SOTALOL, BUT NOT DIGOXIN IS ASSOCIATED WITH DECREASED PROSTATE CANCER RISK. A POPULATION-BASED CASE-CONTROL STUDY.

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TIIVISTELMÄ

Rytmihäiriölääke digoksiinilla on raportoitu olevan apoptoosia lisäävää ja sytotoksista vaikutusta eturauhassyöpäsoluihin. Selvitimme rytmihäiriölääkkeiden käytön ja eturauhassyöpäriskin yhteyttä väestöpohjaisessa tapaus-verrokkitutkimuksessamme. Aineisto sisälsi kaikki uudet todetut eturauhassyöpätapaukset Suomessa vuosina 1995-2002 Suomen Syöpärekisteristä ja kullekin tapaukselle kaltaistetun verrokin Väestörekisterikeskuksesta (24657 tapaus-verrokkiparia). Tiedot rytmihäiriölääkeostoista haettiin kansallisesta reseptitietokannasta.

Aineiston analysoinnissa käytettiin monivakioitua ehdollista logistista regressiomallia. Emme löytäneet tilastollisesti merkitsevää yhteyttä digoksiinin käytöllä ja yleisen (OR 0.95, 95% CI 0.89-1.01) tai levinneen (OR 0.90, 95% CI 0.77-1.05) eturauhassyövän riskillä verrattuna ei-käyttäjiin. Tulokset olivat samanlaiset kaikille rytmihäiriölääkkeille lukuunottamatta sotalolia, jonka käyttäjillä oli alhaisempi levinneen eturauhassyövän riski (OR 0.73, 95% CI 0.56-0.96). Myös yleinen eturauhassyövän riski laski sotalolin käyttöajan funktiona.

Tutkimuksemme osoittaa, että digoksiinin tai muiden tavallisten rytmihäiriölääkkeiden käyttö ei yleisesti ole yhteydessä eturauhassyöpäriskiin väestötasolla maksimissaan kahdeksan vuoden seurannalla. Kuitenkaan emme voi sulkea pois digoksiinin pitkäaikaisempa suojavaikutusta. Kaliumkanavan estäjä sotalolin mahdollinen suojavaikutus vaatii vielä lisätutkimusta.

SOTALOL, BUT NOT DIGOXIN IS ASSOCIATED WITH DECREASED PROSTATE CANCER RISK. A POPULATION-BASED CASE-CONTROL STUDY.

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Abbreviations: BPH: benign prostatic hyperplasia, BMI: body mass index, CI: confidence interval, DDD: defined daily dose, HIF: hypoxia-inducible factor, NSAID: non-steroidal anti-inflammatory drug, OR: odds ratio, PSA: prostate-specific antigen, SII: Social Insurance Institution of Finland
Article category: Epidemiology

Novelty and impact of the work:
This is the first study to comprehensively evaluate the association between antiarrhythmic drug use and prostate cancer risk. We could not confirm previously reported decreased prostate cancer risk among digoxin users, but found lower risk of advanced prostate cancer among men using beta-blocker/K+-channel inhibitor sotalol. These findings lessen the enthusiasm to study digoxin as prostate cancer preventive agent, but the effects of sotalol warrant further study.

ABSTRACT

Antiarrhythmic drug digoxin has been reported to have apoptosis-inducing and cytotoxic effects on prostate cancer cells. We evaluated the association between antiarrhythmic drug use and prostate cancer risk in a population-based case-control study. The study included all new prostate cancer cases diagnosed in Finland during 1995-2002 and matched controls (24,657 case-control pairs) obtained from the Finnish Cancer Registry and the Population Register Center, respectively. Information on antiarrhythmic drug purchases was obtained from national prescription database.

Multivariable-adjusted conditional logistic regression model was used for data analysis. Compared to never-users of antiarrhythmic drugs, we found no significant association between digoxin use and prostate cancer risk overall (OR 0.95, 95% CI 0.89-1.01) or for advanced prostate cancer risk (OR 0.90, 95% CI 0.77-1.05). The result was similar also for other antiarrhythmic drugs, with the exception of sotalol, users of which had decreased risk of advanced prostate cancer (OR 0.73, 95% CI 0.56-0.96). Also the overall prostate cancer risk decreased by duration of sotalol use (p for trend 0.038).

