Antidiabetic drugs and prostate cancer prognosis in a Finnish population-based cohort

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ABSTRACT

Hyperinsulemia and glycemic control may play a role as prostate cancer prognostic factors, while use of certain antidiabetic drugs, such as metformin, could improve the prognosis. We examined the link between anti-diabetic medication use and prostate cancer survival taking into account simultaneous use of multiple drugs.

The study cohort composed of 6,537 men in The Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) with prostate cancer diagnosed in 1996-2009. Information on medication usage was attained from the nationwide prescription database of the Social Insurance Institution of Finland. Median follow-up time was 9.2 years post-diagnosis. A total of 1,603 (24,5%) men had used antidiabetic medication. Total of 771 men died of prostate cancer during the follow-up. We used multivariable-adjusted Cox regression to evaluate the risk of prostate cancer death and onset of androgen deprivation therapy (ADT) with adjustment for prostate cancer clinical characteristics, co-morbidities and use of other drugs. Separate analyses were further adjusted for blood glucose level.

Risk of prostate cancer death was higher among antidiabetic drug users overall (HR 1.42, 95% CI 1.18-1.70) compared to non-users, and separately also among insulin and metformin users. Further adjustment for blood glucose level abolished the risk increase. Also risk of ADT initiation was increased among the medication users; HR 1.26 (95% CI 1.05-1.49).

Men with prostate cancer using antidiabetic medication are generally at increased risk of dying from prostate cancer compared to non-users. The risk association is driven by underlying diabetes, as adjustment for blood glucose level ameliorates the risk increase. Our study does not support protective effects of metformin.

Introduction

The prognosis of prostate cancer is multifactorial. The most established prognostic factors are pre-diagnostic PSA (prostate-specific antigen), Gleason score and TNM stage. Several comorbid diseases likely also affect prostate cancer prognosis, either directly by influencing tumour biology or indirectly by limiting prostate cancer treatment choices and through competing mortality. Type 2 diabetes mellitus (DM2) has been associated with a poor prostate cancer prognosis, even though DM2 has been associated with lowered overall Prostate cancer risk (1-4). In several cancer types, the uptake of glucose is elevated due to changes in cancer cell metabolism to anaerobic glycolysis, a phenomenon known as Warburg effect (5). Also, hyperinsulinemia accelerates growth of cancer cells by increasing activation of IGF (insulin-like growth factor) receptor (6-8).

People with DM2 and hyperglycemia tend to also have other conditions comprising metabolic syndrome, such as elevated blood pressure, abnormal cholesterol and triglyceride levels, and complications caused by these conditions, such as cardiovascular disease, neuropathies and nephropathy. Multiple co-morbidities limit the choice of curative treatments for prostate cancer, thus the primary treatment among prostate cancer patients with DM2 may be often non-curative androgen deprivation therapy (ADT).

There is also evidence that metformin, a common drug used to treat DM2, could be protective against high-grade prostate cancer and tumor progression (9-11).

However, in epidemiologic studies, the limitation is that patients generally use multiple drugs for DM2 management, such as metformin and insulin, especially when the disease progresses and endogenous insulin production becomes insufficient. Therefore, it is challenging to estimate separate effect of a single drug on cancer prognosis in epidemiological study. Control for usage of multiple antidiabetic drugs, as well as co-morbidities, while examining associations with prostate cancer prognosis is crucial. Also, when examining possible protective effects of anti-DM medication, such

as metformin, the challenge is that DM2 itself is a possible risk factor for worse prognosis, thus potentially masking protective effects of antidiabetic medication.

Therefore, we conducted a study to investigate how different antidiabetic drugs associate with risk of Prostate cancer death and of starting ADT, while considering simultaneous usage of multiple antidiabetic drugs and tumor clinical characteristics.

Materials and methods

Study cohort

The study cohort is based on study population of the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) (12), which is the largest component of the multinational European Randomized Study of Prostate Cancer Screening (ERSPC) (13). In the FinRSPC study, men aged 55-67 years from Helsinki and Tampere residential areas were identified between 1996 and 1999. All prevalent Prostate cancer cases at baseline were identified from the Finnish Cancer Registry and excluded from the study. The remaining men were randomly assigned either to no intervention (control arm) or were offered screening with serum PSA test at four-year intervals (screening arm). After the exclusion of prevalent Prostate cancer cases, 80,144 men (screening arm 31,886 men, control arm 48,278 men) were enlisted to the FinRSPC. The follow-up for cancer cases in this study is through 2015, even though the FinRSPC study screening intervention finished in 2007.

