STATIINIEN VAIKUTUS ETURAUHASSYÖPÄKUOLLEISUUTEEN FINRSPC-TUTKIMUKSEEN OSALLISTUNEILLA MIEHILLÄ

Antti Peltomaa
Syventävien opintojen kirjallinen työ
Tampereen yliopisto
Lääketieteen ja biotieteiden tiedekunta
Tammikuu 2017

Tampereen yliopisto
Lääketieteen ja biotieteiden tiedekunta

PELTOMAA ANTTI: Statiinien vaikutus eturauhassyöpämortaliteettiin FinRSPC-tutkimukeen osallistuneilla miehillä

Syventävien opintojen opinnäytetyö, 33 sivua.
Ohjaaja: Teemu Murtola

Tammikuu 2017

Avainsanat: statiinit, eturauhassyöpä, epidemiologia, FinRSPC

Statiinien vaikutus sydän- ja verisuonitautikuolleisuuteen on tunnettu pitkään. Viimeaikaisten tutkimusten perusteella statiinien käytöllä on havaittu olevan yhteys myös syöpäpotilaiden ennusteeseen.

Tutkimme statiinien vaikutusta FinRSPC-tutkimukseen osallistuneilla 6537:llä miehellä, jolla oli todettu eturauhassyöpä. Vertasimme statiinien käyttäjien eturauhassyöpäkuolleisuutta ei-käyttäjien kuolleisuuteen. Havaitsimme syöpädiagnoosin jälkeen statiineja käyttäneiden miesten olevan pienemmässä syöpäkuoleman riskissä kuin ei-käyttäjien. Kuolleisuuden lasku suureni statiinien käytön määrän, keston ja intensiteetin suurentuessa ja voimakkais kuolleisuuden alenema havaittiin hormonihoidetuilla miehillä.

Tutkimuksen perusteella statiinien käyttö voi hidastaa eturauhassyövän etenemistä. Jotta syy-yhteys varmistuisi, tulee jatkossa suorittaa kaksoissokkoutettu satunnaistettu kliininen tutkimus.

Statin use and prostate cancer survival in the Finnish Prostate Cancer Screening Trial

Teemu J. Murtola[1,2*], Antti I. Peltomaa[1*], Liisa Määttänen [3], Kimmo Taari [4,5], Teuvo LJ Tammela [1,2], Anssi Auvinen [6]

1. University of Tampere, School of Medicine, Tampere, Finland
2. Tampere University Hospital, Department of Urology, Tampere, Finland
3. Finnish Cancer Registry, Helsinki, Finland
4. University of Helsinki, Medical School, Helsinki, Finland
5. Helsinki University Hospital, Department of Urology, Helsinki, Finland
6. University of Tampere, School of Health Sciences, Tampere, Finland

Key words: prostate cancer, mortality, statins

Word count of text: 2,852

Word count of abstract: 293

Abbreviations: BMI: body mass index, CI: confidence interval, DDD: defined daily dose, HR: hazard ratio, LDL: low density lipoprotein, NSAIDs: non-steroidal anti-inflammatory drugs, PSA: prostate specific antigen, SII: Social Insurance Institute of Finland

*These authors contributed equally

ABSTRACT

Background Recent research has suggested statins to have effect on prostate cancer prognosis. It is currently unknown how prostate cancer screening, tumor and patient characteristics or treatment selection may affect this association.

Objective To evaluate the risk of prostate cancer death among statin users. To determine how disease and treatment characteristics affect the association.

Design Population-based cohort study.

Setting General male population of Finland participating in the Finnish Prostate Cancer Screening Trial (FinRSPC).

Participants Cohort of 6,537 prostate cancer cases diagnosed in the FinRSPC population during 1996-2009. The cohort was linked to national prescription database for information on use of statins and other drugs.

Intervention Statin use before and after prostate cancer diagnosis compared to non-use.

Outcome measurements and statistical analysis Hazard ratios (HRs) for risk of prostate cancer death by amount, duration and intensity of statin use. Cox proportional hazards regression with post-diagnostic statin use as time-dependent variable.

Results During the median follow-up of 7.5 years post-diagnosis 617 men died of prostate cancer. Statin use after diagnosis was associated with decreased risk of prostate cancer death (HR 0.80; 95% CI 0.65-0.98). A decreasing risk trend was observed by increasing intensity of usage (doses/year). The risk decrease was clearest in men managed with androgen deprivation therapy.

