Antihypertensive drugs and prostate cancer survival after radical prostatectomy in Finland – a nationwide cohort study

Eerik Santala

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Tietyt verenpainelääkkeet, kuten ATR-salpaajat sekä ACE-estäjät, on yhdistetty parempaan ennusteeseen eturauhassyöpäpotilailla. Me tutkimme verenpainelääkkeiden ja eturauhassyöpäpotilaiden kuolleisuuden välistä yhteyttä sekä hormonihoidon aloituksen riskiä suomalaisilla prostatektomiapotilailla.

Aineistonamme oli 14 422 eturauhassyöpäpotilaan aineisto Suomen Syöpärekisteristä. Laskimme Cox regressiolla riskisuhteet (HR:t) ja 95 % luottamusvälit eturauhassyöpäkuolemille ja hormonihoidon aloituksen riskille. Vakioimme analyyseissä iän, kasvaimen levinneisyyden ja statiinien käytön sekä lisäsimme analyysiin Charlson comorbidity indeksin.

Verenpainelääkkeiden käyttö oli yhteydessä kasvaneeseen eturauhassyöpäkuolleisuuteen pitkäaikaisseurannassa. Ennen syöpädiagnoosia käytetyt ATR-salpaajat pienensivät syöpäkuoleman riskiä (HR: 0.43, 95% CI:0.26-0.72). Samanlaista riskin alenemaa ei havaittu millään muulla verenpainelääkeryhmällä. Myös diagnoosin jälkeen käytetyt ATR-salpaajat pienensivät eturauhassyöpäkuoleman riskiä (HR: 0.60, 95% CI 0.37-0.97). ATR-salpaajat myös pienensivät hormonihoidon aloituksen riskiä (HR: 0.81 CI:0.71-0.92).

ATR-salpaajien käyttäjät poikkesivat muista potilaista, sillä eturauhassyöpäkuolleisuus oli heillä pienempi ja heille aloitettiin harvemmin hormonihoito. ATR-salpaajat ovat lupaava lääkeryhmä, jota voisi hyödyntää eturauhassyövän hoidossa, mutta lisää tutkimusta tarvitaan mekanismin selvittämiseksi.

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Novelty and Impact

Antihypertensive drugs are a very common drug group and in our study they are associated with worse prostate cancer survival after radical prostatectomy. Use of antihypertensive drugs also may also increase risk of starting androgen-deprivation therapy. In contrast use of ATR-blockers may be associated with lower risk of prostate cancer death as well as lower risk of starting androgen-deprivation therapy.

1 ABSTRACT

Antihypertensive (anti-HT) drugs targeting renin-angiotensin-aldosterone (RAA)- system have been associated with improved prostate cancer (PCa)-specific survival. Challenge is that often multiple drugs are used simultaneously. We evaluated the association between use of anti-HT drugs and PCa survival among 14,422 surgically treated Finnish PCa patients. Information on drug purchases was obtained from a national prescription database. We used Cox regression to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for risk of PCa death and initiation of androgen deprivation therapy (ADT) with adjustment for age, tumor extent, use of statins and for Charlson Comorbidity Index. Angiotensin-converting enzyme (ACE)- inhibitors, angiotensin- receptor (ATR)-blockers, diuretics, calcium -channel blockers, beta-blockers and other anti-HT drugs were analyzed as separate time-dependent variable to model simultaneous use. Overall anti-HT drugs were associated with an increased risk of PCa death. Conversarily use of ATR-blockers was associated with decreased risk of PCa death (HR: 0.43, 95% CI: 0.26-0.72 and HR: 0.60, 95% CI 0.37-0.97 for pre- and post-diagnostic use). Similar risk decrease was not observed in other drug groups. Anti-HT drugs were also associated with an increased risk of starting ADT, with the exception of ATR -blockers (HR: 0.81 CI:0.71-0.92). ATR- blockers differ from other anti-HT drugs as the survival is better in users of this drug group. The result partly supports the role of RAA system in PCa progression. Nevertheless, the risk decrease was not observed in ACE-inhibitor users. Further research is needed to elucidate the molecular mechanism for the potential anticancer effect of ATR- blockers.

