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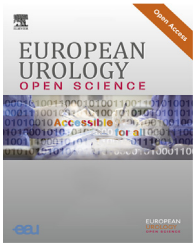

European Association of Urology

Prostate Cancer

Prostate Cancer–specific Survival After Radical Prostatectomy Is Improved Among Metformin Users but Not Among Other Antidiabetic Drug Users

Roni M. Joentausta [a,*], *Antti Rannikko* [b], *Teemu J. Murtola* [a,c]

[a] *Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland;* [b] *Department of Urology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland;* [c] *TAYS Cancer Center, Department of Urology, Tampere, Finland*

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Abstract

Background: Metformin has been linked to improved survival among diabetic prostate cancer (PCa) patients, while hyperinsulinemia and insulin usage has been related to worse prognosis.
Objective: To evaluate the association of metformin and other antidiabetic drugs with PCa death and androgen deprivation therapy (ADT).
Design, setting, and participants: The study cohort included 14 424 men who underwent radical prostatectomy in Finland during 1995–2013. Cases were identified, and clinical data were collected from patient files and national registries using personal identification numbers.
Intervention: Information on the use of each antidiabetic drug during 1995–2014 was collected from prescription registry of the Social Insurance Institution of Finland.
Outcome measurements and statistical analysis: The risks of PCa death and initiation of ADT were analyzed by antidiabetic drug use with the Cox regression method. Each antidiabetic drug group was analyzed separately to model simultaneous usage. Pre- and postdiagnostic uses were analyzed separately.
Results and limitations: Prediagnostic use of antidiabetic drugs in general had no association with the risk of PCa death. Prediagnostic use of metformin was related to a reduced risk of ADT initiation (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.59–0.96), while high-dose insulin users had an increased risk. Overall, antidiabetic drug use after PCa diagnosis was associated with an elevated risk of PCa death. Only postdiagnostic metformin use was associated with reduced risks of PCa death (HR 0.47, 95% CI 0.30–0.76) and ADT initiation compared with nonusers. Study limitations are missing information on glycemic control, smoking, living or exercise habits, prostate-specific antigen, and Gleason score.
Conclusions: Among surgically treated PCa patients, use of metformin was associated with improved disease-specific survival, while insulin and insulin

* Corresponding author at: Arvo Ylpön katu 34, 33520 Tampere, Finland. Tel.: +3582945211.
E-mail address: roni.joentausta@fimnet.fi (R.M. Joentausta).

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secretagogues were associated with poor survival. Metformin might be a favorable diabetes treatment among men with PCa.

Patient summary: In this Finnish nationwide study, we found that the risks of prostate cancer death and cancer progression are lowered among metformin users, but not among other antidiabetic drug users. Metformin might be a favorable treatment choice for diabetes in men with prostate cancer.

1. Introduction

Hyperglycemia, increased insulin secretion, and insulin resistance have been proposed to act in carcinogenesis. Metformin increases insulin sensitivity and reduces gluconeogenesis, leading to decreased plasma glucose and insulin levels [1] Metformin has been suggested to have antitumorigenic actions. By activating AMP kinase, metformin leads to inhibition of mTOR, which is important to many functions of cells, for example, angiogenesis, metabolism, cell growth, and proliferation. Metformin might have beneficial hormonal and inflammatory functions against cancer [2].

Type 2 diabetes mellitus is linked with an increased risk of high-grade prostate cancer (PCa) [3]. Among diabetic men, poor glycemic control seems to be associated with increased risks of metastatic and castration-resistant PCa [4] and PCa death [5]. However, men with diabetes might be also less often eligible for curative treatment [6].

On the contrary, antidiabetic drug (AD) use might influence PCa outcomes. Metformin has preventive effects against PCa in laboratory studies, but the risk associations have been contradictory in epidemiological studies. Metformin use is associated with a decreased PCa risk among men with benign prostate hyperplasia [7]. However, a meta-analysis of observational studies suggests that metformin has no association with PCa risk [8,9]. Still, metformin usage has been linked to improved PCa-specific and recurrence-free survival [9].

While beneficial effects have been suggested for metformin, use of other ADs such as sulfonylureas and insulin may increase the risks of high-grade PCa and disease progression [10]. Sulfonylureas increase blood insulin levels. Both hyperglycemia and hyperinsulinemia may be risk factors for PCa [5,11].