Pre-diagnostic statin use was not associated with risk of prostate cancer death (HR 0.92; 95% CI 0.75-1.12).

Conclusions The decreased risk of prostate cancer death among men who use statins after diagnosis suggests that statins may delay or prevent prostate cancer progression. This effect may be strongest in men managed with androgen deprivation therapy.

Patient summary Use of statins after prostate cancer diagnosis was associated with decreased risk of prostate cancer death. The risk decrease was dose-dependent and most clearly seen among patients treated with hormone therapy.

INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are well established in cardiovascular disease prevention. Recent research has linked statin usage with decreased risk of advanced prostate cancer,[1,2] improved recurrence-free survival after radical treatment,[3] and lowered prostate cancer mortality.[4-7] Not all studies agree, however[8]. It is currently unclear how prostate cancer screening, tumor and patient characteristics or treatment selection may affect this association.

We evaluated risk of prostate cancer death among statin users in a cohort of prostate cancer cases from the Finnish Prostate Cancer Screening Trial (FinRSPC), with pre-specified hypothesis that statins would be associated with lowered risk.

MATERIAL AND METHODS

Study cohort

FinRSPC is a randomized population-based trial evaluating whether systematic prostate specific antigen (PSA) based screening reduces prostate cancer mortality.[8] In 1996-1999, all 55-67 year old men residing in the metropolitan areas of Helsinki or Tampere (80,458 men) were identified from the Finnish Population Register Centre. After excluding prevalent prostate cancer cases, 80,144 men were randomized either to be invited for PSA screening at four year intervals (31,866 men, the screening arm), or to the control arm without any intervention. (48,278 men).

Information on prostate cancer TNM stage and Gleason score and primary treatment (radical prostatectomy, external beam radiotherapy, brachytherapy, androgen deprivation therapy (ADT) or observation) were retrieved from hospital records.[8] Cases with missing information in any of the variables were included in the analysis as a separate group. Prostate cancer cases were categorized into high- and low-risk according to EAU guidelines: cases with PSA at diagnosis 20 ng/ml or lower, T1-T2b and Gleason 7 or less were considered as low/medium risk, whereas cases with PSA above 20 ng/ml, Gleason 8-10, T2c-T4 and all N+ cases were considered as high-risk cases.[10]

Statistics Finland registers all deaths occurring in Finland. The registry has used the 10th revision of the International Classification of Diseases (ICD-10) since 1996. The causes for all deaths occurring between 1996 and 2003 among participants diagnosed with prostate cancer in each trial arm were validated by a cause-of-death committee.[8] Excellent concordance was found between recorded causes of death and clinical files (kappa=0,95) thus proving reliability of cause of death registry. In this analysis deaths with prostate cancer (ICD-10 code C61) as the primary cause of death were defined as prostate cancer deaths.

Information on socioeconomic factors from population censuses was available from the Statistics Finland for 1,444 cases (22.1% for the total cohort).

The trial population was linked to the Care Registers for Social Welfare and Health Care (HILMO) maintained by the National Institute for Health and Welfare to obtain diagnoses from inpatient periods during the follow-up; 317 additional men had prostate cancer among the recorded diagnoses, raising the number of prostate cancer cases to 6,537.

Information on medication use

The screening trial population was linked to the national prescription database maintained by the Social Insurance Institute (SII) of Finland. SII is a governmental agency providing reimbursements for physician-prescribed medication as part of the national health insurance.[9] For each purchase of a prescription drug approved by the SII (most prescription drugs in Finland), all Finnish citizens are entitled to at least 50% reimbursement, deducted usually from the customer payment at the pharmacy.

All reimbursed drug purchases are recorded at the SII prescription database since 1995. The recorded information includes the date, anatomical therapeutic chemical (ATC) code, product number and number of packages for each drug purchase. The product-specific number was used to determine the drug strength and number of pills for each purchase.

We obtained information on all cholesterol-lowering drugs (statins, fibrates, bile-acid binding resins, ezetimibe and acipimox), antidiabetic drugs (both oral drugs and insulins), antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and drugs used in treatment of benign prostatic hyperplasia (alpha-blockers and 5α-reductase inhibitors) for 1995-2009.

We standardized the daily dose between statins using the Defined Daily Doses (DDDs) listed by World Health Organization[10] The yearly cumulative mg amount of statin purchases was divided by 1 DDD for the yearly amount of usage. Each year with recorded statin purchases was considered as year of usage. Duration of usage was the cumulative number of years of usage. Intensity of statin use was further calculated by dividing the yearly amount of statin use with the number of years of usage.