2 INTRODUCTION

Prostate cancer is the most common cancer among men in the Western countries. It causes great losses in terms of health- care expenditure and life-years. Nevertheless, etiology of the disease is poorly understood.

It has been suggested that hypertension, by itself or as part of metabolic syndrome, may be a prostate cancer risk factor [1-4]. Furthermore, other factors that associate with hypertension, such as elevated heart rate and obesity, may also be associated with prostate cancer risk.[5,6]

Although hypertension is a putative prostate cancer risk factor, it is unclear whether use of antihypertensive drugs might reduce the risk or improve the prognosis. According to some studies antihypertensive medication can increase the risk of PCa diagnosis [7]. Some classes of antihypertensive drugs, such as angiotensin-receptor blockers and ACE-inhibitors have been associated to better PCa survival and better prognosis [8,9]. Not all studies agree, though [10,11]. Also beta-blockers have been associated with a reduction in PCa risk [12]. In addition to studies estimating antihypertensive drugs as a group, captopril as a single drug may reduce the risk of prostate cancer [13]. Challenge for epidemiological studies on antihypertensive drugs is that it is common to simultaneously use several different antihypertensive drugs, especially among the elderly. Therefore, when studying the independent effect of one drug or drug group, it is imperative to take into account simultaneous use of other drugs for the same indication. Here, we evaluated prostate cancer survival and risk of starting androgen-deprivation therapy after radical prostatectomy by anti-HT drug use in a nationally comprehensive cohort while taking into account simultaneous use of multiple drug groups. Our pre-specified hypothesis was that use

of ACE-inhibitors, ATR blockers, beta-blockers and calcium-channel blockers might be associated with better survival.

3 MATERIALS AND METHODS

Study cohort

Our study cohort consisted of 14,422 men with prostate cancer who were treated with radical prostatectomy in Finland during years 1995-2013. The cases were identified from the Finnish Cancer Registry, which covers approximately 95 % of cases diagnosed yearly in Finland. Information in the registry is gathered via mandatory reports of all cancer diagnoses made in Finnish health care units.[14] The Registry collects data on the primary site of cancer, histology, date and method of diagnosis, primary treatment method and date and cause of death. Limited information on tumor extent is also available. The registry does not record Gleason score or PSA level at diagnosis.

Information on antihypertensive medication use

The study cohort was linked to a national prescription database for comprehensive information on antihypertensive drug use during 1995-2013. The linkage was done using unique personal identification number. The national prescription database is maintained by the Finnish Social Insurance Institution (SII). SII provides reimbursements for physician-prescribed drug purchases to all Finnish citizen as part of the national health insurance. Reimbursements are available for all purchases of SII-approved drugs in an outpatient setting. Drugs administered during inpatient periods are not recorded in the database. The information on each purchase includes dose, the date, package size and number of packages bought.

All purchases of anti-HT drugs were identified using drug-specific ATC-codes (Supplementary table 1). Antihypertensive drugs were categorized into six separate drug groups: Angiotensin converting enzyme (ACE) -inhibitors, Angiotensin-receptor blockers (ATR-blockers), diuretics, beta-blockers, calcium-channel blockers and other antihypertensive drugs. The diuretics group includes thiazides, loop-diuretics and potassium-sparing diuretics. The Angiotensin-receptor blocker group includes drugs blocking the AT_1 receptor, a receptor for angiotensin 2.

In addition to anti-HT drugs, information on use of statins was also collected from database as they are often used simultaneously with anti-HT medication. No information on use of other drugs than statins and anti-HT drugs was collected.

Information on androgen deprivation therapy

Information on purchases of GnRH-agonists and -antagonists and antiandrogens were obtained from the prescription database, identified by drug-specific ATC-codes (Supplementary table 1).

The cohort was linked to Care Registry (HILMO) maintained by the National Institute For Health And Welfare to collect information on orchiectomies (Nordic Classification of Procedures code KFC00) conducted in study population during 1995-2013. The Registry records all diagnoses and medical procedures from in- and outpatient hospital visits in Finland.