In our previous study cohort of 1314 surgically treated PCa patients, diabetic men had an increased risk of high-grade PCa. The risk was highest among metformin users, but was not reflected in disease progression or death [12]. To evaluate PCa death in men with surgically managed PCa, the study population must be large and follow-up time long. To estimate the potential antineoplastic role of metformin after prostatectomy, we performed a nationwide cohort study with a median follow-up of 8 yr after surgery. To distinguish the possible effect of metformin from that of the underlying diabetes, we also analyzed other ADs with the assumption that diabetes would affect the risk estimates for all ADs similarly.

2. Patients and methods

2.1. Study population

The study cohort consists of 14 424 men with PCa who underwent radical prostatectomy in Finland during 1995–2013. The procedure code of radical prostatectomy was used to identify men from the Care Registry of the Finnish Institute for Health and Welfare (FIHW). Age, date of diagnosis, and clinical TNM stage were gathered from patient archives. Statistics Finland maintains a comprehensive national database of causes of deaths, reported using ICD-10 codes. Progression of PCa after surgery is often managed by androgen deprivation therapy (ADT). Information on ADT use during 1995–2014 was gathered from Social Insurance Institution of Finland (SII) prescription registry and from the Care Registry of the FIHW (Supplementary Table 1). Data between registries were linked using personal identification numbers.

2.2. Information on AD use

As part of national health insurance, Finnish residents receive reimbursements for the price of physician-prescribed drug purchases. Each reimbursed purchase is registered to the SII database. The database includes information on ATC code, date, dose, and amount for each purchase. All purchases of ADs during 1995–2014 were collected from the database (Supplementary Table 1).

AD uses were separated by the mechanism of action to metformin, drugs increasing insulin secretion, insulins, and glitazones (Supplementary Table 2).

2.3. Information on comorbidities and other drug use

Information on radiation or chemotherapy for PCa during 1996–2014 as an adjuvant or secondary treatment was collected from the FIHW Care Registry. The information was collected using procedure codes classified by NCPS. Diagnoses are registered using ICD-10 codes. Main comorbidities collected from the database were hypercholesterolemia, arterial hypertension, type 1 and 2 diabetes mellitus, coronary artery disease (CAD), and obesity (Supplementary Table 1).

Comorbidity data were complemented with medication use for hypercholesterolemia, arterial hypertension, and CAD (Supplementary Table 1). The data of drug use and recorded diagnoses were combined to form one variable for each comorbidity.

2.4. Statistical analysis

Apart from analyses evaluating overall risk association by AD use, all AD groups were analyzed separately. Participants categorized as users in one group could also be included in one or more other groups, depending on registered purchases. For example, patients using both insulin and metformin were categorized as users of insulin and metformin. The amount (mg/IU) of yearly use of each drug was calculated by the number of packages bought yearly, multiplied by package size and the amount (mg [IU])

per dose. To quantify usage across ADs, the yearly amount of drug use was divided by the drug-specific defined daily dose (DDD) [13]. Duration of use was determined as the number of years with at least one purchase. Intensity of medication use (DDDs per year) was calculated by dividing the cumulative DDD amount by the duration of usage.

Prediagnostic use of ADs was determined as the use occurring before PCa diagnosis. AD use during or after the year of diagnosis was determined as postdiagnostic use. Amount, duration, and intensity of AD use were stratified by median for prediagnostic use and by tertiles for postdiagnostic use.

In order to minimize protopathic bias, we employed lag-time analysis [14]. The risk association was reanalyzed with a time lag of 1, 3, or 5 yr. For example, in the 3-yr lag-time analysis, the risks of PCa death and ADT initiation in 2003 were analyzed by AD use occurring in 2000. Lag-time variables were calculated for all ADs, metformin, drugs increasing insulin secretion, and insulins.

In sensitivity analyses, the risk associations were evaluated among new users, that is, men with no record of prediagnostic AD use. The risks of PCa death and ADT initiation were calculated for new users of all ADs, metformin, insulins, and drugs increasing insulin secretion. A competing risk analysis, where death due to other causes was analyzed as a competing risk to PCa death, was used to evaluate postdiagnostic AD use. The risk of all-cause death was calculated for each AD subgroups and intensity groups of AD usage, to evaluate whether there is any difference between PCa-specific and overall mortality.

Follow-up started in the year of PCa diagnosis; the endpoint was death, end of year 2014, or emigration, whichever came first. ADT initiation was an additional endpoint in the analyses of the risk of disease progression.

Analyses were adjusted for age, additionally in multivariable-adjusted analysis for tumor stage at diagnosis, chemotherapy, radiation therapy, statin use, hypertension, CAD, and obesity.