For the purposes of this study, we identified men in the FinRSPC who had been diagnosed with a diagnosis of prostate cancer during 1996-2009, a total of 6,537 men. This information was obtained from the nationally comprehensive Finnish Cancer Registry (FCR) (14) for men in both arms. Tumor clinical data and primary treatment were obtained from medical records. The information included date of diagnosis, tumor Gleason score (available for 6,358 men 97.3%), tumor stage (6,506 men, 99.5%) and PSA level at diagnosis (5,478 men, 83,8%). Primary treatment was available for 6,474 men (98.5% of the cohort).

Information on participants' deaths was obtained from the Statistics Finland (15) Causes of Death Registry. The statistics on causes of death are based on data derived from mandatory death certificates that are complemented with data on deaths from the Population Information System of the Population Register. The statistics on causes of death include all deaths in Finland or abroad of persons who permanently reside in Finland at the time of their death.

Deaths caused by prostate cancer (ICD-10 code C61) were validated by an independent cause of death committee of the FinRSPC study (16,17). In these studies, a randomly selected sample of men with Prostate cancer recorded as the main cause of death were reviewed. Agreement with official cause of death registry was 94.6% in the screening arm and 95.4% in the control arm and $\kappa = 0.95$. In total 14 Prostate cancer deaths were estimated to be due to other causes in both study arms. We considered deaths with prostate cancer recorded as the primary cause as prostate cancer specific.

Information on procedures and diagnoses from in- and outpatient hospital visits were obtained from national Care Register for Health Care, which registers information through mandatory notifications on diagnoses and procedures on in- and outpatient visits to Finnish tertiary health care units. Based on this information, we identified men who had undergone surgical castration (Nordic Classification of Surgical Procedures code KFC10) after prostate cancer diagnosis. This information was merged with the information on purchases of GnRH agonist or antagonist and antiandrogens obtained from the prescription database of the Social Insurance Institution (SII) of Finland (18) to identify men who had had hormonal treatment for prostate cancer.

Information on BMI was available for 495 men (7.5% of the cohort) who participated on the third FinRSPC screening round during 2004-2008 and responded to a survey sent along the screening invitations (19).

Information on medication use

To obtain information on usage of GnRH agonists and antagonists, antiandrogens, prescribed antidiabetic drugs, anticoagulants, antihypertensive drugs, statins, NSAIDs and aspirin during 1995-2015, the study cohort was linked to a nationwide prescription database of the Social Insurance Institution (SII) of Finland. The SII is a governmental agency, which provides reimbursements for the cost of physician-prescribed drugs to all Finnish citizens (18). Over-the-counter drug purchases or drugs administered during hospital inpatient periods are not available from the database.

Antidiabetic drugs were categorized into four groups according to mechanism of action: metformin; glitazones; insulins and drugs increasing secretion of insulin, including gliptins, glinids and sulphonylureas (Supplementary table 1).

Information on blood glucose measurements

The study cohort was linked to the Tampere regional laboratory database (Fimlab) to acquire information on fasting plasma or blood glucose and glycated haemoglobin (HbA1c) measurements during 1995-2016 using individual identifier number as the key. Information on each measurement included the date and the result. Fasting blood glucose and HbA1C measurements were available for 1,676 and 1,359 men, respectively. As Fimlab operates in the Tampere region. most measurements are from men recruited from that area.

Fimlab provides laboratory services in Pirkanmaa, Central Finland and Tavastia regions (20). Majority of laboratory measurements, including all measurements in the hospitals in the Pirkanmaa region, are performed by Fimlab laboratories.

For each person with at least one blood glucose measurement, we calculated a yearly average blood glucose level based on measurements within that calendar year.

The yearly average HbA1c levels were calculated similarly and then divided into three categories: normoglycemic if HbA1c was under 39 mmol/mol (under 5.7%), prediabetic if HbA1c was between 39 and 47mmol/mol (between 5.7% and 6.4%), and diabetic if HbA1c level was over 47mmol/mol (over 6.4%).

Statistical analysis

Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for risk of Prostate cancer death by antidiabetic medication usage. Analyses were

adjusted for age (age-adjusted analyses), and further for usage of other drugs (anticoagulants, acetylsalicylic acid, NSAID, antihypertensive drugs, statins), EAU Prostate cancer risk group (21) and primary Prostate cancer treatment (surgery, radiation therapy, surveillance or androgen-deprivation therapy/antiandrogen) (multivariable-adjusted analyses). For each antidiabetic drug, a separate time-dependent variable was calculated based on the cumulative usage of the drug to model simultaneous usage of multiple antidiabetic drugs. Participants remained as non-users until the first antidiabetic medication purchase, and remained as users thereafter to minimize selection bias due to discontinuation of other than palliative medication use during terminal phase of cancer.