We show that digoxin or other common antiarrhythmic drugs generally do not associate with prostate cancer risk at population level during maximum follow-up of eight years. However, we cannot rule out longer-term protective effects of digoxin. Possible prostate cancer preventive effects of K^+-channel blocker sotalol deserve further study.

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1 INTRODUCTION

Prostate cancer is the most common malignancy among men in most countries.[1] Despite being a major public health problem, its etiology is still not well-known. A deeper knowledge of the risk factors is needed for prevention and better treatment of the condition.

Digoxin, a commonly used antiarrhythmic agent, inhibits prostate cancer cell growth by increasing apoptosis.[2,3] The mechanism of action for cardiac glycosides such as digoxin involves inhibition of the plasma membrane Na+/K+-ATPase, leading to changes in intracellular K+- and Ca2+-concentrations. The apoptosis-inducing effect of digoxin has been proposed to be caused by increased Ca2+-uptake in prostate cancer cells,[2,3] leading to changes in activity of cyclin-dependent kinase Cdk5, p35 cleavage and p25 formation.[4] Cardiac glycosides also decrease prostate specific antigen (PSA) secretion in prostate cancer cells.[5] In a mouse model digoxin treatment caused decreased blood vessel density and inhibition of HIF-1α expression in castration-resistant xenograft tumors, but no reduction in tumor volume.[6]

On the other hand, digoxin possesses estrogen-mimicking effects, and its use is associated with an increased incidence of breast and uterine cancer.[7] This would provide another plausible mechanism for prostate cancer inhibiting effects.

Recently, a novel two-stage study both confirmed the cytotoxic effects of digoxin against prostate cancer cells, and also reported decreased prostate cancer incidence among men who had used digoxin regularly for over ten years within a cohort of 47,884 men.[8]

We evaluated whether the use of digoxin or, for comparison, other antiarrhythmic agents is related to overall or advanced prostate cancer risk at population level.

2 MATERIALS AND METHODS

2.1 study population

We used a nationwide case-control study population including all newly diagnosed prostate cancer cases in Finland during 1995-2002. The study population has been extensively described previously.[9-12]

In brief, all new prostate cancer cases in Finland between 1995 and 2002 (25,029 men) were obtained from the Finnish Cancer Registry. The nationwide registry covers over 99% of all prostate cancer patients in Finland.[13] The registry data includes information on primary site of cancer, histology, date, and method of diagnosis. Tumor stage was available for 13,616 cases (55% of all cases). Of these, 73% were localized. The registry had no information on Gleason score or PSA values or screening activity prior to the diagnosis.

Practically all the cases were histologically confirmed (99.3%). In a small portion the diagnosis was based on clinical (0.4%), radiological (0.3%), other specific laboratory findings (0.02%). 185 cases were excluded for unknown method of diagnosis (0.7%). In addition, 66 duplicate cases were excluded.

For each case, the Population Registry Center of Finland randomly selected a control from among the men who were of the same age (±1 year), living in the same area and were free of prostate cancer at the time of the cases' diagnosis. We used incidence density sampling for control selection, and thus 963 men were considered twice in the analysis; first as a control and then as a case in another case-control pair after being diagnosed with prostate cancer at a later time. Matched controls could not be found for 121 cases in the oldest age group. In the end, a total of 24,657 individually matched case-control pairs were included in the analysis.

The study was approved by the ethics committee of the Pirkanmaa health care district, Finland (ETL R03290).

2.2 information on medication use

Information on reimbursed physician-prescribed medication purchases during 1995–2002 was obtained from the comprehensive nationwide prescription database of the Social Insurance Institution (SII) of Finland. The SII is a governmental agency financed through tax revenues, providing reimbursements for the cost of medicines prescribed by a physician with the exception of hospital inpatients.[14] The reimbursement is available for all Finnish residents, for each purchase of a SII approved reimbursable drug and covers 50-100% of the costs depending on the severity of the disease.