Information on orchiectomies was combined to information on use of GnRH-agonists and -antagonists and antiandrogens to identify men starting androgen deprivation therapy (ADT) after radical prostatectomy. Combined information was used as a proxy for disease recurrence after prostatectomy.

Diagnoses recorded in the HILMO database were also used to calculate Charlson co-morbidity index [15] for each participant. Conditions used in the index calculation are listed in Supplementary table 2.

Statistical analysis

Separate analyses were performed for drug usage before and after PCa diagnosis. We compared risk of prostate cancer death between users and non-users of anti-HT drugs.

The total yearly mg amount of purchases of each anti-HT drug was calculated for each participant based on the dosing, number of packages and package sizes from each purchase. Then, the purchased yearly mg amount was divided with the dose corresponding to drug-specific Defined Daily Dose (DDD) [16] for the total number of DDDs the person had purchased per year. Each year with recorded medication purchases was considered as year of usage regardless of the purchased amount.

Cumulative number of DDDs and years of usage were calculated separately for each year after PCa diagnosis. Yearly dosing was evaluated by forming an intensity variable dividing cumulative number of DDDs with cumulative number of years of usage. Anti-HT medication use before PCa diagnosis was estimated by adding together usage from all years between 1995 and the year of the diagnosis. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the risk of prostate cancer death and for starting ADT after diagnosis. Time metric was years and months since PCa diagnosis. In analyses for the risk of death the follow-up continued until death, emigration or the common closing date Dec 31, 2013, whichever came first. In analyses for the risk of starting ADT after diagnosis the follow-up continued until first record of

any ADT (medical or surgical castration, antiandrogen use), death or the common closing date. Cox regression analyses were adjusted for age at diagnosis, tumor extent (categorized as local, locally advanced, metastatic or unknown), Charlson co-morbidity Charlson co-morbidity index and use of statins during the follow-up. Sensitivity analyses were stratified by time of PCa diagnosis (1995-1999, 2000-2009, 2010 or later) to estimate role of changed criteria for operative management in the risk association by anti-HT drug use over the course of time.

Anti-HT drug use before diagnosis was analyzed as time-fixed variable taking into account the duration and cumulative dose of use occurring between 1995 and year of PCa diagnosis. Post-diagnostic use was analyzed as time-dependent variable to minimize immortal time bias. Time-dependent variables were formed by updating medication user status as well as cumulative amount, duration and intensity of use separately for each follow-up year after PCa diagnosis. Dose dependence was evaluated by stratifying medication users by tertiles of DDD amount, duration and intensity of use based on the level reached on each follow-up year

Simultaneous use of multiple anti-HT drug groups was modelled by forming separate time-dependent variables for use of each drug group, i.e. ACE-inhibitors, ATR-blockers, beta-blockers, calcium channel blockers, diuretics and other anti-HT drugs not belonging to these groups. These variables were included in the Cox regression model simultaneously. Participants who had purchased more than one anti-HT drug group in a given year were considered as users for each drug group variable of which they had purchases.

Long-term association between anti-HT drug use and risk of prostate cancer death was investigated in lag time analyses where the exposure was lagged forward in the follow-up time;

analyzing medication use that occurred one, three or five years before.

The data was analysed using the IBM SPSS statistics 24 program. All reported p-values are two-sided.

4 RESULTS

Population characteristics

Anti-HT drug use was very common in our study population. Of the 14,422 men 9,799 (67.9%) had used at least one anti-HT drug before or after diagnosis; 4,625 (32.1%) men had not used any kind of anti-HT medication. Compared to non-users, anti-HT medication users were older at diagnosis (median age 63 years), had more often localized tumor extent and also used more often statins and antidiabetic medication. During the median follow-up of 9.9 years after PCa diagnosis, a total of 1,581 men (11/100 men) died. Of these, 424 (3/100) died of PCa (Table 1). Ten year overall mortality was 7.5/100 men. A total of 2,849 men (20/100 men) started androgen deprivation therapy during the follow-up.