The ethics committee of the Pirkanmaa health care district, Finland approved the study protocol (tracking numbers R03209 and R09159).

Statistical analysis

The analysis was limited to prostate cancer cases. Separate analyses were performed to evaluate the impact of medication use before and after prostate cancer diagnosis.

Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% CI intervals (95% CI) for risk of prostate cancer death by medication use. The regression model was adjusted for age only (model 1), additionally for tumor Gleason score, tumor stage (M1 tumors vs. localized tumor) and PSA level at diagnosis (model 2) and additionally for usage of other drugs (antidiabetic drugs, antihypertensive drugs, aspirin and other NSAIDs, alpha-blockers and 5α-reductase inhibitors) and the screening trial arm (model 3). Non-users were used as the comparison group. Follow-up started at the date of prostate cancer diagnosis (the baseline), and was continued until death, emigration or January 1, 2013, whichever came first. The time scale was years since prostate cancer diagnosis.

Cholesterol-lowering medication use after the diagnosis was included into the model as time-dependent variable, i.e. the usage status, cumulative amount, duration and intensity of use were updated each year of follow-up based on yearly medication purchases. Men who discontinued statin

use during follow-up retained the cumulative amount/duration they had reached before discontinuation.

The impact of pre-diagnostic statin use on risk of prostate cancer death was evaluated with multivariable adjusted Cox regression model with pre-diagnostic statin use as time-independent variable. This analysis included statin use from 1995 until the year of prostate cancer diagnosis. Pre-diagnostic users were categorized into current users (usage continued until the diagnosis) and previous users (usage stopped before prostate cancer diagnosis).

The validity of the proportional hazard assumption was checked for time-independent variables by including an interaction term with follow-up time into the model. For each the term was not statistically significant, thus confirming the assumption.

Trends in prostate cancer survival were evaluated by stratifying the study population by tertiles (post-diagnostic statin use) or by the median (prediagnostic use) of the amount, duration or intensity of statin use and repeating the analysis for each stratum. P-values for trend were calculated by entering the stratified cumulative usage as a continuous variable into the Cox regression model.

Sensitivity analyses are described in supplementary text 1.

The differences in baseline variables between medication users and non-users were compared using Chi-square test (categorical variables) and Mann-Whitney-U test (continuous variables). All reported p-values are two-sided. Analyses were done with IBM SPSS statistics 20 statistical software (Chicago, Illinois, USA) and STATA version 12 (StataCorp LP, College Station, Texas, USA).

RESULTS

Population characteristics

In total, 3,059 prostate cancer cases (46.8% of all) had used statins after 1995, while 256 men (3.9%) had used non-statin cholesterol-lowering drugs (Table 1). The most commonly used statins were simvastatin (2,393 users) and atorvastatin (1,088 users); most commonly used non-statin drugs were ezetimibe (93 users) followed by bezafibrate (71 users). Of the non-statin drug users 222 (86.7%) had also used statins. *During the median follow-up of 7.5 years after diagnosis, 617 men died due to prostate cancer. Of these 202 were statin users (Table 1).*

Compared to the non-users, cholesterol-lowering drug users had higher median body mass index (BMI); had higher prevalence of ischemic heart disease, type II diabetes and hypertension; used more often other drug groups; had lower annual income and education level; were less often diagnosed with metastatic or high-grade cancer and were more often primarily managed with external beam radiation therapy (Table 1). No marked differences in baseline characteristics were observed between users of statin and non-statin cholesterol-lowering drugs.

Risk of prostate cancer death by pre-diagnostic statin use

In age-adjusted analysis, men who had used statins before the diagnosis had decreased risk of prostate cancer death compared to non-users (HR 0.80, 95% CI 0.66-0.96) (Table 2). The risk decrease was strongest among men still on statins at diagnosis. After further adjustment tumor characteristics and use of other medications the risk decrease was no longer significant (OR 0.92,

95% CI 0.75-1.12). The result was similar for low-medium risk and high-risk cases[10]. No risk trends by amount, duration or intensity of statin use were observed (Table 2).

Risk of prostate cancer death by post-diagnostic statin use

Statin use after the diagnosis was associated with decreased risk of prostate cancer death even after multivariable adjustment (HR 0.80, 95% CI 0.65-0.98) (Table 3). The risk decrease was significant among men diagnosed with low/medium risk cancer at baseline. However, significant inverse risk trends by amount, duration and intensity of statin use were observed in high-risk cases: p for trend 0.021, 0.018 and 0.031, respectively.