Marginal structural model (MSM) using inverse probability weighting (IPW) was used to correct for the confounding effect between post diagnosis blood glucose and antidiabetic drug, metformin, use. We estimated IPWs using metformin as the time-dependent exposure and post diagnosis blood glucose as the time-dependent confounder, adjusted for age, EAU prostate cancer risk group, FinRSPC study arm, primary prostate cancer treatment, and use of anticoagulants, acetylsalicylic acid, NSAID, antihypertensive drugs, and statins. The MSM model was fitted using the inverse probability weights in the Cox proportional hazards model for risk of prostate cancer death by antidiabetic medication usage adjusted for the same covariates as the primary model.

We standardized amount of medication use between separate drugs by dividing purchased cumulative mg amount of a given antidiabetic drug with drug-specific amount corresponding to defined daily dose (DDD) as listed by the WHO (22). By adding together DDDs for drugs within a given drug group, we obtained cumulative amount of use for a drug group. This was updated for each follow-up year separately in time-dependent Cox regression analysis. All years with any recorded medication purchases were considered as years of usage, and cumulative number of years of usage was considered as duration of use. With these variables, we calculated intensity of drug usage (DDDs/year) for each calendar year by dividing cumulative amount with cumulative duration of use, again this was updated separately for each follow-up year.

We conducted separate analyses with onset of ADT as the outcome of interest as a surrogate for prostate cancer prognosis. Follow-up time began at prostate cancer diagnosis and ended on either death or the onset of ADT, emigration from Finland or common closing date 31 December 2015, whichever came first. Same model adjustments were used as for the main analysis.

To evaluate the possible underestimation of the duration of DM2, sensitivity analyses were performed using the new user design, i.e. excluding men with any recorded antidiabetic drug use before prostate cancer diagnosis.

We evaluated dose-dependence of risk trends in prostate cancer survival and ADT initiation through stratification by cumulative intensity (DDDs/year) of antidiabetic drug usage. To further assess risk of initiating secondary ADT for disease relapse we performed separate analyses for ADT which started minimum of two years after prostate cancer diagnosis. These analyses were performed for each antidiabetic drug group separately.

We further investigated association between prostate cancer death and antidiabetic drugs after initiation of ADT, as ADT initiation can alter blood glucose levels. In this analysis, the follow-up time started from the first date of ADT drug purchase or orchiectomy. Again, same model adjustments were used as for the main analysis, with the exception of primary prostate cancer treatment; instead we adjusted on whether participants received radiation therapy in addition to ADT.

Development of prostate cancer is a long process, and many factors long before the diagnosis can affect the tumorigenesis. To evaluate latency of the effects of antidiabetic drug usage, we conducted lag time analyses relating outcomes to antidiabetic medication purchases one, three and five years earlier as the exposure. Lag time approach also controls for protopathic bias.

To evaluate whether the risk association depends on serum glucose level, we performed analysis limited to men with at least one fasting glucose measurement available. Within this subgroup,

fasting glucose level was included as another time-dependent variable in Cox regression model. For years with no glucose measurements available, we used the results of the latest measurement.

Diabetic men are at increased risk of cardiovascular disease and hence of dying from non-cancer causes. We evaluated role of competing causes of death in the risk association between prostate cancer specific death and antidiabetic drug usage before prostate cancer diagnosis by comparing results from Cox regression analysis with results from Fine & Gray regression analysis with deaths due to cardiovascular disease (ICD-10 codes I20-I25) as the competing risk. Additionally, we used all non-prostate cancer deaths as the competing risk in another Fine & Gray regression model.

We used IBM SPSS statistics software (version 25) to perform Cox regression analyses. All p-values are two-sided. The IPWs for the MSM was estimated using R (version 3.6.3) and *ipw* package (version 1.0-11). The hazards ratios and 95% confidence intervals of the MSM Cox proportional hazards model was estimated using survival package (version 3.1-8).

Results

Population characteristics

Of 6,537 men with prostate cancer, 1,603 (24,5%) used at least one type of antidiabetic drug during the follow-up (Table 1). Men who used antidiabetic drugs also used more often non-steroidal anti-inflammatory drugs (NSAID), ASA, antihypertensive drugs and anticoagulants. A total of 2,516 deaths (38.5 % of the cohort) occurred during the follow-up period, 657 among antidiabetic drug users and 1,859 among non-users. Of these deaths, prostate cancer was the cause of death in 170 cases (25.9% of deaths) among users and 601 (32.3% of deaths) among non-users.

