IQR: interquartile range; NMIBC: non-muscle-invasive bladder cancer.

Discussion

Over the last decade, there have been an increasing number of publications supporting the role of metformin as an anti-neoplastic agent.[7-13] Metformin lowers blood glucose by activating AMP-activated protein kinase (AMPK). Activation of AMPK reduces mammalian target of rapamycin (mTOR) signaling which in turn leads to inhibition of cancer cell growth and proliferation.[24] Activation of the mTOR pathway has been previously implicated in the tumorigenesis of UBC, while its inhibition has been shown to inhibit tumorigenesis.[25,26]

Despite this rationale, the result of this large population-based study failed to demonstrate an association between metformin use in NMIBC patients and DSS or OS. Similarly, in a smaller study by Rieken et al, which included 125 patients with DM, no difference in OS or DSS was attributed to metformin use.[12] Interestingly, the authors did report that metformin users were at lower risk of disease recurrence (HR 0.48, 95% CI:0.26-0.89) than non-DM patients.

Table 2. Anti-diabetic exposure before and after bladder cancer diagnosis

Medicines	Frequency (%)	Years, median (IQR)
Metformin use		
Before NMIBC diagnosis	523 (30)	1.5 (0.6–3.2)
After NMIBC diagnosis	813 (47)	1.9 (0.6–3.7)
Glyburide use		
Before NMIBC diagnosis	419 (24)	1.6 (0.5–3.7)
After NMIBC diagnosis	545 (31)	1.5 (0.5–3.4)
Thiazolidinedione use		
Before NMIBC diagnosis	23 (1)	1.2 (0.4–2.3)
After NMIBC diagnosis	53 (3)	1.0 (0.4–2.9)
Other oral anti-diabetic agents use		
Before NMIBC diagnosis	90 (5)	0.9 (0.3–1.5)
After NMIBC diagnosis	297 (17)	1.3 (0.4–2.5)
Insulin use		
Before NMIBC diagnosis	68 (4)	0.5 (0.1–1.5)
After NMIBC diagnosis	168 (10)	0.3 (0.1–2.9)
Non-medical management	245 (14)	—

IQR: interquartile range; NMIBC: non-muscle-invasive bladder cancer.

Table 3. Time-dependent multivariable Cox proportional hazards model for overall survival

Characteristics	HR	95% CI	p
Year of diagnosis			
Before 1998	REF		
1998–2003	0.87	0.72–1.01	0.15
2004–2008	0.66	0.53–0.81	<0.001
2009–2012	0.61	0.48–0.78	<0.001
Age at bladder cancer diagnosis			
66–69	REF		
70–74	1.9	1.3–3.0	0.003
75–79	2.4	1.6–3.7	<0.001
80–84	3.8	2.5–5.9	<0.001
85–high	6.6	4.3–10	<0.001
Time between DM and NMIBC diagnosis, per year	1.01	0.99–1.03	0.31
Gender (male vs. female)	1.2	1.02–1.4	0.03
Area of residency (rural vs. urban)	1.2	1.04–1.4	0.02
Neighborhood income quintile			
First	REF		
Second	0.9	0.79–1.1	0.51
Third	1.0	0.82–1.2	0.89
Fourth	1.1	0.87–1.3	0.63
Fifth	0.9	0.76–1.1	0.42
Charlson comorbidity score			
0	REF		
1	1.4	1.1–1.8	0.002
2	1.2	1.0–1.4	0.005
3+	1.5	1.2–1.7	<0.001
Pre-NMIBC exposure, per year of use			
Metformin	1.0	0.97–1.1	0.65
Glyburide	1.06	1.02–1.1	<0.001
Thiazolidinedione	0.1	0.83–1.1	0.51
Other oral anti-diabetic agents	0.97	0.86–1.1	0.58
Insulin	1.3	1.11–1.5	<0.001
Post-NMIBC exposure, per year of use			
Metformin	0.96	0.92–1.01	0.08
Glyburide	1.01	0.97–1.1	0.72
Thiazolidinedione	0.91	0.77–1.1	0.30
Other oral anti-diabetic agents	1.06	0.85–1.2	0.31
Insulin	1.09	0.87–1.2	0.14

CI: confidence interval; DM: diabetes mellitus; HR: hazard ratio; NMIBC: non-muscle-invasive bladder cancer.