The effect of disease and population characteristics

When stratified by tumor characteristics, only tumor stage modified the survival benefit, survival improvement by post-diagnostic statin use being observed only in men with localized or N+ disease (p for interaction) (Table 4). Also primary treatment modified the survival association: improved survival by post-diagnostic statin usage was observed only in men receiving ADT as the primary treatment (Table 4).

Survival benefit by post-diagnostic statin use was observed in men who were 67 years or older, not among younger men (Table 4). PSA screening, use of other drug groups or socioeconomic status did not have significant modifying effect on the survival association either for pre- or post-diagnostic statin use.

Sensitivity analyses

Propensity for statin usage did not clearly affect the association between post-diagnostic statin use and risk of prostate cancer death, although a decreasing trend by intensity of usage was observed only among men with highest propensity for statin use (Supplementary Table 1).

Patterns of statin use at the end of life were evaluated in lag-time analyses censoring changes to statin usage in one or more years at the end of follow-up, and by stratifying users to men who continued usage until the end of follow-up (active users) and those who discontinued previous usage (previous users). Decreased prostate cancer-specific survival was observed in men who discontinued post-diagnostic statin usage, while active use was associated with improved survival compared to non-use. The risk increase among previous users vanished when changes to statin use during the final year of follow-up were censored, while the improved survival among active users persisted even in 8 year lag-time analysis (Supplementary table 2).

Decreased risk among post-diagnostic statin users persisted when deaths due to cardiovascular causes (coronary artery disease, cerebrovascular disease or sudden death) were analyzed as the competing causes of death in Fine and Gray regression analysis; HR 0.39, 95% CI 0.32-0.49.

Risk death due to any cause was lower both among post-diagnostic and pre-diagnostic statin users, with a decreasing trend by intensity of statin usage (Supplementary Table 3).

Of the three most commonly used statins (simvastatin, atorvastatin and fluvastatin) only simvastatin users had significantly lowered risk of prostate cancer death compared to non-users both for pre-diagnostic and post-diagnostic use (Supplementary Table 4). However, the risk estimates were similar for all three statins. No risk reduction was observed on users of non-statin cholesterol-lowering drugs.

DISCUSSION

We have shown in a large population-based cohort of Finnish prostate cancer cases that use of statin drugs after prostate cancer diagnosis is associated with lowered risk of prostate cancer death compared to non-use even after adjusting for differences between statin users and non-users, such as co-morbidities and tumor characteristics. When stratified by primary treatment the risk reduction was observed only in men managed with ADT. This suggests that statins may reduce risk of prostate cancer progression; possibly in interaction with ADT use. No risk decrease was observed by statin use before the diagnosis.

Previously, statin usage has been associated with a lowered risk of advanced prostate cancer and improved recurrence-free survival following radical treatment, especially after radiation therapy.[1-3] However, there has also been controversial results as one recent study found no statistically significant association between post-diagnostic statin use and risk of lethal prostate cancer.[11] In our analysis, the risk decrease was significant only among men whose primary treatment was ADT. This finding is in line with previous study reporting that statin use is associated with improved relapse-free survival during androgen deprivation therapy.[14] Discrepancy with the previous negative study may thus be explained by differences in study population characteristics; only 5% of cases received primary androgen deprivation therapy in the previous study, compared to 16.8% in our study population. However, non-significantly lowered risk estimates among statins users were observed also for other primary treatments, thus the number of prostate cancer deaths after other treatment types may have been too low, limiting statistical power of the analysis. Studies with longer follow-up will be needed to confirm whether the mortality decrease among statin users differs by primary treatment.

Five other studies have previously addressed prostate cancer mortality among statin users, [4-7,11] but none have been able to evaluate the association among screened men or by disease and treatment characteristics as comprehensively as in our study. One was a case-control study comparing odds of prostate cancer death by statin usage,[4] three other were cohort studies evaluating the effect of statin use on overall cancer mortality or prostate cancer mortality.[5-7] All previous studies reported lower prostate cancer mortality among statin users. Our study is the first to demonstrate that the risk

decrease is strongest in men with low or medium risk prostate cancer at diagnosis. We further demonstrate that the decrease in the risk of prostate cancer death is observed also in the context of comprehensive systematic prostate cancer screening, demonstrating that the association is not explained by more active screening participation or stage migration among statin users.