Men using antidiabetic medication had a higher mean BMI compared to non-users. However, there was no difference in PSA values or tumor characteristics, such as Gleason score or tumor stage, between the two groups (Table 1).

Information on fasting blood glucose level and HbA1c level were available for 1,741 and 1,351 men, respectively. Anti-DM medication users had statistically significantly higher blood glucose levels (median 7.0 vs. 5.7 mmol/l) compared to men without anti-DM medication, and had more often diabetic HbA1c level (52.4% vs. 4.0%) (Table 1).

Risk of prostate cancer death by antidiabetic drug use

Prostate cancer mortality was 11.6 per 1000 person-years among men with any anti-DM medication and 13.6 among men with no anti-DM medication purchases. After multivariable adjustment, risk of Prostate cancer death was non-significantly increased by anti-DM drug use before prostate cancer diagnosis (HR 1.22, 95% CI 0.96-1.54), but significantly increased compared to non-users in men who used anti-DM drugs after prostate cancer diagnosis (HR 1.42, 95% CI 1.18-1.70) (Table 2). Of separate drug groups, post-diagnostic use of metformin was associated with significantly increased risk of prostate cancer death in multivariable-adjusted analysis, whereas elevated but non-

significant risk estimated were observed for insulin and insulin secretagogues after multivariable adjustment).

No clear dose-dependence was observed for antidiabetic medication overall, but in separate analysis risk of prostate cancer death appeared to be elevated in low-dose use of metformin and insulin but lowered to similar level with non-users in high-dose use. This risk increase was not observed for insulin secretagogues, although risk estimates were highest for low-dose usage also for this drug group (Table 2).

In lag-time analyses, increased risk for prostate cancer death remained for metformin usage occurring up to five years earlier (Table 2). The risk associations with insulin and insulin secretagogues attenuated in lag time analyses, but the risk estimates remained non-significantly elevated compared to non-users.

Risk of starting androgen deprivation therapy by antidiabetic drug use

Use of antidiabetic drugs was associated with an increased risk of starting ADT compared to non-users in both age-adjusted and multivariable-adjusted analyses, HR 1.31 (95% CI 1.11-1.55) and 1.26 (95% CI 1.05-1.49), respectively (Table 3). The risk increased by intensity of antidiabetic medication use.

For specific drug groups, the risk increase was observed for insulin (multivariable adjusted HR 1.47, 95% CI 1.07-2.01), and a non-significant risk increase was observed also among metformin users (HR 1.22, 95% CI 0.96-1.55).

The association with ADT vanished after excluding ADT initiations within the first two years of prostate cancer diagnosis.

Sensitivity analyses

After ADT initiation, risk of prostate cancer death was clearly increased among antidiabetic medication users compared to non-users (multivariable-adjusted HR 2.58, 95% CI 2.14-3.12) (Table 4). Again, use of metformin and insulins were associated with increased risk in the drug group-specific analyses. When stratified by intensity of usage, an inverse association was observed; low-dose use of metformin and insulin were associated with elevated risk of prostate cancer death compared to non-users, whereas in high-dose use the risk difference was attenuated.

Similar to the main analysis, in the competing risks regression analyses antidiabetic drug usage before prostate cancer diagnosis was not associated with prostate cancer specific death compared to non users with cardiovascular deaths as the competing risk (HR 1.06, 95% CI 0.82-1.36) or with all non-prostate cancer deaths as the competing cause (HR 0.96, 95% CI 0.75-1.24).

When limiting the analysis to include only men with any antidiabetic medication during the study period, risk of prostate cancer death was markedly increased for current drug usage (multivariable adjusted HR: 5.86, 95% CI 2.57-13.39), as well as for current metformin users (HR 2.12, 95% CI 1.41-3.19). However, the risk increase for ADT initiation was no longer statistically significant for current use (HR 1.17, 95% CI 0.94-1.47).

In new user analysis metformin remained associated with increased risk of prostate cancer death (HR 1.41, 95% CI 1.05-1.89) while the risk increase was even stronger among insulin users (HR 2.14, 95% CI 1.26-3.64). Insulin secretacogues or glitazones were not associated with the risk.

Role of serum glucose level

Among the 1,676 men with fasting blood glucose measurements available, further adjustment for glucose level changed the risk increase among users of metformin and insulin to statistically non-

significant (HR 1.14, 95% CI 0.62-2.07 and HR 1.43, 95% CI 0.74-2.78) whereas a significant risk increase was observed among users of insulin secretagogues (HR 2.01, 95% CI 1.08-3.76) (Table 5).