Antihypertensive drug usage before prostate cancer diagnosis

Compared to non-users, men who had used ATR- blockers before the diagnosis had a lower risk for prostate cancer death both in the age-adjusted and multivariable adjusted analysis (multivariable adjusted HR: 0.43 CI: 0.26-0.72) (Table 2). When stratified by duration of use also the other anti-HT drug groups, such as ACE inhibitors, calcium channel blockers and beta blockers were associated with lowered risk of PCa death in some strata. However, when stratified by average yearly dose of usage the decreased risk was observed only at low-dose use for drug groups other than ATR-blockers (Table 2). In users of ATR-blockers the risk decrease was observed regardless of

yearly dosage.

In contrast, usage of diuretics before the diagnosis was associated with borderline significant increase in risk of PCa death (HR 1.62, 95% CI 0.97-2.70). When stratified by cumulative use, the risk increase was observed only in the strata of lowest cumulative amount (HR: 1.67 CI: 1.10-2.54), but not in longer-term or high-dose use.

Antihypertensive drug use after the diagnosis

Post-diagnosis use of ATR- blockers was associated with better prostate cancer survival compared to non-users both in the age-adjusted and multivariable-adjusted analyses (Table 3). The risk decrease persisted even with five years' lag time.

In contrast, use of any other antihypertensive drugs was associated with an increased risk compared to non-users (Table 3). When drug groups were analyzed separately, the risk increase was significant only for post-diagnosis use of beta-blockers. The increased risk estimates attenuated within five years' lag-time, but remained elevated compared to non-users for beta-blockers and ACE inhibitors.

Dose-dependence of the risk association between ATR- blocker use and prostate cancer death

The risk of PCa death decreased in inverse association with average annual dose of ATR-blocker use post-diagnosis, although the stratified risk estimates were non-significant (Table 4). For ATR-blocker use before PCa diagnosis no clear dose-dependence in the risk association was observed.

Anti-HT drug use and risk of starting androgen deprivation therapy (ADT)

Pre-diagnostic use of most anti-HT drug groups was associated with elevated risk of starting ADT

after prostatectomy compared to non-users (Table 5). Only exception was ATR-blockers, which were associated with a reduced risk of starting ADT (HR: 0.81 CI: 0.71-0.92).

For post-diagnostic use, ATR-blockers remained to be associated with lowered risk of starting ADT (HR: 0.80 CI: 0.69-0.92) (Table 5). However, no significant risk difference was observed between users and non-users of other groups of anti-HT drugs.

Sensitivity analyses

When analyzing all cause mortality a decreased risk among users of ATR-blockers (HR: 0.73, CI: 0.58-0.92) and increased risk among users of all other anti-HT drug types was observed.

To test whether the risk decrease observed in ATR-blocker users was only due to telmisartan, we re-ran the analysis after exclusion of telmisartan users. ATR blocker use remained associated with lowered risk of PCa death (HR 0.50, 95% CI 0.28-0.88).

We also tested whether captopril had differing risk association compared to ATR-blockers. After excluding captopril the risk of PCa death was lowered in ATR-blocker users compared to non-users (HR: 0.35 CI: 0.21-0.57). Captopril alone was associated with increased risk of PCa death (HR: 2.09 CI: 0.67-6.58).

After excluding use of all other anti-HT drugs except ATR-blockers the risk decrease wasn´t statistically significant but stayed decreased (HR: 0.64 CI: 0.09-4.65).

To test effect of ATR-blockers on PCa survival in different time periods we divided our data in three groups based on year of diagnosis: 1995-1999, 2000-2009 and 2010-2014. We re-run the

analyses in those three groups. The risk decrease among ATR-blockers was observed only in group 1995-1999 but not in other groups. The risk associations weren´t statistically significant as the number of PCa deaths was low. Risk estimates for ATR-blockers in group 1995-1999 (HR: 0.246 CI: 0.034-1.788), in group 2000-2009 (HR: 1.018 CI:0.588-1.762) and in group 2010-2013 (HR: 1.772 CI: 0.134-23.479).