IBM SPSS statistics 25 software (Chicago, IL, USA) was used in all analyses. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) for the risks of PCa death and ADT initiation. The risk estimates were calculated with Cox regression. Prediagnostic AD use was analyzed as a time-fixed variable. Postdiagnostic use of ADs was analyzed as a time-dependent variable, where the user status was updated for each follow-up year according to purchases, to minimize immortal time bias [14]. All participants with no baseline medication usage remained as nonusers until the year of first AD purchase. All p values are two sided.

FIHW approved the study protocol (THL/490/5.05.00/2016).

3. Results

3.1. Population characteristics

Among metformin users, a lower proportion of men died during follow-up than nonusers. All comorbidities were more common among AD users than among nonusers. Prediagnostic metformin users had more often radiation therapy as an adjuvant treatment. Otherwise, there was no difference in the use of radiation therapy or chemotherapy. ADT usage was slightly less common among prediagnostic users of metformin or glitazones than among nonusers. ADT was more common among postdiagnostic AD users than among nonusers (Table 1).

3.2. Risks of PCa death and ADT initiation by AD use before PCa diagnosis

During the follow-up, 21/1000 men among AD users died of PCa, whereas 30/1000 died among the nonusers. Prediagnostic AD use showed no association with the risk of PCa death compared with nonusers (multivariable-adjusted HR 1.04, 95% CI 0.67–1.60). Increasing duration, and the amount and intensity of AD use overall tended toward a decreased risk of PCa death. In a drug group analysis, the risk of PCa death did not differ significantly for any AD (Table 2 and Supplementary Table 3).

The risk of ADT initiation was lower among AD users than among the nonusers, with risk estimates approaching statistical significance (HR 0.86, 95% CI 0.74–1.01). The association was driven by metformin users. Metformin users had a significantly reduced risk of ADT initiation (HR 0.75, 95% CI: 0.59–0.96) compared with nonusers. No logical dose dependence by cumulative usage was observed; the risk association was attenuated by increasing intensity of metformin use. Among insulin users, the risk of ADT initiation was elevated with high-intensity use (Table 2).

3.3. Risks of PCa death and ADT initiation by AD use after PCa diagnosis

Among men with postdiagnostic AD use, PCa death occurred in 27/1000 men during the follow-up and in 30/1000 nonusers. AD users had a significantly higher overall risk of PCa death after multivariable adjustment (HR 1.41, 95% CI 1.07–1.87). The association was not dose dependent. Postdiagnostic use of ADs increasing insulin secretion was clearly associated with an increased risk of PCa death (HR 3.04, 95% CI 1.98–4.67). Again, the risk association was not dose dependent (Table 3).

In an age-adjusted analysis, postdiagnostic use of insulin was associated with an elevated risk of PCa death compared with nonusers (HR 1.79, 95% CI 1.07–2.99). The association was statistically significant only in the lowest-intensity users. The risk increase was no longer significant after multivariable adjustment (Table 3).

Postdiagnostic use of metformin had a strong inverse association with PCa death (HR 0.47, 95% CI 0.30–0.76). The association was not dependent on the amount of metformin use. Decreased risk estimates were observed in all strata of cumulative metformin use (Table 3 and Supplementary Table 3).

Overall, postdiagnostic AD use had no association with the risk of ADT initiation. Compared with nonusers, men using drugs increasing insulin secretion had a higher risk of starting ADT (HR 1.37, 95% CI 1.11–1.70). The risk estimates remained statistically significant only in low-intensity use. Using insulin after PCa diagnosis was not clearly related to the risk of ADT initiation. Metformin users had a decreased risk of ADT initiation (HR 0.73, 95% CI 0.61–0.88) compared with nonusers. The risk estimates were tending toward a diminished risk of ADT initiation with any intensity of postdiagnostic metformin use (Table 3).

3.4. Sensitivity analyses

Use of ADs overall had no statistically significant association with the risk of PCa death or initiation of ADT compared with nonusers in 1-, 3-, and 5-yr lag-time analyses. Drugs increasing insulin secretion remained associated with increased risks of PCa death and ADT initiation only in short

Table 1 – Population characteristics: pre- and postdiagnostic use of antidiabetic drugs compared with nonusers