We included all antiarrhythmic agents being used within our study population during 1995-2002. Beta-blockers, which are used both as antihypertensive and as antiarrhythmic drugs, have been analyzed in an earlier study along with antihypertensive medication.[10] The only beta-blocker included in this analysis was sotalol, which is mainly used as an antiarrhythmic agent.
The drugs included in this analysis were amiodarone, digoxin, disopyramide, etilefrine, flecainide, quinidine, mexiletine, propafenone, sotalol and tocainide. Of these, quinidine, disopyramide, mexiletine, tocainide, propafenone and flecainide function as Na+-channel inhibitors. Amiodarone and sotalol are K+-channel inhibitors. Amiodarone also has beta-blocker function. Etilefrine is a sympathomimetic agent that is suggested to stimulate both alpha- and beta-receptors. Digoxin's mechanism of action is not completely understood, but it involves an effect on Na+/K+ ATPase pump.

2.3 statistical analysis

Medication use was followed from January 1st, 1995 up to the month of diagnosis of the prostate cancer cases. For the controls, medication use was followed until the date of diagnosis of the corresponding matched case, ensuring equal available exposure time for the cases and the controls. The amount of antiarrhythmic medication use was standardized across the drug groups by dividing the purchased mg amount of a drug with a quantity corresponding one Defined Daily Dose (DDD) recommended by the WHO.[15] Total number of DDDs for each individual drug was combined for a total sum of DDDs of all antiarrhythmic drugs used by each person.

Propensity for antiarrhythmic drug usage as function of age and usage of other types of drugs was estimated using a logistic regression method with antiarrhythmic drug usage as the dependent variable and age, use of 5α-reductase inhibitors, alpha-blockers, anti-diabetic drugs, cholesterol-lowering drugs and antihypertensive drugs as independent variables. The propensity score for each was added together for total propensity score. The analysis was repeated by quartiles of the total

propensity score to estimate the drugs effect within subpopulations that are comparable in their likelihood to use antiarrhythmic drugs.

Non-users of antiarrhythmic drugs were the reference group in all analyses. We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for overall prostate cancer risk and risk of advanced prostate cancer among the medication users. The analysis was adjusted for age alone (age-adjusted model) or additionally for use of above mentioned drug groups (multivariable-adjusted model).

Each drug was analyzed separately and in combination with other antiarrhythmic drugs. We compared prostate cancer risk by ever-use of the drugs, and also in analysis stratified in quartiles of the amount and duration of medication use. We analyzed trends in prostate cancer risk by cumulative medication use by adding total DDDs or years of usage into the logistic regression model as a continuous variable.

In sensitivity analyses we aimed to estimate the effect of previous PSA-testing by stratifying the analysis by simultaneous usage of drugs used in management of benign prostatic hyperplasia (BPH); 5α-reductase inhibitors and alpha-blockers.

The data was analyzed using Stata 8.2 software (College Station, Texas).

3 RESULTS

3.1 population characteristics

Overall, the prevalence of digoxin use was similar between the cases and controls; 10.6% for the cases (2,616 men) and 10.3% for the controls (2,550 men) (*Table 1*). The overall prevalence of antiarrhythmic drug use was 13.6%, with no difference between cases and controls. Of the other drug groups, prevalence of use for non-steroidal anti-inflammatory drugs (NSAIDs), BPH medication, cholesterol-lowering medication and antihypertensive drugs was higher among the cases, whereas the prevalence of antidiabetic medication use was lower (*Table 1*).

3.2 digoxin use and prostate cancer

Digoxin use was not significantly associated with overall prostate cancer risk either in the age-adjusted analysis (OR 1.03, 95% CI 0.97-1.09) or the multivariable-adjusted analysis (OR 0.96, 95% CI 0.90-1.02). (*Table 2*).

The risk of advanced prostate cancer in digoxin users was lower than the overall prostate cancer risk (multivariable-adjusted OR 0.89, 95% CI 0.76-1.05), but the difference compared to the non-users remained non-significant (*Table 2*).

There was no association between digoxin use and prostate cancer risk, either overall or advanced, within any quartile of digoxin usage (*Table 3*). The multivariable-adjusted trend analysis in prostate cancer risk by cumulative amount or duration of digoxin use likewise showed no associations with overall or advanced prostate cancer.