We also tested if year of diagnosis affected the results. Operative management is conducted soon after diagnosis and we supposed that year of surgery was the same as the year of diagnosis. We added year of PCa diagnosis in our multivariable analyses before and after PCa diagnosis. The risk decrease among ATR-blockers became statistically non-significant in pre-diagnostic analyses (Table 6). The decreasing effect of diuretics and beta-blockers on PCa survival increased (Supplementary table 3 and 4). In analyses before PCa diagnosis some changes in risk estimates were observed but at non-significant level (Table 7).

5 DISCUSSION

In our study antihypertensive drugs are generally associated with increased risk of PCa progression after radical prostatectomy as measured by starting ADT use and prostate cancer death. The risk association was observed for multiple anti-HT drug groups with distinctly different mechanisms of action, like beta-blockers and diuretics. This suggests that the risk increase is caused by underlying common indication for medication use, i.e. hypertension. The risk association was strongest when anti-HT medication use had started before PCa diagnosis, suggesting that hypertensions may be a risk factor for PCa progression in long-term.

In contrast, use of ATR- blockers was associated with lowered risk of starting ADT and improved

prostate cancer survival. The risk decrease was significant both for usage before and after PCa diagnosis. No clear dose-dependence was observed for usage before PCa diagnosis, but for post-diagnostic use the risk of PCa death decreased in inverse correlation with the intensity, cumulative amount and years of ATR-blocker use. The differing risk association as compared to other anti-HT drugs and the dose-dependent risk association support causal association between ATR-blocker use and PCa prognosis. The risk of starting ADT after prostatectomy was high also among ATR-blocker users which argues against selection bias of more favorable risk cases among them. However, also non-causal explanations should be considered.

In subgroup analyses where we analyzed the effect of year of diagnosis the risk decrease among ATR-blockers remained decreased. Because of low numbers of PCa deaths the risk decrease was observed only in cases diagnosed in the 90s and which therefore have had sufficient time to reach any significant PCa mortality. There may be selection bias among ATR-blocker users that cause the difference between ATR-users and other anti-HT users. ATR-blocker users may be healthier as we don´t have information on therapeutic equilibrium of other diseases. However there are no differences in comorbidity indexes or risk of starting ADT between ATR-users and non-users.

ACE inhibitors and ATR-blockers both affect renin-angiotensin-aldosterone system (RAA-system), lowering blood pressure. In addition, RAA-system also controls vascular growth by inhibiting cell proliferation and mitosis via AT1 receptor [17]. However, our results do not directly support importance of RAA system in PCa progression as the risk decrease was observed only for users of ATR-blockers, whereas ACE inhibitors were associated even with an increased risk of PCa death.

Thus, the specific mechanism of how ATR-blockers may decrease the risk of PCa death and reduce

disease recurrence remains unclear. *In vitro,* telmisartan but not other sartans has been reported to cause apoptosis in prostate cancer cells [18]. However, in sensitivity analyses the survival benefit among ATR-blocker users compared to non-users remained after exclusion of telmisartan users, confirming that the risk decrease is observed for ATR blockers as a group. Further studies are needed to elucidate the possible mechanism for the risk decrease only among ATR-blocker users.

All anti-HT drugs except beta-blockers are the first line treatment of hypertension in Finland. Beta-blockers are used to treat hypertension combined with coronary artery disease. It is also possible that men using ATR-blockers are systematically different from men using other types of anti-HT drugs, which may cause selection bias to cause the difference compared to other anti-HT drug groups. Nevertheless, selection bias should not be dose-dependent, whereas in our study a dose-dependent inverse risk association between ATR-blocker use and PCa death was observed. This argues against selection bias. Further, all men had been treated with radical prostatectomy at baseline, which presumably makes the study population fairly homogenous. Concordantly, the distribution of measured background characteristics were similar in men using ATR-blockers and those using other types of anti-HT drugs.

The strengths of our study are long follow up -time, detailed information on timing and amount of medication use and a nationwide study cohort, covering all PCa patients managed with prostatectomy in Finland since 1995. We were able to take into account use of other drugs and analyze separately each anti-HT drug group. Our registry-based data on medication use was exceptionally detailed and free of recall bias.