Initiation of ADT increased median fasting glucose level by 0.3 mmol/l. Compared to men whose fasting glucose level remained stable or fell after ADT initiation (n=179), men whose level rose (n=388) were at lower risk of prostate cancer-specific death (HR 0.60, 95% CI 0.39-0.62).

Subgroup analysis

In the subgroup analysis, risk association between antidiabetic medication and prostate cancer death was not modified by age, EAU risk group, Charlson index or main prostate cancer treatment method (ADT vs. others) (Supplementary figure 1).

Discussion

We observed a risk increase for prostate cancer death among men using antidiabetic drugs compared to non-users. The risk increase was even higher in the subgroup of men on ADT and was sustained for years in lag time analyses. In dose-dependency analyses, an inverse risk association was observed; the risk increase was clearest for low-dose usage of antidiabetic medication and attenuated with continued and high-dose use. Thus, the risk is increased at the start of antidiabetic medication use, i.e. at the time when men are still hyperglycemic and/or hyperinsulinemic. Supposedly glycemic control improves with continued use and higher doses, and the risk increase attenuates. This supports role of untreated hyperglycemia as a risk factor for prostate cancer death, concordant to our previous findings (23). This notion was further supported by sensitivity analyses where the risk association with antidiabetic drugs vanishes after adjustment for blood glucose level.

Regarding timing of antidiabetic medication use in relation to prostate cancer diagnosis, the risk increase was limited to usage occurring after the diagnosis. This suggests that diabetes or its management affect mainly progression, rather than initiation of prostate cancer. Higher risk of starting ADT among drug users supports this, although sensitivity analyses suggest the ADT association may be explained by higher tendency to have ADT as the primary prostate cancer treatment among diabetic men.

The risk increase was associated with certain antidiabetic drugs, namely metformin and insulins. These two types of drugs are also most commonly used to treat hyperglycemia and have a large weight in our overall drug analyses. Other antidiabetic drugs did not significantly associate with prostate cancer survival, although slightly elevated risk estimates were observed also for insulin secretagogues. However, the number of men using glitazones was low in our cohort. Glitazones were available in Finnish market between 2000 and 2010, and therefore it is more uncertain to evaluate effect of their long-term use.

The observed risk increase was similar for metformin and insulins, even though the mechanism of action differs. Additionally, metformin is typically used in management of early DM2 when patient still has endogenous insulin production, whereas insulins are used to manage more advanced phase. Despite these differences, both drug groups were associated with similar risk increases. This indicates that the usage of anti-diabetic drugs per se does not increase risk of prostate cancer death but rather suggests DM2 and poor glycemic control to be the real culprit both indicating the medication use and affecting the risk. Earlier studies (24-29) have shown that men with DM2 are more likely to be diagnosed with a high-grade prostate cancer and have worse prognosis, even though their overall prostate cancer risk might be lower compared to non-diabetic men. Men with DM2 tend to have lower PSA levels, which leads to fewer prostate biopsies due to increased PSA. This in turn may cause prostate cancer to be found in more developed stages and can also delay the diagnosis of high-grade prostate cancer.

Hyperinsulinemia has been suggested to be a risk factor for prostate cancer, and it is one possible mechanism for the risk association between diabetes and worse prostate cancer prognosis. In the cellular level, hyperinsulinemia and high levels of insulin like growth factor 1 (IGF-1) promote cell growth and mitogenic activity, thus increasing cell proliferation (30-32). In this study, the risk increase for insulins was slightly higher compared to metformin. This observation reinforces hyperinsulinemia as a risk factor of prostate cancer. In an earlier study in the same FINRSPC cohort (33) use of sulphonyl ureas, which increase insulin production, increased the risk of metastatic prostate cancer. However, in this current study, insulin secretagogues did not alter prostate cancer survival.

We have shown earlier that diabetic blood glucose level is associated with higher prostate cancer risk and worse prostate cancer survival compared to normoglycemia (23, 34). In the earlier study (34) the risk increase by hyperglycemia was observed in men with no antidiabetic drug use, not among medication users. As could be expected given the risk modifying role of the drug use, the

risk association with medication use disappeared after adjustment for blood glucose. This provides further support to the notion that diabetes and untreated hyperglycemia, rather than antidiabetic medication use directly, is behind the observed risk associations. Even though the risk of prostate cancer death was increased among anti-DM medication users, this does not suggest discontinuing of medication would be beneficial for men with DM2 considering prostate cancer progression.