Table 4. Time-dependent multivariable competing risk model for bladder cancer-specific survival

Characteristics	HR	95% CI	p
Year of diagnosis			
Before 1998	REF		
1998–2003	1.0	0.71–1.5	0.85
2004–2008	0.58	0.37–0.88	0.01
2009–2012	0.10	0.05–0.20	<0.001
Age at bladder cancer diagnosis			
66–69	REF		
70–74	1.2	0.58–2.5	0.60
75–79	0.96	0.46–2.0	0.91
80–84	1.4	0.64–3.0	0.43
85–high	1.9	0.91–4.2	0.09
Time between DM and NMIBC diagnosis, per year	1.0	0.96–1.1	0.70
Gender (male vs. female)	0.80	0.59–1.1	0.15
Area of residency (rural vs. urban)	0.91	0.62–1.3	0.62
Neighborhood income quintile			
First	REF		
Second	1.0	0.68–1.5	0.99
Third	1.2	0.80–1.7	0.41
Fourth	1.0	0.66–1.5	0.99
Fifth	0.9	0.56–1.3	0.49
Charlson comorbidity score, n (%)			
0	REF		
1	1.3	0.74–2.2	0.39
2	1.5	1.1–2.0	0.008
3+	1.4	0.96–2.1	0.08
Pre-NMIBC exposure, per year of use			
Metformin	1.0	0.90–1.1	0.80
Glyburide	0.97	0.88–1.1	0.50
Thiazolidinedione	0.85	0.36–2.0	0.71
Other oral anti-diabetic agents	0.99	0.70–1.4	0.93
Insulin	1.1	0.65–1.9	0.73
Post-NMIBC exposure, per year of use			
Metformin	1.1	0.92–1.2	0.45
Glyburide	1.17	1.02–1.3	0.03
Thiazolidinedione	0.85	0.30–1.3	0.21
Other oral anti-diabetic agents	0.86	0.53–1.4	0.54
Insulin	1.17	0.76–1.8	0.47

CI: confidence interval; DM: diabetes mellitus; HR: hazard ratio; NMIBC: non-muscle-invasive bladder cancer.

Given the limitations of our database, we were unable to validate the benefit of metformin on disease recurrence. As they suggested, their findings could be the result of the beneficial use of metformin, but another possible explanation is that the DM itself potentiated recurrence secondary to impaired glucose tolerance, promoting tumour growth.[27]

Regardless, given the absence of impact on survival, the true benefit of metformin among individuals diagnosed with NMIBC needs to be questioned. Conversely, metformin may have a potential role among individuals with MIBC. Two retrospective studies have demonstrated that, among individuals who had undergone cystectomy for their UBC, metformin use had a protective effect on DSS while the use of other oral hypoglycemics agents did not.[11,13]

This study is the first to suggest a detrimental effect of glyburide on DSS among diabetic individuals with NMIBC. This effect became non-significant when the cohort was restricted to individuals diagnosed with DM after 1996, but with a HR in the same direction. Therefore, this absence of statistical significance may simply reflect an underpowered analysis. Glyburide, also known as glibenclamide, is a second-generation sulfonylurea and is often used as first- or second-line therapy for the treatment of DM.[6] It improves glucose control by promoting insulin secretion and by enhancing insulin action and function.[28] This effect seems to be the result of reduced conductance of ATP-sensitive K+ channels. Interestingly, various studies have demonstrated that several types of K+ channels are present in different tumour

cells (including urothelial carcinoma) and that they played an important role in the regulation of tumour cell proliferation and apoptosis.[14,15] It has been suggested that a reduction in K+ channel activity is associated with a decrease in apoptosis rates through unknown mechanisms. On the other hand, an increase in K+ channels activity has also been shown to inhibit tumorigenesis through a downregulation of proliferation rates.