	Prediagnostic use of antidiabetic drugs					No use of antidiabetic drugs
	All antidiabetic drugs	Metformin	Insulin	Drugs increasing insulin secretion	Glitazones	
Number of men	1044	668	191	518	89	13 380
Age at diagnosis[a]	63.0 (59.0–67.0)	63.0 (60.0–67.0)	63.0 (58.0–66.0)	64.0 (59.8–67.0)	63.0 (58.0–66.0)	62.0 (57.0–66.0)
PCa death, *n* (%)	22 (2.1)	9 (1.3)	4 (2.1)	16 (3.1)	0 (0)	405 (3.0)
Death, *n* (%)	109 (10.4)	50 (7.5)	28 (14.7)	81 (15.6)	5 (5.6)	1473 (11.0)
Follow-up time[a]	6.3 (3.9–10.5)	5.3 (3.4–8.1)	6.6 (4.0–10.8)	7.9 (4.4–11.6)	4.6 (3.5–6.5)	8.6 (5.2–12.2)
Comorbidities, *n* (%)						
Use of cholesterol-lowering drugs	806 (77.2)	549 (82.8)	157 (82.2)	377 (72.8)	74 (83.1)	6433 (48.1)
Obesity[b]	27 (2.6)	21 (3.1)	7 (3.7)	13 (2.5)	4 (4.5)	121 (0.9)
Hypertension	890 (85,2)	588 (88.0)	172 (90.1)	493 (95.2)	76 (85.4)	8981 (67.1)
Coronary artery disease	328 (31,4)	212 (31.7)	76 (39.8)	190 (36.7)	26 (29.2)	3110 (23.2)
Additional treatments after prostatectomy, *n* (%)						
Chemotherapy	3 (0.3)	2 (0.3)	2 (1.0)	2 (0.4)	0 (0)	56 (0.4)
Radiation therapy	49 (5.7)	40 (6.0)	8 (4.2)	24 (4.6)	6 (6.7)	520 (3.9)
ADT	173 (16.6)	100 (15.0)	39 (20.4)	107 (20.7)	9 (10.1)	2676 (20.0)
	Postdiagnostic use of antidiabetic drugs					
	All antidiabetic drugs	Metformin	Insulin	Drugs increasing insulin secretion	Glitazones	
Number of men	2332	2042	503	1043	130	12 092
Age at diagnosis[a]	62.0 (58.0–66.0)	62.0 (58.0–66.0)	63.0 (58.0–67.0)	63.0 (59.0–66.0)	62.0 (58.0–66.0)	62.0 (57.0–66.0)
PCa death, *n* (%)	63 (2.8)	35 (1,7)	21 (4.2)	45 (4.3)	1 (0.8)	364 (3.0)
Death, *n* (%)	285 (12.2)	190 (9.3)	101 (20.1)	181 (17.4)	13 (10 5)	1297 (10.7)
Follow-up time[a]	9.3 (5.6–13.1)	9.25 (5.7–13.0)	9.9 (5.6–13.5)	10.1 (6.1–13.9)	8.8 (5.8–11.0)	8.3 (5.0–11.8)
Comorbidities, *n* (%)						
Use of cholesterol-lowering drugs	1803 (77.3)	1607 (78.7)	398 (79.1)	797 (76.4)	110 (84.6)	5436 (45.0)
Obesity[b]	51 (2.1)	44 (2.1)	15 (3.0)	31 (3.0)	6 (4.6)	97 (0.8)
Hypertension	2079 (89.2)	1821 (89.2)	468 (93.0)	954 (91.5)	117 (90.0)	7792 (64.4)
Coronary artery disease	800 (34.3)	677 (33.2)	230 (45.7)	415 (39.8)	43 (33.1)	2638 (21.8)
Additional treatments after prostatectomy, *n* (%)						
Chemotherapy	7 (0.3)	4 (0.2)	3 (0.6)	3 (0.3)	0 (0)	52 (0.4)
Radiation therapy	85 (3.6)	75 (3.7)	22 (4.4)	33 (3.2)	6 (4.6)	484 (4.0)
ADT	524 (22.4)	440 (21.5)	130 (25.8)	288 (27.6)	25 (0.2)	2325 (19.2)

Only variables with $p < 0.05$ in univariable analysis were included in multivariable analysis (MVA).
[a] Median years (IQR).
[b] Obesity recorded by using diagnostic code E66.

Table 2 – Risk of PCa death and initiation of ADT by prediagnostic use of antidiabetic drugs compared with nonusers