3.3 other antiarrhythmic drugs and prostate cancer

Usage of any antiarrhythmic drug use was not associated with the risk of either overall (OR 0.96, 95% CI 0.91-1.01) or advanced prostate cancer risk (OR 0.90, 95% CI 0.77-1.04) (*Table 2*). The difference between users and non-users of antiarrhythmic drugs remained non-significant in each quartile of total DDD amount of use, although there was a borderline significant decreasing trend in

overall prostate cancer risk by duration of usage (p for trend = 0.058) (*Table 3*).

When analyzed separately, use of Na^+-channel blockers was not associated with prostate cancer risk (*Table 2*). No individual Na^+-channel blocker had an effect on overall or advanced prostate cancer risk, either. The amount or duration of Na^+-channel blockers use did not affect the risk in the analysis stratified by quartiles (*Table 3*) nor in the trend analysis.

The K^+-channel blockers amiodarone and sotalol as a group were not associated with either overall or advanced prostate cancer risk; multivariable-adjusted OR 0.94, 95% CI 0.85-1.03 and OR 0.78, 95% CI 0.60-1.02, respectively (*Table 2*). However, use of sotalol was associated with a decreased risk of advanced prostate cancer; OR 0.73, 95% CI 0.56-0.96 (*Table 2*). Also overall prostate cancer risk was lower among men who had used sotalol for five years or longer; OR 0.68, 95% CI 0.55-0.85 (*Table 3*). The association with advanced prostate cancer risk was not dose-dependent, but we observed an inverse association between overall prostate cancer risk and years of sotalol usage (p for trend = 0.038) (*Table 3*).

3.4 sensitivity analyses

A sensitivity analysis stratified by quartiles of propensity score confirmed the lack of association between prostate cancer and use of digoxin or other antiarrhythmic drugs, confirming that the association is not modified by the likelihood of being a user of this drug group (*Table 4*). The risk estimates of advanced prostate cancer among sotalol users were uniformly lowered, but statistically non-significant.

An analysis stratified by simultaneous use of BPH drugs (5α-reductase inhibitors and/or alpha-blockers) shower no clear effect modification, either (*Table 5*). The risk of advanced prostate cancer was decreased among sotalol users regardless of BPH-medication usage (OR 0.70, 95% CI 0.50-0.96 and OR 0.21, 95% CI 0.04-1.24 among users and non-users of BPH medication, respectively) (*Table 5*).

When we limited the analysis to include only cases diagnosed during 2000-2002, both digoxin use and antiarrhythmic drug use in general were associated with slight reduction in overall prostate cancer risk (OR 0.89, 95% CI 0.80-0.98 and OR 0.91, 95% CI 0.84-0.99, respectively), but no trend by the cumulative dose of medication use was observed for either. The risk of advanced prostate cancer among digoxin, sotalol and any antiarrhythmic drug users did not differ significantly from

the non-users in this sensitivity analysis.

4 DISCUSSION

Our results suggest that use of digoxin or other antiarrhythmic agents in general does not affect prostate cancer risk at population level with maximum exposure time of eight years. However, sotalol use was inversely associated both with advanced prostate cancer risk, and long-term users also had lower risk of overall prostate cancer. This drug deserves further study as prostate cancer preventive agent.

A previous study has reported promising results of digoxin's inhibitory effects on prostate cancer cell lines and also that regular long-term use of digoxin is related to a lower prostate cancer risk in the Health Professional´s Follow-up Study.[8] In the present study we found no evidence of lower overall or advanced prostate cancer risk among digoxin users at population-level. Furthermore, we found no dose-response in the risk by the cumulative amount or duration of digoxin use. The difference between our results and the earlier study is likely explained with our exposure time being eight years at maximum. In the Health Professional´s Follow-up Study the decreased prostate cancer risk among digoxin users was driven by the very long-term users, i.e. when the analysis was stratified by duration of digoxin use the risk decrease was observed only in men who had used the drug for 10 years or longer.[8] In concordance to our results, digoxin use for less than 10 years was not associated with prostate cancer risk in Health Professional's Follow-up Study, either.[8] This strongly suggests that digoxin's protective effects against prostate cancer likely require a considerably long induction period when the drug is being used at the clinical dose range. This lessens the enthusiasm to study digoxin's prostate cancer preventive effects in clinical trials.