This study has several strengths. First, the large study cohort decreases the effect of chance on the results. We also have comprehensive and detailed information on prostate cancer prognostic factors and co-medications, thus allowing us to take them into account in the analysis. Detailed information on prescribed medication purchases from a long time span allowed us to use time-dependent analyses to minimize immortal time bias and to evaluate simultaneous use of major antidiabetic drug groups and common concomitant medications. This way we could also evaluate confounding by indication. As the material was based on a screening trial, we had information on provision of systematic prostate cancer screening. Also, information on blood glucose level in a subgroup allowed us to examine separately hyperglycemia and antidiabetic medication use as prognostic risk factors. Quality of data on prostate cancer-specific deaths in FinRSPC has previously been validated by cause-of-death committee by comparing data from national registries to patient files (16,17).

This study also has some limitations. Antidiabetic medication use was not based on random allocation, and therefore the comparability of users of different medication is uncertain, despite adjustment for major prognostic factors. We did not have information on time of diagnosis of DM2, only medication usage. Therefore, it is possible that the duration of DM2 is underestimated. However, this may not affect results to any great degree, as the results remained similar in new user-analysis. In our study cohort, usage of newer SGLT2-transporter drugs (i.e. empagliflotzin) was limited to few single purchases, and no analyses were possible. Further studies are needed to evaluate the possible risk associations between SGLT2- medication on prostate cancer prognosis. Further, we have no information on lifestyle factors, such as diet, smoking and physical activity and

only limited information on BMI. These factors have the potential to bias our result, most likely exaggerating the observed differences by antidiabetic drug use.

In conclusion, use of anti-DM medication, especially metformin and insulins, are associated with worse prostate cancer prognosis. This is likely explained by the underlying diabetes rather than the usage of anti-DM medication per se. DM2 should be considered as a risk factor when considering prostate cancer prognosis.

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Table 1. Population characteristics. Study cohort of 6,537 men from the the Finnish Randomized Study of Screening for Prostate Cancer with prostate cancer diagnosed during 1996-2009.

	Usage of antidiabetic drugs	
n of men (%)	Users 1,603 (24,5)	Non-users 4,934 (75,5)
FinRSPC study arm		
Screening; n (%)	721 (45,0)	2,148 (43,5)
Control; n (%)	882 (55,0)	2,786 (56,5)
Median age (range)	63 (55-67)	63 (55-67)
Deaths during the follow-up	657 (41.0)	1,859 (37.7)
Prostate cancer as a cause of death (% of deaths)	170 (25.9)	601 (32.3)
Median (IQR) follow-up (year)	9.2 (6.0-12.1)	9.1 (5.9-12.1)
Total follow-up time (person years)	14,683	44,265
Prostate cancer mortality / 1000 person years	11.6	13.6
Gleason score; n (%)		
6 or less	873 (54.5)	2,749 (55.7)
7-10	692 (43.2)	2,044 (41.4)
Missing	38 (2.4)	141 (2.9)
Tumor stage; n (%)		
Localized	1,282 (80.0)	3,967 (80.4)
Metastatic	317 (19.8)	940 (19.1)
Missing	4 (0.2)	27 (0.5)
Median (IQR) PSA (ng/ml) at the time of Prostate cancer diagnosis	8.9 (5.6-15.7)	8.9 (5.7-16.0)
Median (IQR) BMI	27.7 (26.0- 30.7) *	25.3 (23.5-27.5)
Median (IQR) blood glucose level (mmol/l)	7.0 (6.4-8.0) *	5.7 (5.4-6.0)
HbA1c-level; n (%)	430	921
Normoglycemic (levels)	21 (4.8)	306 (33.2)
Pre-diabetic	188 (42.8)	587 (62.8)
Diabetic	230 (52.4)*	37 (4.0)
Statin use; n(%)	1,226 (76.5)*	2,434 (49.3)
Antihypertensive drug use; n (%)	1,513 (94.4)*	3,852 (78.1)
NSAID use; n (%)	1,495 (93.3)*	4,494 (91.1)
ASA use; n (%)	321 (20.0)*	703 (14.2)
Use of anticoagulants; n (%)	671 (41.9)*	1,635 (33.1)

* P-value for difference < 0.01, calculated with Mann-Whitney U-test

NSAID= Non-steroidal anti-inflammatory drugs ASA= Acetylsalicylic acid

Anticoagulants include warfarin and small-molecular heparins

Table 2. Risk of prostate cancer death by antidiabetic medication use. Study cohort of 6,537 men from the the Finnish Randomized Study of Screening for Prostate Cancer with prostate cancer diagnosed during 1996-2009.