Prediagnostic use	Risk of PCa death		Risk of initiation of ADT	
	Age adjusted HR (95% CIs)	Multivariable adjusted model HR (95% CIs)	Age adjusted HR (95% CIs)	Multivariable adjusted model HR (95% CIs)
Antidiabetic drugs				
Any use	0.86 (0.56–1.33)	1.04 (0.67–1.60)	0.88 (0.75–1.02)	0.86 (0.74–1.01)
Intensity of use (DDDs/yr)				
<245	0.98 (0.57–1.71)	1.26 (0.72–2.20)	0.80 (0.64–0.99)	0.81 (0.64–1.01)
>245	0.74 (0.38–1.43)	0.82 (0.43–1.60)	0.96 (0.78–1.18)	0.92 (0.75–1.14)
Drugs increasing insulin secretion				
Any use	1.28 (0.73–2.25)	1.45 (0.81–2.59)	1.09 (0.87–1.37)	1.14 (0.91–1.44)
Intensity of use (DDDs/yr)				
<262.5	1.19 (0.57–2.47)	1.43 (0.68–3.02)	1.23 (0.94–1.61)	1.29 (0.98–1.70)
>262.5	1.46 (0.67–3.20)	1.51 (0.69–3.32)	0.94 (0.67–1.31)	0.96 (0.69–1.35)
Insulin				
Any use	0.93 (0.33–2.60)	0.98 (0.35–2.75)	1.25 (0.89–1.76)	1.25 (0.89–1.76)
Intensity of use (DDDs/yr)				
<300	1.21 (0.36–4.07)	1.34 (0.40–4.52)	0.98 (0.59–1.61)	0.98 (0.59–1.63)
>300	0.48 (0.07–3.47)	0.50 (0.07–3.61)	1.54 (1.00–2.37)	1.54 (1.00–2.39)
Metformin				
Any use	0.72 (0.34–1.51)	0.77 (0.35–1.65)	0.82 (0.65–1.04)	0.75 (0.59–0.96)
Intensity of use (DDDs/yr)				
<224.82	0.55 (0.20–1.54)	0.59 (0.21–1.67)	0.75 (0.55–1.02)	0.70 (0.52–0.96)
>224.82	0.80 (0.29–2.18)	0.82 (0.29–2.28)	0.94 (0.68–1.31)	0.85 (0.61–1.18)

ADT = androgen deprivation therapy; CI = confidence interval; DDD = defined daily dose; HR = hazard ratio; PCa = prostate cancer.
The amount and duration of antidiabetic drug use are shown in Supplementary Table 3.

Table 3 – Risk of PCa death and initiation of ADT by postdiagnostic use of antidiabetic drugs compared with nonusers

Postdiagnostic use	Risk of PCa death		Risk of initiation of ADT	
	Age adjusted OR (95% CIs)	Multivariable adjusted model OR (95% CIs)	Age adjusted OR (95% CIs)	Multivariable adjusted model OR (95% CIs)
Antidiabetic drug use				
Any use	1.17 (0.89–1.54)	1.41 (1.07–1.87)	1.02 (0.90–1.15)	1.00 (0.88–1.14)
Intensity of use (DDDs/yr)				
≤195	1.13 (0.70–1.84)	1.40 (0.86–2.28)	0.92 (0.73–1.17)	0.93 (0.73–1.18)
195–<431	1.49 (0.97–2.29)	1.73 (1.11–2.67)	0.97 (0.78–1.22)	0.94 (0.75–1.18)
≥431	0.83 (0.48–1.44)	1.03 (0.32–1.79)	1.08 (0.89–1.32)	1.06 (0.87–1.30)
Drugs increasing insulin secretion				
Any use	2.73 (1.79–4.15)	3.04 (1.98–4.67)	1.36 (1.10–1.69)	1.37 (1.11–1.70)
Intensity of use (DDDs/yr)				
≤248	3.11 (1.85–5.24)	3.44 (2.02–5.86)	1.51 (1.13–2.01)	1.52 (1.14–2.03)
248–<359	3.82 (1.94–7.54)	4.42 (2.22–8.81)	1.28 (0.85–1.95)	1.32 (0.87–2.00)
≥359	1.06 (0.43–2.64)	1.26 (0.51–3.14)	1.05 (0.75–1.47)	1.03 (0.73–1.44)
Glitazones				
Any use	0.19 (0.03–1.37)	0.20 (0.03–1.47)	0.94 (0.58–1.53)	0.92 (0.57–1.50)
Intensity of use (DDDs/yr)				
≤217	–	–	1.65 (0.81–3.57)	1.59 (0.78–3.24)
217–<325	1.55 (0.21–11.45)	1.47 (0.20–10.95)	0.25 (0.04–1.80)	0.24 (0.03–1.68)
≥325	–	–	1.05 (0.46–2.40)	1.09 (0.48–2.48)
Insulin				
Any use	1.79 (1.07–2.99)	1.58 (0.95–2.63)	1.24 (0.95–1.62)	1.22 (0.94–1.59)
Intensity of use (DDDs/yr)				
≤206	3.49 (1.49–8.14)	3.66 (1.56–8.60)	1.66 (1.03–2.68)	1.72 (1.08–2.77)
206–<442	2.31 (1.03–5.16)	2.73 (0.77–3.88)	1.02 (0.64–1.62)	1.01 (0.63–1.61)
≥442	0.98 (0.31–3.16)	1.11 (0.34–3.59)	1.28 (0.84–1.95)	1.28 (0.83–1.96)
Metformin				
Any use	0.40 (0.25–0.63)	0.47 (0.30–0.76)	0.75 (0.62–0.90)	0.73 (0.61–0.88)
Intensity of use (DDDs/yr)				
≤176	0.36 (0.17–0.76)	0.43 (0.20–0.90)	0.62 (0.46–0.84)	0.62 (0.45–0.84)
176–<303	0.34 (0.16–0.74)	0.39 (0.18–0.86)	0.84 (0.63–1.11)	0.82 (0.62–1.09)
≥303	0.41 (0.20–0.85)	0.46 (0.22–0.94)	0.81 (0.61–1.09)	0.79 (0.59–1.06)