The main limitation of the study is low number of PCa deaths in this cohort of operatively managed PCa patients. This limited statistical power in subgroups analyses. We did not have information on therapeutic equilibrium of the participants' hypertension and we cannot be sure if anti-HT drugs were used to control other diseases than hypertension. Beta-blockers and diuretics are also used to treat coronary artery disease which has been suggested as PCa risk factor [19,20]. Our data on medication use was based on recorded medication purchases, we had no information whether the drugs were actually consumed. Further, we had no information on life-style factors such as BMI, smoking, diet or exercise activity which could have served as confounding factors. However, role of these conditions as risk factors for PCa progression or death is unclear.

In conclusion, antihypertensive drugs are associated with increased risk of PCa death and starting of ADT after radical prostatectomy. An exception are ATR-blockers which are associated with better PCa survival and lowered risk of starting ADT. The risk decrease is observed in inverse association with annual dose of ATR-blocker use. Our results support further studies elucidating the mechanism behind the possible anticancer effect, and ultimately doing clinical trials testing ATR-blockers in men with prostate cancer.

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7 TABLES

Table 1. Population characteristics.

	non-users	ACE-inhibitors	ATR-blockers	beta-blockers	calcium-channel blockers	diuretics	other anti-HT drugs
n of men	4624	5045	4153	6367	4806	5016	410
median follow time (IQR)	8.08 (5.4-11.6)	10.6 (6.7-14.0)	10 (6.4-13.6)	10.4 (6.7-14.2)	10.3 (6.6-14.0)	10.5 (6.8-14.1)	11.1 (7.3-14.9)
n of Pca deaths (% of users)	85 (1.8%)	131(2.6%)	77 (1.9%)	207 (3.3%)	133 (2.8%)	247 (4.9%)	16 (3.9%)
n (%) of starting ADT	729 (15.8)	1089(21.6)	792 (19.1)	1439 (22.6)	1055 (22.0)	1239 (24.7)	107 (26.1)
Charlson comorbidity index , median (IQR)	2 (2-4)	2 (2-6)	2 (2-6)	2 (2-6)	2 (2-6)	2 (2-6)	2 (2-4)
Age at diagnosis, median (IQR)	61 (33-91)	63 (40-93)*	62 (40-93)	63 (39-92)*	63 (40-88)*	63 (40-93)*	63 (42-87)
Tumor extent at diagnosis, n(%)							
Localized	3252 (70.3)	3626 (71.9)*	3028 (72.9)*	4547 (71.4)*	3447 (71.7)*	3604 (71.8)*	299 (72.9)
Locally advanced	851 (18.4)	779 (15.4)	637 (15.3)	989 (15.5)	756 (15.7)	779 (15.5)	57 (13.9)
Unknown	522 (11.3)	640 (12.7)	488 (11.8)	831 (13.1)	603 (12.5)	634(12.6)	54 (13.2)
Statin use, n (%)	1274 (27.5)	3390 (67.2)*	2618 (63.0)*	4164 (65.4)*	3034 (63.1)*	3161 (63.0)*	269 (65.6)*
Antidiabetic medication use; n (%)	279 (6.0)	1370 (27.2)*	1038 (25.0)*	1453 (22.8)*	1227 (25.5)*	1328(26.5)*	125 (30.5)*

* $P < 0.05$ for difference compared to non-users

Table 2. Risk of prostate cancer death by antihypertensive drug use before prostate cancer diagnosis.

		Risk of PCa death	
Drug group	n of users/PCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multiavariable\ adjusted*}$
ACE inhibitors	530 / 28	1.02 (0.66-1.57)	1.10 (0.70-1.72)
ATR-blockers	1781 / 15	0.39 (0.23-0.65)	0.43 (0.26-0.72)
Average yearly dose of ATR-blocker (mg/yr)			
0-286.22	592 / 5	0.34 (0.14-0.81)	0.38 (0.16-0.92)
286.22-460.00	596 / 6	0.43 (0.19-0.95)	0.50 (0.22-1.11)
460→	593 / 4	0.40 (0.15-1.09)	0.48 (0.18-1.28)
beta-blocker	670 / 43	1.54 (1.01-2.14)	1.82 (1.30-2.56)
calcium-channel blocker	448 / 17	0.77 (0.47-1.27)	0.84 (0.51-1.40)
diuretics	319 / 22	1.48 (0.89-2.45)	1.62 (0.97-2.70)
other anti-HT drugs	27 / 5	3.03 (1.24-7.43)	3.90 (1.59-9.62)

*= calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

Table 3. Risk of prostate cancer death by antihypertensive drug use after prostate cancer diagnosis.