Ultimately, the net impact of glyburide on tumour cells remains poorly understood.[15] The current literature evaluating the impact of glyburide (and sulfonylureas in general) on cancer incidence and cancer-related mortality is highly discordant.[9,11-13,29-32] Additionally, most studies have not evaluated glyburide separately from other sulfonylureas and very little has been published on the impact of the drug on UBC.[11-13] Therefore, further studies of the impact of glyburide on DSS are needed to validate our findings. Nevertheless, our study does provide evidence of an association between an increase in UBC-related death and glyburide after adjusting for baseline characteristics. It is also important to note that this is not the first time that oral hypoglycemic agents have been implicated in UBC progression. Thiazolidinediones, a class of medications introduced in the late 1990s to treat type II DM, have recently been associated with a slightly higher risk of developing UBC.[22]

To the best of our knowledge, this study is the largest to evaluate the impact of metformin on UBC oncological outcomes, which makes it less prone to spurious findings compared to small single-institution cohorts. Moreover, although we restricted the population to individuals ≥66 years, our population-based design renders our findings more generalizable.

Nevertheless, this study does have limitations. First, our analysis was limited to individuals ≥66 years of age because of the inherent limitation of ODB coverage. As a result, it is unclear whether our findings apply to a younger population. Second, compliance to medication and reasons for medication changes over time are unknown. It is possible that changes in medication reflect varying severity of DM, which may, in turn, have impacted survival outcomes. Third, stage and pathological data were not readily available. Therefore, in order to define our NMIBC study population, we had to make assumptions (which have yet to be validated) regarding treatment delivery to define our cohort. We cannot exclude the possibility that some individuals with MIBC were included in the current study, although it is expected that the proportion of patients with MIBC managed with radical transurethral resection alone should be low. Similarly, it is possible that some very high-risk NMIBC were excluded because of early/immediate cystectomy within six months of diagnosis. However, given the progression rate of NMIBC and infrequent use of immediate cystectomy, it is suspected that only a small number of these patients were excluded for this reason. Fourth, we were also unable to capture the severity of diabetes, presence or absence of metabolic syndrome, body mass index, smoking status, and whether or not an individual received intravesical chemotherapy or Bacillus Calmette-Guerin treatment. These factors may have influenced our results. Fifth, we were unable to draw any meaningful conclusions with regards to the impact of thiazolidinedione, insulin, and other oral anti-diabetic agents due to the small number of patients who used these agents during the study period. Finally, we were not able to evaluate the impact of anti-diabetic drugs on disease recurrence or progression.

Conclusion

This large, population-based study provided strong evidence that metformin use was not associated with either improved DSS or OS among diabetic individuals diagnosed with NMIBC. Although metformin may have anti-neoplastic properties, our data do not support its use for NMIBC. Meanwhile, diabetic individuals taking glyburide were at increased risk of cancer-specific mortality compared to individuals not on this drug. Further studies are warranted to validate these findings.

Competing interests: Dr. Richard has attended advisory boards for BMS and Sanofi; and has been a speaker for AbbVie, Astellas, and Jasssen. Dr. Zlotta has attended advisory boards for Amgen, Astellas, Ferring, Paladin, and Sanofi; has received educational grants from Pfizer, Red Leaf Medical, and Sanofi; and has participated in clinical trials supported by Sanofi. Dr. Fleshner has been a consultant for Amgen, Astellas, and Janssen; has participated in clinical trials for Amgen, Astellas, Ferring, and Janssen; and has received grant funding from Canadian Cancer Society Research Institute and Prostate Cancer Canada. The remaining authors report no competing personal or financial interests related to this work.

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This paper has been peer-reviewed.