ADT = androgen deprivation therapy; CI = confidence interval; DDD = defined daily dose; OR = odds ratio; PCa = prostate cancer.
The amount and duration of antidiabetic drug use are shown in Supplementary Table 3.

term. The association with PCa death was lost with 5-yr lag time and with initiation of ADT was lost with 3-yr lag time. Among insulin users, the risk of ADT initiation was elevated nonsignificantly in the 1-yr lag-time analysis, but no difference in 3-yr lag time. Use of metformin lost the beneficial association with PCa death in 5-yr lag time; the association with the risk of ADT initiation was lost with 3-yr lag time (Table 4).

In a new-user analysis, that is, after exclusion of all prediagnostic AD users, no clear difference from the main analysis was observed. The risk increase was stronger among postdiagnostic users of insulin and drugs increasing insulin secretion than among nonusers (Table 5). In a competing-risk analysis, the risk of PCa death remained statistically significantly decreased among metformin users and increased among insulin users, when noncancer deaths were analyzed as the competing cause of death (Supplementary Table 4).

The risk of all-cause death was increased among men using ADs and drugs increasing insulin secretion compared with that among nonusers. Postdiagnostic insulin users had

Table 4 – Lag-time analysis

Lag-time analysis	Risk of PCa death		Risk of initiation of ADT	
	Age adjusted OR (95% CIs)	Multivariable adjusted model OR (95% CIs)	Age adjusted OR (95 % CIs)	Multivariable adjusted model OR (95 % CIs)
All antidiabetic drug use				
1 yr lag time	1.01 (0.76–1.34)	1.13 (0.84–1.52)	1.06 (0.93–1.21)	1.00 (0.87–1.14)
3 yr lag time	0.96 (0.69–1.33)	1.06 (0.76–1.48)	1.10 (0.94–1.28)	1.03 (0.89–1.21)
5 yr lag time	1.06 (0.74–1.51)	1.16 (0.80–1.67)	1.15 (0.96–1.38)	1.10 (0.91–1.32)
Drugs increasing insulin secretion				
1 yr lag time	2.35 (1.53–3.61)	2.59 (1.67–4.01)	1.37 (1.10–1.70)	1.37 (1.10–1.71)
3 yr lag time	1.86 (1.15–3.01)	2.08 (1.28–3.40)	1.23 (0.95–1.58)	1.24 (0.97–1.60)
5 yr lag time	1.41 (0.82–2.45)	1.60 (0.92–2.80)	1.24 (0.92–1.66)	1.26 (0.94–1.69)
Metformin				
1 yr lag time	0.43 (0.27–0.68)	0.51 (0.32–0.82)	0.77 (0.64–0.94)	0.75 (0.62–0.91)
3 yr lag time	0.49 (0.29–0.83)	0.58 (0.34–0.99)	0.87 (0.70–1.09)	0.84 (0.68–1.05)
5 yr lag time	0.69 (0.39–1.23)	0.83 (0.47–1.48)	0.96 (0.73–1.26)	0.93 (0.71–1.22)
Insulin				
1 yr lag time	1.17 (0.64–2.12)	1.05 (0.58–1.89)	1.30 (0.99–1.70)	1.29 (0.98–1.70)
3 yr lag time	0.78 (0.35–1.74)	0.71 (0.32–1.56)	1.17 (0.84–1.62)	1.18(0.85–1.64)
5 yr lag time	0.98 (0.44–2.21)	0.90 (0.40–2.00)	1.06 (0.72–1.58)	1.09 (0.73–1.62)

ADT = androgen deprivation therapy; CI = confidence interval; OR = odds ratio; PCa = prostate cancer.
Risks of PCa death and initiation of ADT by 1-, 3-, and 5-yr lag time of postdiagnostic use of antidiabetic drugs.