The relationship between use of other antiarrhythmic drugs and prostate cancer has not been studied earlier. Overall, use of any antiarrhythmic drug was not associated with the risk of overall or advanced prostate cancer. An exception was sotalol, which has both K^+-channel inhibitor and beta-blocker activity. Sotalol users had decreased risk of advanced prostate cancer, and also lowered overall prostate cancer risk in long-term users. This is a novel finding. Further, inverse association with advanced prostate cancer persisted in all sensitivity analyses, suggesting that sotalol may indeed prove to be an interesting prostate cancer preventive agent.

In our previous study on antihypertensive drugs and prostate cancer risk within this same study population we observed a slightly increased overall prostate cancer risk, but no change in risk of advanced disease among beta-blocker users.[10] Thus it is probably not sotalol's beta-blocking

properties that affect prostate cancer risk. We analyzed sotalol together with antiarrhythmic drugs because this is the most common indication of use for this drug. The difference between sotalol and other beta-blockers is sotalol's function as a potassium-channel inhibitor in addition to its beta-blocker function. Potassium-channel activity and expression have been suggested to affect prostate carcinogenesis,[16] possibly by altering intracellular Ca2+ concentrations.[17] Interestingly, also digoxin's antitumor effects have been suggested to be mediated by changes in intracellular Ca2+.[2,3] Control of intracellular Ca2+ as a way to limit prostate cancer cell growth merits further study. However, the association between sotalol and advanced prostate cancer risk was not dose-dependent, and use of the other potassium-channel blocker, amiodarone, was not associated with prostate cancer risk in our study. Thus further study is required to affirm our findings.

Our study has important strengths. We had a large population-based study population representing the entire Finland. This allowed enough statistical power to analyze the impact of rarely used drugs, such as digoxin on prostate cancer incidence, and even on advanced prostate cancer. Our information on medication usage was obtained from a comprehensive nationwide prescription database which records information on drug purchases independent of disease status. The controls in our population were individually matched to the cases for age and residence area at the time of diagnosis to avoid confounding by these attributes. The population in Finland is racially homogenous consisting of 98% Caucasians. Thus race is unlikely to be a confounding factor in our study.

Our study also has weaknesses that should be considered. We had no information on the antiarrhythmic drug use prior to 1995 which may lead to underestimation of cumulative duration and amount of medication use for those persons who had a long history of antiarrhythmic drug use prior to 1995. This would presumably bias our results towards the null. Indeed, when we evaluated this bias in a sensitivity analysis limited to include only the cases diagnosed during 2000-2002, i.e. using the case-control pairs with longest information on medication use before the diagnosis, we found slightly decreased overall prostate cancer risk among digoxin users. This further supports the notion that very long-term digoxin use might have a prostate cancer risk decreasing effect.
We did not have information on PSA testing activity within our study population, which could have been more common among antiarrhythmic drug users than non-users, possibly creating a detection bias that elevates the observed prostate cancer risk in medication users and masks possible protective associations. We evaluated this bias by stratifying our analysis by BPH medication usage. Diagnostic work-up of BPH involves PSA testing for exclusion of prostate cancer. Thus BPH medication users present a group of PSA tested men. However, the association between

antiarrhythmic drug use and prostate cancer risk was not modified by BPH medication usage, thus this detection bias is unlikely to affect our results to any great degree.
Tumor stage was known for slightly more than half of the cases (55%). The proportion of cases with missing information on stage was higher among antiarrhythmic drug users and digoxin users (48.7% and 48.5%, respectively) than among non-users of antiarrhythmic drugs (44.6%). This could have masked possible protective associations for advanced prostate cancer among users of digoxin or other antiarrhythmic drugs.

Finally, we did not have information on lifestyle factors apart from medication use, such as BMI, smoking or diet. These could have caused confounding in either direction depending on their association with antiarrhythmic medication usage.