References

1. American Cancer Society. Cancer facts and figures 2015. Atlanta, Ga: American Cancer Society; 2015.
2. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol* 2013;63:234-41. https://doi.org/10.1016/j.eururo.2012.07.033
3. van der Heijden AG, Witjes JA. Recurrence, progression and followup in non-muscle-invasive bladder cancer. Eur *Urol* 2009;8:S556-62. https://doi.org/10.1016/j.eursup.2009.06.010
4. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49:466-77. https://doi.org/10.1016/j.eururo.2005.12.031

5. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2014 [cited 2016 February 23rd]. Available at: https://www.cdc.gov/diabetes/pdfs/data/2014-report-estimates-of-diabetes-and-its-burden-in-the-united-states.pdf. Accessed April 17, 2018.
6. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for developing a diabetes mellitus comprehensive care plan, 2015. *Endocr Pract* 2015;S1:1-87. https://doi.org/10.4158/EP15672.GLSUPPL
7. He XK, Su TT, Si JM, et al. Metformin is associated with slightly reduced risk of colorectal cancer and moderate survival benefits in diabetes mellitus: A meta-analysis. *Medicine (Baltimore)* 2016;95:e2749. https://doi.org/10.1097/MD.0000000000002749
8. Kozak MM, Anderson EM, von Eyben R, et al. Statin and metformin use prolongs survival in patients with resectable pancreatic cancer. *Pancreas* 2016;45:64-70. https://doi.org/10.1097/MPA.0000000000000470
9. Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *J Clin Oncol* 2013;31:3069-75. https://doi.org/10.1200/JCO.2012.46.7043
10. Zhang T, Guo P, Zhang Y, et al. The antidiabetic drug metformin inhibits the proliferation of bladder cancer cells in vitro and invo. *Int J Mol Sci* 2013;14:24603-18. https://doi.org/10.3390/ijms141224603
11. Nayan M, Bhindi B, Yu JL, et al. The effect of metformin on cancer-specific survival outcomes in diabetic patients undergoing radical cystectomy for urothelial carcinoma of the bladder. *Urol Oncol* 2015;33:386.e7-13. https://doi.org/10.1016/j.urolonc.2015.05.024
12. Rieken M, Xylinas E, Kluth L, et al. Association of diabetes mellitus and metformin use with oncological outcomes of patients with non-muscle-invasive bladder cancer. *BJU Int* 2013;112:1105-12. https://doi.org/10.1111/bju.12448
13. Rieken M, Xylinas E, Kluth L, et al. Effect of diabetes mellitus and metformin use on oncologic outcomes of patients treated with radical cystectomy for urothelial carcinoma. *Urol Oncol* 2014;32:49.e7-14. https://doi.org/10.1016/j.urolonc.2013.07.006
14. Bortner CD, Cidlowski JA. Ion channels and apoptosis in cancer. *Philos Trans R Soc Lond B Biol Sci* 2014;369:20130104. https://doi.org/10.1098/rstb.2013.0104
15. Wang Z. Role of K+ channels in regulating tumour cell proliferation and apoptosis. *Pflugers Arch* 2004;448:274-86. https://doi.org/10.1007/s00424-004-1258-5
16. Robles S, Marrett L, Clarke E, Risch H. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 1988;41:495-501. https://doi.org/10.1016/0895-4356(88)90052-2