Table 5 – Analysis restricted to patients with no use of antidiabetic drug before diagnosis

New users after diagnosis	Risk of PCa death		Risk of ADT initiation	
	Age adjusted OR (95% CIs)	Multivariable adjusted model OR (95% CIs)	Age adjusted OR (95% CIs)	Multivariable adjusted model OR (95% CIs)
Antidiabetic drugs				
Any use	1.16 (0.84–1.62)	1.39 (1.00–1.95)	1.07 (0.89–1.29)	1.06 (0.88.–1.28)
Intensity of use (DDDs/yr)				
≤195	0.98 (0.56–1.70)	1.19 (0.68–2.09)	0.87 (0.65–1.17)	0.88 (0.66–1.17)
195–<431	1.49 (0.90–2.46)	1.79 (1.08–2.97)	1.21 (0.88–1.65)	1.18 (0.86–1.61)
≥431	0.71 (0.27–1.91)	0.85 (0.32–2.30)	1.21 (0.76–1.93)	1.15 (0.72–1.83)
Drugs increasing insulin secretion				
Any use	3.24 (1.96–5.34)	3.24 (1.96–5.34)	1.84 (1.37–2.48)	1.89 (1.41–2.53)
Intensity of use				
≤248	3.24 (1.77–5.91)	3.67 (1.99–6.79)	1.78 (1.22–2.60)	1.80 (1.23–2.64)
248–<359	3.05 (1.25–7.44)	3.35 (1.36–8.29)	1.77 (0.98–3.19)	1.75 (0.97–3.15)
≥359	0.88 (0.24–3.19)	1.06 (0.29–3.82)	1.35 (0.68–2.69)	1.43 (0.72–2.83)
Insulin				
Any use	3.66 (1.85–7.24)	3.66 (1.85–7.24)	1.92 (1.08–3.41)	1.57 (0.89–2.77)
Intensity of use				
≤206	6.41 (2.39–17.17)	7.06 (2.60–19.15)	2.52 (1.14–5.55)	2.24 (1.02–4.92)
206–<442	8.89 (2.96–26.76)	8.27 (2.77–24.74)	2.14 (0.65–7.04)	1.65 (0.50–5.40)
≥442	–	–	1.55 (0.37–6.48)	1.50 (0.36–6.25)
Metformin				
Any use	0.40 (0.23–0.71)	0.40 (0.23–0.71)	0.69 (0.53–0.89)	0.68 (0.53–0.89)
Intensity of use				
≤176	0.36 (0.16–0.79)	0.40 (0.18–0.90)	0.56 (0.39–0.82)	0.56 (0.38–0.81)
176–<303	0.26 (0.09–0.74)	0.29 (0.10–0.84)	0.80 (0.52–1.21)	0.78 (0.51–1.19)
≥303	0.43 (0.17–1.11)	0.48 (0.18–1.25)	0.67 (0.37–1.21)	0.67 (0.37–1.21)

ADT = androgen deprivation therapy; CI = confidence interval; DDD = defined daily dose; OR = odds ratio; PCa = prostate cancer.
Risks of PCa death and initiation of ADT among patients with antidiabetic medication initiated after diagnosis.

a higher risk of death (HR 1.91, 95% CI 1.50–2.43). Among metformin users, risk estimates were tending toward a diminished risk, but after multivariate adjustment, a significant association was observed only for the highest intensity of use (HR 0.52, 95% CI 0.36–0.75; Supplementary Table 5).

4. Discussion

Men using ADs have worse PCa-specific prognosis after prostatectomy than nonusers. This suggests that AD use or the underlying diabetes might promote progression of PCa. The risk increase was observed for multiple AD groups separately, especially among users of insulin and drugs increasing insulin secretion. Thus, the risk increase may be caused by poor glycemic control that indicated the use of these drugs or the resulting hyperinsulinemia. Concordantly, untreated hyperglycemia has previously been suggested as a risk factor for poor PCa prognosis [3]. On the contrary, hyperinsulinemia and insulin resistance have also been proposed to increase the risk of cancer, and in vitro insulin is known to accelerate the growth of cancer cells [1].