		Prostate cancer death risk				
				1 year lag time	3 year lag time	5 year lag time
Anti-diabetic drug use after Prostate cancer diagnosis	n of men/Prostate cancer deaths	HR (95% CI) age-adjusted	HR (95% CI) multivar.-adjusted	HR (95% CI) multivar.-adjusted	HR (95% CI) multivar.-adjusted	HR (95% CI) multivar.-adjusted
None	4,934/601	Ref	Ref	Ref	Ref	Ref
Any	1,603/170	1.41 (1.19-1.68)	1.42 (1.18-1.70)	1.50 (1.24-1.80)	1.37 (1.12-1.68)	1.41 (1.13-1.76)
Intensity of anti-DM medication use						
1st tertile *	596/70	1.77 (1.37-2.30)	1.83 (1.40-2.38)	1.77 (1.32-2.36)	1.53 (1.05-2.23)	1.29 (0.78-2.14)
2nd tertile *	504/39	0.99 (0.71-1.39)	1.01 (0.72-1.41)	1.05 (0.74-1.51)	0.94 (0.59-1.49)	1.08 (0.63-1.86)
3rd tertile*	503/61	1.47 (1.13-1.90)	1.44 (1.11-1.88)	1.65 (1.26-2.16)	1.76 (1.28-2.42)	1.63 (1.09-2.42)
Metformin use						
None	5,218/637	Ref	Ref	Ref	Ref	Ref
Any	1,319/134	1.21 (0.94-1.56)	1.36 (1.06-1.750)	1.52 (1.18-1.96)	1.42 (1.07-1.89)	1.33 (0.96-1.86)
Intensity of metformin use						
1st tertile**	463/55	1.58 (1.17-2.15)	1.79 (1.32-2.43)	1.92 (1.38-2.66)	1.90 (1.27-2.82)	1.85 (1.11-3.06)
2nd tertile**	428/41	1.04 (0.72-1.50)	1.17 (0.81-1.69)	1.19 (0.79-1.78)	0.71 (0.39-1.29)	0.65 (0.30-1.40)
3rd tertile**	428/38	0.87 (0.58-1.30)	0.98 (0.66-1.45)	1.40 (0.93-2.11)	1.60 (0.99-2.58)	1.60 (0.87-2.94)
Insulin use						
None	6,020/709	Ref	Ref	Ref	Ref	Ref
Any	517/62	1.48 (1.09-2.00)	1.24 (0.91-1.69)	1.19 (0.87-1.64)	1.13 (0.79-1.61)	1.07 (0.71-1.60)
Intensity of insulin use						
1st tertile***	183/26	2.30 (1.47-3.59)	1.70 (1.09-2.66)	1.26 (0.72-2.22)	0.71 (0.31-1.66)	0.67 (0.21-2.16)
2nd tertile***	167/21	1.33 (0.82-2.15)	1.21 (0.74-1.97)	1.20 (0.70-2.04)	1.01 (0.51-2.03)	1.22 (0.52-2.84)
3rd tertile***	167/15	1.14 (0.69-1.87)	0.96 (0.59-1.58)	1.31 (0.68-1.88)	1.02 (0.55-1.88)	0.91 (0.41-2.05)
Insulin secretagogues use						

None	5,742/674	Ref	Ref	Ref	Ref	Ref
Any	795/97	1.13 (0.84-1.53)	1.09 (0.81-1.48)	1.06 (0.78-1.43)	1.17 (0.86-1.61)	1.30 (0.92-1.94)
Intensity of Insulin secretagogues use						
1st tertile ****	265/38	1.44 (0.98-2.10)	1.33 (0.91-1.94)	1.20 (0.78-1.84)	1.71 (0.67-2.05)	1.08 (0.53-2.20)
2nd tertile ****	265/21	0.81 (0.49-1.33)	0.79 (0.48-1.30)	0.80 (0.46-1.29	1.11 (0.59-2.10)	1.63 (0.80-3.29)
3rd tertile****	265/38	1.06 (0.71-1.58)	1.03 (0.70-1.54)	1.20 (0.79-1.83)	1.48 (0.91-2.41)	1.22 (0.66-2.27)

Multivariable adjusted hazard ratios for prostate cancer death calculated using Cox regression with adjustment for age, usage of other drugs (anticoagulants, acetylsalicylic acid, NSAID, antihypertensive drugs, statins), EAU prostate cancer risk group and primary prostate cancer treatment (surgery, radiation therapy, surveillance or androgen-deprivation therapy/antiandrogen)