17. Holowaty E, Moravan V, Lee G, et al. A reabstraction study to estimate the completeness and accuracy of data elements in the Ontario Cancer Registry. Report submitted to Health Canada. 1996.
18. Juurlink D, Preyra C, Croxford R, et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: Institute for Clinical Evaluative Science, 2006.
19. Hux JE, Ivis F, Flintoft V, et al. Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512-6. https://doi.org/10.2337/diacare.25.3.512
20. Levy AR, O'Brien BJ, Sellors C, et al. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol* 2003;10:67-71.
21. Nayan M, Juurlink DN, Austin PC, et al. Medication use and kidney cancer risk: A population-based study. *Eur J Cancer* 2017;83:203-10. https://doi.org/10.1016/j.ejca.2017.07.001
22. Ferwana M, Firwana B, Hasan R, et al. Pioglitazone and risk of bladder cancer: A meta-analysis of controlled studies. *Diabet Med* 2013;30:1026-32. https://doi.org/10.1111/dme.12144
23. Austin PC BL. Inflation of the type I error rate when a continuous confounding variable is categorized in logistic regression analyses. *Stat Med* 2004;23:1159-78. https://doi.org/10.1002/sim.1687
24. Zakikhani M, Dowling RJ, Sonenberg N, et al. The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. *Cancer Prev Res (Phila)* 2008;1:369-75. https://doi.org/10.1158/1940-6207.CAPR-08-0081
25. Chiong E, Lee IL, Dadbin A, et al. Effects of mTOR inhibitor everolimus (RAD001) on bladder cancer cells. *Clin Cancer Res* 2011;17:2863-73. https://doi.org/10.1158/1078-0432.CCR-09-3202
26. Makhlin I, Zhang J, Long CJ, et al. The mTOR pathway affects proliferation and chemosensitivity of urothelial carcinoma cells and is upregulated in a subset of human bladder cancers. *BJU Int* 2011;108:E84-90. https://doi.org/10.1111/j.1464-410X.2010.09844.x
27. MacKenzie T, Zens MS, Ferrara A, et al. Diabetes and risk of bladder cancer: Evidence from a case-control study in New England. *Cancer* 2011;117:1552-6. https://doi.org/10.1002/cncr.25641
28. Luzi L, Pozza G. Glibenclamide: An old drug with a novel mechanism of action? *Acta Diabetol* 1997;34:239-44. https://doi.org/10.1007/s005920050081
29. Ruiter R, Visser LE, van Herk-Sukel MP, et al. Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: Results from a large, population-based, followup study. *Diabetes Care* 2012;35:119-24. https://doi.org/10.2337/dc11-0857
30. Bo S, Castiglione A, Ghigo E, et al. Mortality outcomes of different sulphonylurea drugs: The results of a 14-year cohort study of type 2 diabetic patients. *Eur J Endocrinol* 2013;169:117-26. https://doi.org/10.1530/EJE-13-0299
31. Bowker SL, Majumdar SR, Veugelers P, JA. J. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006;29:254-8. https://doi.org/10.2337/diacare.29.02.06.dc05-1558
32. Gandini S, Puntoni M, Heckman-Stoddard BM, et al. Metformin and cancer risk and mortality: A systematic review and meta-analysis taking into account biases and confounders. *Cancer Prev Res (Phila)* 2014;7:867-85. https://doi.org/10.1158/1940-6207.CAPR-13-0424