We have shown that use of antiarrhythmic drugs in general does not associate with prostate cancer risk. Further, our study confirms that digoxin does not have a population-level prostate cancer preventive effect during a maximum exposure period of eight years. However, we cannot rule out longer-term protective effects of digoxin that have been suggested by previous research. Studies with longer follow-up time will be needed. The K^+-channel inhibitor/beta-blocker sotalol showed promise for a protective effect against advanced prostate cancer. If this is confirmed in further studies, sotalol may prove to be a promising prostate cancer preventive agent.

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Table 1. Prevalence of Medication Use Among the Study Population of 24,657 Diagnosed Prostate Cancer Cases in Finland in 1995 to 2002 and Their Individually Matched Controls.

	Cases		**Controls**	
	No.	**%**	**No.**	**%**
Total	24,657	50	24,657	50
Digoxin use	2,616	10.6	2,550	10.3
Any antiarrhythmic drug use	3,408	13.8	3,316	13.4
Non-steroidal anti-inflammatory drugs	13,265	53.8	11,475	46.5
Benign prostatic hyperplasia medication[a]	4603	18.7	3086	12.5
Anti-diabetic medication[b]	2209	9.0	2391	9.7
Cholesterol-lowering medication[c]	2621	10.6	2439	9.9
Antihypertensive medication[d]	12,719	51.6	11,749	47.6

[a]Includes finasteride and alpha-blockers tamsulosin and alfuzosin

[b]Includes oral antidiabetic medication and insulin

[c]includes statins, fibric acid derivatives, bile acid binding resins and acipimox

[d]includes diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Table 2. Age-adjusted and Multivariable-adjusted Odds Ratios and 95% Confidence Intervals for Any Prostate Cancer and Advanced Prostate Cancer in Users of Antiarrhythmic Drugs Compared With Nonusers Among 24,657 Finnish Prostate Cancer Cases and Matched Controls During 1995-2002.

Drug type	Overall prostate cancer			Advanced disease[a]		
	N of cases	OR (95% CI) age-adjusted	OR (95% CI) multivar.-adjusted[b]	N of cases	OR (95% CI) age-adjusted	OR (95% CI) multivar.-adjusted[b]
Any antiarrhythmic drug	3,408	1.03 (0.98-1.09)	0.96 (0.91-1.01)	465	0.92 (0.80-1.05)	0.90 (0.77-1.04)
Digoxin	2,616	1.03 (0.97-1.09)	0.96 (0.90-1.02)	375	0.92 (0.79-1.07)	0.89 (0.76-1.05)
Na^+-channel blockers	378	1.06 (0.92-1.23)	0.98 (0.84-1.13)	39	0.78 (0.51-1.19)	0.76 (0.50-1.18)
Quinidine	207	1.04 (0.85-1.26)	0.94 (0.77-1.15)	22	0.73 (0.41-1.27)	0.73 (0.41-1.31)
Disopyramide	93	1.11 (0.82-1.49)	1.04 (0.77-1.40)	14	1.56 (0.68-3.61)	1.73 (0.74-4.05)
Mexiletine	44	1.05 (0.69-1.60)	0.93 (0.61-1.43)	5	0.71 (0.23-2.25)	0.61 (0.19-1.97)
Propafenone	47	1.42 (0.91-2.22)	1.21 (0.77-1.91)	4	0.80 (0.21-2.98)	0.55 (0.15-2.06)
Flecainide	84	1.22 (0.89-1.68)	1.05 (0.76-1.45)	4	0.44 (0.14-1.44)	0.35 (0.10-1.15)
K^+-channel blockers	858	1.01 (0.92-1.12)	0.94 (0.85-1.03)	103	0.78 (0.60-1.01)	0.78 (0.60-1.02)
Amiodarone	99	1.05(0.79-1.40)	0.99 (0.74-1.32)	11	1.57 (0.61-4.05)	1.74 (0.66-4.57)
Sotalol	823	1.02 (0.93-1.13)	0.94 (0.85-1.04)	98	0.73 (0.56-0.96)	0.73 (0.56-0.96)
Other:						
Etilefrine	133	0.87 (0.69-1.10)	0.80 (0.63-1.01)	13	0.72 (0.35-1.48)	0.66 (0.32-1.37)

[a] Includes all stage T3 and T4, N+ and M+ tumors

[b] Calculated with conditional logistic regression adjusted for age and use of antihypertensive drugs, cholesterol-lowering drugs, antidiabetic drugs, non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors and alpha-blockers

Table 3. Multivariable-adjusted Odds Ratios (With 95% Confidence Intervals) of Prostate Cancer Overall and Advanced Prostate Cancer by the Amount and Duration of Antiarrhythmic Drug use Among 24,657 Finnish Prostate Cancer Cases and Matched Controls During 1995-2002.