		Risk of PCa death		Lag-time		
Drug group	n of users/PCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multiavariable\ adjusted*}$	1yr	3yrs	5yrs
ACE inhibitors	4515/103	1.16 (0.85-1.58)	1.10 (0.81-1.49)	1.14 (0.84-1.56)	1.14 (0.83-1.56)	1.40(1.00-1.95)
ATR blockers	2372/62	0.59 (0.36-1.00)	0.60 (0.37-0.97)	0.55 (0.34-0.89)	0.52 (0.31-0.86)	0.55 (0.30-0.98)
Beta-blockers	5697/164	1.37(1.07-1.75)	1.30 (1.01-1.67)	1.43 (1.11-1.84)	1.40(1.08-1.81)	1.30(0.98-1.73)
Calcium-channel blockers	4358/116	1.04 (0.77-1.40)	1.01 (0.75-1.37)	1.02 (0.75-1.37)	0.92 (0.67-1.26)	0.97 (0.69-1.37)
Diuretics	4698/225	1.30(0.93-1.82)	1.32 (0.95-1.85)	1.31 (0.94-1.84)	1.14 (0.80-1.62)	0.94 (0.63-1.40)
Other antihypertensive drugs	383/11	2.18(0.97-4.91)	1.89 (0.84-4.26)	1.96 (0.87-4.43)	2.18(0.96-4.92)	2.34 (0.96-5.71)

*= calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

Table 4. Risk of prostate cancer death by cumulative amount, duration and average yearly dose of ATR-blocker use after diagnosis.

Amount of use (mg)	n of men/PCa deaths	Riski of Pca death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI) multiavariable adjusted*
0-1339.33	1351 / 36	1.13 (0.72-1.43)	1.13 (0.80-1.61)
1339.33-4200.00	1392 / 30	0.85 (0.58-1.25)	0.91 (0.62-1.34)
4200.00→	1404 / 11	0.51 (0.25-1.05)	0.54 (0.26-1.10)
Duration of use (years)	n of men/PCa deaths	Riski of Pca death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI)
0-4	1547 / 44	0.84 (0.62-1.15)	0.91 (0.66-1.24)
4-9	1367/ 24	0.61 (0.40-0.92)	0.64 (0.42-0.97)
9→	1239 / 9	0.03 (0.00-0.08)	0.02 (0.01-0.08)
Average yearly dose (mg/yr)	n of men/PCa deaths	Riski of Pca death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI)
0-310.33	1352 / 36	1.19 (0.83-1.67)	1.37 (0.96-1.97)
310.33-536.27	1398 / 24	0.80 (0.52-1.23)	0.86 (0.56-1.33)
536.27→	1403 / 17	0.60 (0.37-0.97)	0.61 (0.38-1.01)

*= calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

Table 5. Risk of starting androgen deprivation therapy (ADT) by antihypertensive drug use before or after prostate cancer diagnosis