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Supplementary Table 1. Ontario Health Insurance Plan (OHIP) physician billing claims used to identify bladder cancer-related management

Billing claims – code	Fee code: OHIP definition
Cystectomy	Cystectomy – partial: S482; S483; S490 Cystectomy – complete: S484; S485; S453; S440
Chemotherapy	Complex single agent or multi-agent therapy: G345 Special single agent or multi-agent therapy: G359
Radiotherapy	Level 1 – Simple treatment planning: X310 Level 2 – Intermediate treatment planning: X311 Level 3 – Complex treatment planning: X312 Level 4 – Full 3D treatment preparation: X313

Supplementary Table 2. Studied drugs and drug identifier numbers used

Drug names	Drug identifier numbers
Metformin	02148765; 00990329; 02167786; 02162822; 02099233 02233999; 02045710; 02230026; 02229516; 02223562 00314552; 02257726; 02388766; 02380722; 02380196 02379767; 02378841; 02242974; 02353377; 02378620 02246820; 02242794; 02269031; 02162849; 02230475 02333872; 02333856; 02333864
Glyburide	00454753; 00808733; 00720933; 02224550; 02236733; 01913670; 01913654; 02230036; 02020734; 01987534; 01900927; 02248008; 02350459; 02248009; 02350467; 02236734; 01913689; 01913662; 02230037; 02020742; 01900935; 02224569; 01987836; 00012599; 00808741; 00720941
Other anti-diabetic drugs	
Other sulfonyureas	
Chlorpropamide Gliclazide Tolbutamide Glimepiride	00399302; 00024708; 00024716; 00021350; 00377937; 00312711; 02297795; 02242987; 02356422; 02245247; 02294400; 02229519; 02238103; 00765996; 00012602; 00013889; 00021849; 00093033; 00312762; 02375842;02333554; 02245272
DPP4	
Sitagliptin Saxagliptin	02303922; 02388839; 02388847; 00012602; 00013889; 00021849; 00093033; 00312762; 02375842; 02333554
Meglitinides	
Nateglinide Repaglinide	02245439; 02245440; 02245438; 02357453; 02355663; 02354926; 02239924; 02239925; 02357461; 02355671; 02354934; 02357488; 02355698; 02354942; 02239926; 02321475; 02321483; 02321491
Thiazolidinedione	
Pioglitazone Rosiglitazone	02241112; 02241113; 02241114; 02245272; 02303442; 02303124; 02302942; 02302861; 02242572; 02301423; 02298279; 02297906; 02397307; 02391600; 02384906; 02375850; 02274914; 02326477; 02307677; 02303450; 02303132; 02242573; 02302950; 02302888; 02301431; 02298287; 02297914; 02375869; 02384914; 02365529; 02274922; 02339587; 02326485; 02307723; 02242574; 02303469; 02303140; 02302977; 02302896; 02301458; 02298295; 02297922; 02384922; 02375877; 02365537; 02274930; 02339595; 02326493
Insulin	00587737; 00612197; 01959239; 00981044; 09853804; 09853782; 02024268; 02024225; 01959220; 00983870; 02024284; 02024233; 01986805; 00632686; 00586714; 09853774; 09853774; 09853766; 00612189; 00980765; 00795879; 00773654; 00632694; 01959212; 00981052; 01986821; 01985973; 09851925; 09853855; 09853871; 09853863; 09853847; 09853839; 09853812; 01962663; 01962639; 01962655; 00889121; 00889105; 00889091; 01962647; 02025248; 02024322; 02024314; 02024306; 02024292; 02024217; 00650925; 00733075; 00612200; 00646148; 00644358; 02024276; 02024241

Supplementary Table 3. Results of the multivariable models for the two sensitivity analyses assessing the impact of oral hypoglycemic use post-NMIBC diagnosis

Models (n)	Post-NMIBC exposure, per year of use*	Disease-specific survival	Overall survival
		HR (95% CI)	HR (95% CI)
Sensitivity analysis #1 (n=2092)†	Metformin	1.1 (0.93–1.2)	0.96 (0.92–1.0)
	Glyburide	1.26 (1.1–1.4)	1.0 (0.97–1.1)
	Thiazolidinedione	0.55 (0.24–1.3)	0.92 (0.78–1.1)
	Other oral anti-diabetic agents	0. 81 (0.49–1.3)	1.0 (0.94–1.2)
	Insulin	1.3 (0.84–1.9)	1.1 (0.98–1.2)
Sensitivity analysis #2 (n=1222)‡	Metformin	0.95 (0.77–1.2)	0.93 (0.88–0.99)
	Glyburide	1.05 (0.81–1.4)	1.02 (0.96–1.09)
	Thiazolidinedione	0.73 (0.27–2.0)	1.07 (0.87–1.3)
	Other oral anti-diabetic agents	0.46 (0.15–1.4)	0.97 (0.85–1.1)
	Insulin	1.7 (1.1–2.4)	1.1 (0.87–1.3)

*Models adjusted for year of diagnosis, age at non-muscle-invasive bladder cancer (NMIBC), time between DM and NMIBC diagnosis, gender, area of residency, neighbourhood income quintile, Charlson comorbidity score and baseline use of anti-diabetic agents. †Cohort composed of individuals included in the main cohort and including individuals who died within six months of NMIBC diagnosis. ‡Cohort restricted to individuals diagnosed with DM and NMIBC after 1996. CI: confidence interval; HR: hazard ratio.