	Any antiarrhythmic drug		Na+-channel blockers		K+-channel blockers		Digoxin		Sotalol	
	Overall PCa	Advanced PCa[a]	Overall PCa	Advanced PCa	Overall PCa	Advanced PCa	Overall PCa	Advanced PCa	Overall PCa	Advanced PCa
Cumulative total amount of medication use[c]	OR (95% CI)[b]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
1st quartile	0.98 (0.88-1.08)	0.99 (0.76-1.29)	0.89 (0.67-1.18)	0.51 (0.21-1.22)	1.01 (0.84-1.23)	0.66 (0.38-1.17)	1.00 (0.89-1.13)	0.90 (0.67-1.21)	1.02 (0.84-1.24)	0.72 (0.41-1.27)
2nd quartile	0.93 (0.84-1.03)	0.70 (0.54-0.92)	1.17 (0.88-1.54)	0.85 (0.36-2.00)	0.88 (0.73-1.06)	0.70 (0.44-1.14)	0.90 (0.80-1.00)	0.73 (0.56-0.97)	0.93 (0.76-1.15)	0.56 (0.33-0.96)
3rd quartile	0.99 (0.89-1.09)	0.97 (0.75-1.27)	0.94 (0.71-1.26)	1.12 (0.52-2.40)	1.03 (0.85-1.26)	0.79 (0.47-1.34)	1.02 (0.91-1.14)	0.94 (0.70-1.27)	0.97 (0.80-1.18)	0.73 (0.44-1.21)
4th quartile	0.93 (0.84-1.03)	0.96 (0.72-1.29)	0.97 (0.73-1.28)	0.65 (0.28-1.49)	0.85 (0.70-1.04)	1.01 (0.59-1.74)	0.94 (0.83-1.05)	1.10 (0.78-1.55)	0.83 (0.67-1.01)	0.99 (0.56-1.73)
Duration of medication use										
1 year	0.97 (0.88-1.07)	0.90 (0.70-1.16)	1.03 (0.80-1.31)	0.50 (0.25-1.00)	0.97 (0.82-1.14)	0.75 (0.47-1.21)	0.99 (0.88-1.10)	0.88 (0.68-1.15)	1.00 (0.85-1.19)	0.70 (0.43-1.15)

2 years	1.00 (0.89-1.12)	0.88 (0.65-1.18)	0.97 (0.71-1.33)	1.32 (0.45-3.86)	0.93 (0.75-1.15)	0.56 (0.33-0.95)	0.99 (0.87-1.13)	0.91 (0.66-1.27)	0.90 (0.72-1.13)	0.54 (0.31-0.92)
3-4 years	0.97 (0.88-1.07)	0.90 (0.70-1.16)	0.97 (0.74-1.27)	0.92 (0.46-1.87)	1.12 (0.93-1.36)	1.31 (0.78-2.21)	0.93 (0.84-1.04)	0.86 (0.64-1.14)	1.15 (0.94-1.40)	1.05 (0.62-1.78)
5 years or longer	0.90 (0.81-1.00)	0.90 (0.66-1.22)	0.96 (0.70-1.32)	0.90 (0.29-2.86)	0.72 (0.59-0.90)	0.65 (0.35-1.21)	0.94 (0.84-1.07)	0.95 (0.66-1.35)	0.68 (0.55-0.85)	0.73 (0.39-1.36)
P for trend[d]	0.058	NS	NS	NS	0.073	NS	NS	NS	0.038	NS

[a] Includes all stage T3 and T4, N+ and M+ tumors

[b] Calculated with conditional logistic regression adjusted for age and use of antihypertensive drugs, cholesterol-lowering drugs, antidiabetic drugs, non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors and alpha-blockers