Unlike other ADs, use of metformin appears to a have beneficial association with the risks of death and progression among PCa patients for both pre- and postdiagnostic use. However, the protective risk associations were not dose dependent and therefore might not be causal. Unlike other ADs, metformin was not associated with an increased risk of all-cause death; risk estimates were rather tending toward a decreased risk, but not as strong as for PCa death. Our finding may be caused by a selection bias: metformin is usually used in early phase of diabetes and for mild hyperglycemia. By contrast, in lag-time analyses, the protective association with the risks of PCa death and ADT initiation remained for metformin usage occurring up to 3 yr earlier, which demonstrates that the risk association is longstanding. In the new-user analysis, the association was even stronger; therefore, it is not explained by the bias caused by prediagnostic use.

Metformin reduces gluconeogenesis and improves insulin sensitivity, which in turn reduces insulin levels and plasma glucose [2]. In vitro use of metformin has been linked to beneficial effects on PCa cells. Metformin regulates cancer cell metabolism and inhibits cancer cell proliferation [2,15,16]. Thus, a biological rationale exists for the protective effects of metformin. However, epidemiological results on metformin have been inconclusive. Our results support the beneficial effects of metformin against PCa, but the association is not unambiguous and uncertainty remains.

Among insulin users, risk estimates of PCa death and progression were elevated. The association was not dose dependent. The risk increase was strongest among short-term, high-intensity insulin users, which suggests a selection bias. Insulin is the treatment of choice for diabetes in patients with poor prognosis, terminal cancer, short need of treatment, or very poor glycemic control. Thus, the association, especially among short-term users, might more likely be caused by selective use among men approaching death, that is, a protopathic bias rather than long-term actions of insulin. Concordantly, the risk increase was lost in lag-time analyses supporting the protopathic bias. However, the risk increase for insulin use might also be caused by untreated hyperglycemia. According to the lag-time analysis, the drugs increasing insulin secretion might have independent adverse effects on PCa prognosis. The risk

increase for PCa death and ADT initiation was observed even with 3-yr lag time. Hyperinsulinemia is biochemically related to more aggressive cancer [17,18]. Cancer cells have overexpression of insulin receptors; high insulin concentration accelerates tumor progression [18]. Therefore, the risk increase by drugs increasing insulin secretion might be due to actions of insulin as a growth factor for tumor cells.

The association between ADs and risk of PCa death remained when other causes of death were taken into account. Therefore, our findings are not likely influenced by the bias due to elevated mortality from noncancer causes among diabetic men.

The main strengths of our study are nationwide study population and long follow-up. The information on drug use and causes of deaths are comprehensive, and the data collected have been of high quality. Comprehensive and accurate medication data enabled us to analyze several AD groups simultaneously. Being able to compare the risk separately for multiple groups of ADs with different mechanisms of action, we were able to estimate whether the association was caused by a specific mechanism of action of a given drug group or rather by the underlying diabetes. We also had comprehensive information on comorbidities. The potential confounding factors were adjusted for in the analyses. The study population is a cohort of PCa patients primarily treated with radical prostatectomy, which makes the study population homogenous at baseline. Surgical treatment requires sufficient physical performance to allow major surgery. On the contrary, in order to evaluate the risks of progression and death in such study population, long follow-up time and a large number of participants are required.

As a limitation, we had no information on glucose control, smoking, living or exercise habits, prostate-specific antigen (PSA), or Gleason score. Progression of PCa was evaluated indirectly based on the information of initiated ADT. This surrogate outcome does not separate if ADT is indicated by an elevation of PSA, or local recurrence or metastatic progression of PCa. However, ADT is standard treatment in metastatic PCa. We are not able to make direct inference regarding how metformin impacts PCa progression, but due to observed improved ADT-free and PCa-specific survival, it is likely that metformin may benefit against progression of PCa after prostatectomy. Initiation of ADT is an unspecific indicator of PCa progression and does not include local recurrence managed with radiation therapy without ADT. Owing to a lack of information on imaging results, we were not able to identify patients with metastatic PCa within ADT users. This limitation must be taken into account when comparing our results with other studies measuring PCa progression.

There is always a potential for residual bias in retrospective cohort studies.

5. Conclusions

Our results add to epidemiological evidence of potential benefits of metformin among PCa patients. In our study, the prognostic association of metformin clearly differed from that of other ADs. Metformin might be a more favorable selection for the treatment of diabetes among men with PCa than insulin or drugs increasing insulin secretion.

***Author contributions*:** Roni M. Joentausta had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Joentausta, Murtola.
Acquisition of data: Rannikko.
Analysis and interpretation of data: Joentausta, Murtola.
Drafting of the manuscript: Joentausta, Murtola.
Critical revision of the manuscript for important intellectual content: Murtola, Rannikko.
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Supervision: Murtola, Rannikko.
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Appendix A. Supplementary data

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