	Anti-HT drug use before diagnosis		
Drug group	n of men starting ADT (%)	HR (95% CI)$_{\text{age-adjusted}}$	HR (95% CI)$_{\text{multiavariable adjusted*}}$
ACE inhibitors	162 (30,6)	1.28 (1.08-1.53)	1.32 (1.11-1.58)
ATR-blockers	250 (14,0)	0.81(0.71-0.93)	0.81 (0.71-0.92)
Beta-blockers	211 (31,5)	1.33 (1.14-1.54)	1.38 (1.19-1.61)
Calcium-channel blockers	135 (30,1)	1.21 (1.01-1.45)	1.26 (1.05-1.51)
Diuretics	89 (27,9)	0.89 (0.70-1.13)	0.90 (0.70-1.14)
Other anti-HT drugs	13 (48,1)	1.91 (1.10-3.30)	2.24 (1.29-3.89)
	Anti-HT drug use after diagnosis		
ACE inhibitors	1089 (24,1)	1.02 (1.03-1.05)	1.01 (0.90-1.13)
ATR-blockers	792 (33,4)	0.80 (0.69-0.92)	0.80 (0.69-0.92)
Beta-blockers	1439 (25,3)	1.11 (1.00-1.22)	1.09 (0.99-1.21)
Calcium-channel blockers	1055 (24,2)	1.06 (0.95-1.19)	1.05 (0.94-1.17)
Diuretics	1239 (26,4)	0.99 (0.87-1.12)	1.00 (0.88-1.14)
Other anti-HT drugs	107 (27,9)	1.43 (0.98-2.10)	1.44 (0.98-2.10)

*= calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

Table 6. Risk of prostate cancer death by antihypertensive drug use after prostate cancer diagnosis. Adjusted analyses with year of diagnosis.

		Risk of PCa death		Lag-time		
Drug group	n of users/PCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multiavariable\ adjusted\ (*)}$	1yr	3yrs	5yrs
ACE inhibitors	4515/103	1.16 (0.85-1.58)	1.28 (0.94-1.74)	1.23 (0.91-1.68)	1.33 (0.97-1.82)	1.45 (1.03-2.04)
ATR blockers	2372/62	0.59 (0.36-1.00)	1.12 (0.68-1.83)	1.02 (0.63-1.68)	1.03 (0.62-1.73)	0.92 (0.49-1.69)
Beta-blockers	5697/164	1.37(1.07-1.75)	1.39 (1.08-1.79)	1.34 (1.04-1.73)	1.39 (1.07-1.80)	1.32 (0.99-1.76)
Calcium-channel blockers	4358/116	1.04 (0.77-1.40)	1.04 (0.77-1.40)	1.01 (0.75-1.36)	0.94 (0.69-1.29)	1.00 (0.71-1.40)
Diuretics	4698/225	1.30(0.93-1.82)	1.30 (0.94-1.82)	1.29 (0.92-1.80)	1.13 (0.79-1.61)	0.99 (0.67-1.49)
Other antihypertensive drugs	383/11	2.18(0.97-4.91)	1.46 (0.65-4.26)	1.44 (0.64-3.26)	1.69 (0.75-3.82)	2.09 (0.86-5.09)

*= calculated cox regression model with adjustments of age, tumor extent, CCI, statin use and year of PCa diagnosis

Table 7. Risk of prostate cancer death by antihypertensive drug use before prostate cancer diagnosis. Adjusted analyses with year of diagnosis.

		Risk of PCa death	
Drug group	n of users/PCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multiavariable\ adjusted*}$
ACE inhibitors	530 / 28	1.02 (0.66-1.57)	1.20 (0.88-1.63)
ATR-blockers	1781 / 15	0.39 (0.23-0.65)	0.96 (0.58-1.57)
Average yearly dose of ATR-blocker (mg/yr)			
0-286.22	592 / 5	0.34 (0.14-0.81)	0.66 (0.27-1.62)
286.22-460.00	596 / 6	0.43 (0.19-0.95)	0.99 (0.44-2.23)
460→	593 / 4	0.40 (0.15-1.09)	1.30 (0.48-3.54)
beta-blocker	670 / 43	1.54 (1.01-2.14)	1.31 (1.02-1.68)
calcium-channel blocker	448 / 17	0.77 (0.47-1.27)	1.00 (0.74-1.34)
diuretics	319 / 22	1.48 (0.89-2.45)	1.28 (0.92-1.79)
other anti-HT drugs	27 / 5	3.03 (1.24-7.43)	1.43 (0.63-3.225)

*= calculated cox regression model with adjustments of age, tumor extent, CCI, statin use and year of PCa diagnosis