[c] Quartile cut-points: Any arrhythmic drugs 1: 6-150 DDD, 2: 155-445DDD, 3:450-950 DDD, 4: 955 DDD or more; Na^+-channel blockers 1: 5-77 DDD, 2: 78-350 DDD, 3: 351-840 DDD 4: 841 DDD or more; K^+-channel blockers 1: 15-100 DDD, 2: 101-400 DDD, 3: 401-900 DDD 4: 901 DDD or more; digoxin 1:5-145 DDD, 2: 150-390 DDD, 3: 400-800 DDD, 4: 810 DDD or more, and sotalol 1: 15-100 DDD, 2: 105-395 DDD, 3: 400-900 DDD, 4: 915 DDD or more

[d] Calculated by analyzing the total number of years of medication use as a continuous variable

Table 4. Risk of Prostate Cancer Overall and Advanced Prostate Cancer in Users of Antiarrhythmic Drugs, Digoxin and Sotalol Among 24,657 Finnish Prostate Cancer Cases and Matched Controls During 1995-2002. Analysis Stratified by Quartiles of Propensity score

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	Any antiarrhythmic drug use		Digoxin users		Sotalol users	
Propensity score	Overall PCa OR (95% CI)[b]	Advanced PCa[a] OR (95% CI)[b]	Overall PCa OR (95% CI)[b]	Advanced PCa[a] OR (95% CI)[b]	Overall PCa OR (95% CI)[b]	Advanced PCa[a] OR (95% CI)[b]
1st quartile	1.05 (0.72-1.54)	0.70 (0.19-2.52)	0.66 (0.37-1.16)	2.00 (0.18-22.06)	1.04 (0.60-1.80)	0.30 (0.06-1.44)
2nd quartile	0.94 (0.75-1.19)	0.57 (0.32-1.03)	0.86 (0.65-1.15)	0.38 (0.19-0.76)	0.89 (0.57-1.40)	0.34 (0.09-1.26)
3rd quartile	1.01 (0.87-1.18)	0.81 (0.50-1.29)	0.99 (0.83-1.17)	0.84 (0.49-1.44)	1.24 (0.95-1.61)	0.63 (0.28-1.41)
4th quartile	1.01 (0.88-1.16)	0.91 (0.64-1.29)	0.99 (0.86-1.14)	0.80 (0.55-1.16)	0.99 (0.77-1.26)	0.64 (0.34-1.23)

[a] Includes all stage T3 and T4, N+ and M+ tumors

[b] Calculated with conditional logistic regression adjusted for age and use of antihypertensive drugs, cholesterol-lowering drugs, antidiabetic drugs, non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors and alpha-blockers

Table 5. Risk of Prostate Cancer Overall and Advanced Prostate Cancer in Users of Antiarrhythmic Drugs, Digoxin and Sotalol Among 24,657 Finnish Prostate Cancer Cases and Matched Controls During 1995-2002. Analysis Stratified by Simultaneous use of Benign Prostatic Hyperplasia Medication

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	Any antiarrhythmic drug use		Digoxin users		Sotalol users	
BPH medication usage	Overall PCa OR (95% CI)[b]	Advanced PCa[a] OR (95% CI)[b]	Overall PCa OR (95% CI)[b]	Advanced PCa[a] OR (95% CI)[b]	Overall PCa OR (95% CI)[b]	Advanced PCa[a] OR (95% CI)[b]
User	0.83 (0.63-1.08)	1.18 (0.47-2.93)	0.94 (0.70-1.26)	0.98 (0.35-2.76)	0.75 (0.49-1.16)	0.21 (0.04-1.24)
Non-users	1.01 (0.95-1.08)	0.88 (0.74-1.04)	1.01 (0.94-1.09)	0.92 (0.77-1.11)	0.95 (0.84-1.08)	0.70 (0.50-0.96)

[a] Includes all stage T3 and T4, N+ and M+ tumors

[b] Calculated with conditional logistic regression adjusted for age and use of antihypertensive drugs, cholesterol-lowering drugs, antidiabetic drugs, non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors and alpha-blockers