*Tertile cut points 220.99 and 476.28 DDD/year
**Tertile cut points 169.58 and 300.44 DDD/year
***Tertile cut points 175.60 and 401.61 DDD/year
****Tertile cut point 224.60 and 404.17 DDD/year

Table 3. Risk of starting androgen deprivation therapy by antidiabetic drug use in a cohort of 6,537 prostate cancer cases from Finnish Randomized Study of Screening for Prostate Cancer

		Risk of starting ADT	
Antidiabetic drug use	n of men/ADT users	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivar.\text{-}adjusted}$
None	4,934/2,594	Ref	Ref
Any	1,603/932	1.31 (1.11-1.55)	1.26 (1.05-1.49)
Intensity of anti-DM medication use			
1st tertile *	596/323	1.10 (0.81-1.48)	1.06 (0.79-1.44)
2nd tertile *	504/294	1.22 (0.92-1.48)	1.17 (0.88-1.55)
3rd tertile*	503/315	1.64 (1.27-2.10)	1.54 (1.19-1.99)
Metformin use			
None	5,218/2,755	Ref	Ref
Any	1,319/771	1.25 (0.99-1.59)	1.22 (0.96-1.55)
Intensity of metformin use			
1st tertile **	463/259	1.41 (1.05-1.90)	1.34 (1.00-1.81)
2nd tertile **	428/252	1.10 (0.77-1.56)	1.11 (0.78-1.58)
3rd tertile**	428/260	1.18 (0.82-1.71)	1.16 (0.80-1.68)
Insulin use			
None	6,020/3,188	Ref	Ref
Any	517/338	1.58 (1.16-2.16)	1.47 (1.07-2.01)
Intensity of insulin use			
1st tertile ***	183/126	2.32 (1.43-3.77)	2.13 (1.31-3.45)
2nd tertile ***	167/104	0.99 (0.58-1.70)	0.94 (0.55-1.61)
3rd tertile***	167/108	1.97 (1.29-3.03)	1.78 (1.16-2.74)

Multivariable adjusted hazard ratios for ADT initiation calculated using Cox regression with adjustment for age, usage of other drugs (anticoagulants, acetylsalicylic acid, NSAID, antihypertensive drugs, statins), EAU prostate cancer risk group and primary prostate cancer treatment

* Tertile cut points 220.99 and 476.28 DDD/year

** Tertile cut points 169.58 and 300.44 DDD/year

*** Tertile cut points 175.60 and 401.61 DDD/year

Table 4. Risk of Prostate cancer death after onset of androgen deprivation therapy. Study cohort of 6,537 men from the the Finnish Randomized Study of Screening for Prostate Cancer with prostate cancer diagnosed during 1996-2009.

	Prostate cancer death after onset of ADT treatment	
	Overall	Onset of anti-diabetic drug use after ADT
Anti-diabetic drug use	HR (95% CI) multivar.-adjusted	
None	Ref	Ref
Any	2.58 (2.14-3.12)	1.19 (0.91-1.55)
Metformin	2.36 (1.80-3.11)	1.41 (1.02-1.97)
Insulin	1.52 (1.11-2.09)	1.02 (0.55-1.86)

Multivariable adjusted hazard ratios for prostate cancer death calculated using Cox regression with adjustment for age, usage of other drugs (anticoagulants, acetylsalicylic acid, NSAID, antihypertensive drugs, statins), EAU prostate cancer risk group and whether participant received radiation therapy in addition to ADT

Table 5. Risk of prostate cancer death after adjustment for blood glucose level. A total of 1,676 men from the the Finnish Randomized Study of Screening for Prostate Cancer with prostate cancer diagnosed during 1996-2009 and at least one blood glucose measurement available.

Risk of Prostate cancer death	
	HR (95% CI) multivar.-adjusted
Blood glucose level	
Normoglycemic *	Ref
Pre-diabetic**	0.68 (0.34-1.21)
Diabetic***	0.83 (0.46-1.52)
Drug usage	
	HR (95% CI) multivar.-adjusted
None	Ref
Metformin	1.14 (0.62-2.07)
Insulins	1.43 (0.74-2.78)
Glitazones	0.51 (0.07-3.82)
Insulin secretagogues	2.01 (1.08-3.76)

Analyses adjusted for age, other drug usage (anticoagulation, acetylsalicylic acid, NSAID, antihypertensive drugs, statins), EAU Prostate cancer risk group and primary Prostate cancer treatment.

* = Fasting blood glucose level under or equal to 6.0 mmol/l

** = Fasting blood glucose level between 6.0 and 7.0 mmol/l

*** = Fasting blood glucose level over 7.0 mmol/l