Another interesting finding of our study is that statin usage is frequently stopped before prostate cancer death, as shown in lag-time analyses by markedly elevated HR of prostate cancer death among post-diagnostic statin users who stopped their usage during the final year of follow-up. If not taken into account this may cause bias favoring statin users in mortality analyses as men dying of their disease may selectively stop statin usage.

In vitro studies give insight into the mechanism how statins would prevent prostate cancer progression. It has been long known that prostate cancer tissue actively produces cholesterol.[15] Recent studies have demonstrated importance of cholesterol for prostate cancer cell growth and gearing of cholesterol metabolism in cancer cells towards high cholesterol production and preservation.[16] Statins appear to interfere with this mechanism, leading to inhibition of cell growth.[17] Nevertheless, it remains unclear whether statins' effects on prostate cancer *in vivo* are mediated by reduction in availability of circulating cholesterol or inhibition of local cholesterol production in the prostate.

Statins have also anti-inflammatory effect in the prostate, which may affect cancer progression.[18] Cholesterol is also necessary for androgen synthesis, and local androgen synthesis has been suggested to be a key feature in development of castration-resistant prostate cancer.[19] Thus an intriguing question arises whether statins can prolong the development of castration resistance. Interestingly, the decreased risk of death was significant only among men whose primary treatment was ADT.

Advanced malignancy has been linked to spontaneously decreasing serum cholesterol levels, which may be explained by increased low density lipoprotein (LDL) receptor expression and high

cholesterol uptake of cancer tissues.[20] Thus men with advanced malignancy may have less often elevated cholesterol levels and less indication to start statin usage. Nevertheless, if this was the case the risk decrease would have been observed regardless of whether statins had been used before or after the diagnosis. Thus the risk decrease observed only for post-diagnosis statin use argues against selection bias.

It has been suggested that statin users are generally healthier compared to non-users, which leads to healthy user bias, i.e. non-causally decreased risk of several adverse health outcomes unrelated to statin use.[21] While this may apply to people who use statins for primary prevention of cardiovascular disease, in our study statin users were not healthier, but instead had a higher prevalence of medication use for comorbid conditions compared to the non-users. Again, the risk decrease observed only for post-diagnosis statin use argues against selection bias.

Strengths of our study include comprehensive and reliable information on clinical characteristics of prostate cancer cases as well as on causes death, unambiguous linkage to national prescription database for detailed and comprehensive information on medication use free of recall bias and our ability to evaluate effects of screening and treatment selection.

The weakness of our study is that it is not a randomized trial, and we cannot indefinitely rule out selection bias in terms of lower baseline risk of prostate cancer death in statin users. Another weakness is missing information on serum cholesterol levels, and thus we were not able to evaluate the mortality association or propensity to statin use by cholesterol level. Our study population is a population-based sample of white Caucasian males 55-67 years at baseline. Our results may not be generalizable to other ethnic groups.

In conclusion, statin use after diagnosis was associated with decreased risk of prostate cancer death. The risk decrease was evident especially in men managed with ADT. Nevertheless, a clinical trial will be needed to solve remaining uncertainties before statins can be endorsed for prostate cancer management.

ACKNOWLEDGEMENTS

TJM and AA conceived and designed the study; all authors acquired the data; TJM, AIP and AA analysed the data; all authors interpreted the data; all authors drafted the article or revised it critically for important intellectual content; all authors approved the submitted version of the manuscript.

TJM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The ethics committee of the Pirkanmaa health care district, Tampere, Finland has approved the study protocol (tracking numbers R03209 and R09159).

This work was supported by competitive research funding from the Pirkanmaa Hospital District to TJ Murtola. None of the funders had any role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; nor preparation, review, or approval of the manuscript.

REFERENCES

1. Murtola TJ, Visakorpi T, Lahtela J, Syvala H, Tammela TL. Statins and prostate cancer prevention: where we are now, and future directions. Nat Clin Pract Urol 2008;5:376–87.

2. Bansal D, Undela K, D'Cruz S, Schifano F. Statin Use and Risk of Prostate Cancer: A Meta-Analysis of Observational Studies. PLoS One 2012;7:e46691.

3. Park HS, Schoenfeld JD, Mailhot RB, et al. Statins and prostate cancer recurrence following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. Ann Oncol 2013;24:1427–34.

4. Marcella SW, David A, Ohman-Strickland PA, Carson J, Rhoads GG. Statin use and fatal prostate cancer: A matched case-control study. Cancer 2012;118:4046–52.

5. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2012;367:1792–802.

6. Geybels MS, Wright JL, Holt SK, Kolb S, Feng Z, Stanford JL. Statin Use in Relation to Prostate Cancer Outcomes in a Population-based Patient Cohort Study. Prostate 2013;73:1214–22.

7. Yu O, Eberg M, Benayoun S et al. Use of Statins and the Risk of Death in Patients With Prostate Cancer. J Clin Oncol. 2013 (in press)

8. Chan JM, Kenfield SA, Paciorek A, Platz EA, Giovannucci EL, Stampfer MJ. Postdiagnostic Statin Use and the Risk of Lethal Prostate Cancer in the Health Professionals Follow-up Study. Cancer Epidemiol Biomarkers Prev. 2015 (in press)

9. Cattarino S; Seisen T; Drouin SJ; Renard-Penna R; Leon P; Comperat E; Mozer P; Cussenot O; Roupret M. Influence of statin use on clinicopathological characteristics of localized prostate cancer and outcomes obtained after radical prostatectomy: a single center study. Can J Urol. 2015;22:7703-8.

10. Mottet N et al. Guidelines on prostate cancer 2015. European Association of Urology website. Available at http://uroweb.org/wp-content/uploads/09-Prostate-Cancer_LR.pdf. Accessed March 28, 2016.

11. Kilpeläinen TP, Tammela TL, Malila N, et al. Prostate Cancer Mortality in the Finnish Randomized Screening Trial. J Natl Cancer Inst 2013;105:719–25.

12. Martikainen J, Rajaniemi S. Drug reimbursement systems in EU Member States, Iceland and Norway. Helsinki: The Social Insurance Institution, Finland, Social security and health reports 2002;54:130.

13. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2013. 2013. Available at: http://www.whocc.no/atc_ddd_index/.

14. Harshman LC, Wang X, Nakabayashi M et al. Statin Use at the Time of Initiation of Androgen Deprivation Therapy and Time to Progression in Patients With Hormone-Sensitive Prostate Cancer. JAMA Oncol. 2015;1:495-504.

15. Krycer JR, Brown AJ. Cholesterol accumulation in prostate cancer: A classic observation from a modern perspective. Biochim Biophys Acta 2013;1835:219–29.

16. Murtola TJ, Syvala H, Pennanen P, et al. The Importance of LDL and Cholesterol Metabolism for Prostate Epithelial Cell Growth. PLoS One 2012;7:e39445.

17. Murtola TJ, Syvala H, Pennanen P, et al. Comparative effects of high and low-dose simvastatin on prostate epithelial cells: The role of LDL. Eur J Pharmacol 2011;673:96–100.

18. Banez LL, Klink JC, Jayachandran J, et al. Association between statins and prostate tumor inflammatory infiltrate in men undergoing radical prostatectomy. Cancer Epidemiol Biomarkers Prev 2010;19:722–8.

19. Tsao CK, Galsky MD, Small AC, Yee T, Oh WK. Targeting the androgen receptor signalling axis in castration-resistant prostate cancer (CRPC). BJU Int 2012;110:1580–8.

20. Ahn J, Lim U, Weinstein SJ, et al. Prediagnostic total and high-density lipoprotein cholesterol and risk of cancer. Cancer Epidemiol Biomarkers Prev 2009;18:2814–21.

21. Brookhart MA, Patrick AR, Dormuth C, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol 2007;166:348–54.

Supplementary references:

1. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc 1999;94:496–509.

2. Rosenbaum PR RD. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984:516–24.

Table 1. Population characteristics. Cohort of prostate cancer cases diagnosed in the Finnish Prostate Cancer Screening Trial between 1996-2012.

	Non-users of cholesterol-lowering drugs	Statin users**	P-value††	Users of NSCLAs**	P-value††
Patient characteristics					
n (%)	3,444 (52.7%)	3,059 (46.8%)		256 (3.9%)	
Median age at randomization (IQR)	63 (59-67)	63 (59-67)		63 (59-67)	
Median age at PCa diagnosis (IQR)	67 (63-71)	67 (64-71)		67 (63-71)	
1st degree PCa family history; n(%)*	3 (0.1%)	6 (0.2%)		0	
BMI; median (IQR)	25.5 (23.7-27.4)	26.7 (24.3-29.0)	< 0.001	27.7 (25.6-30.8)	< 0.001
Deaths; n (% of the cases)	1,192 (33.3%)	714 (23.3%)		65 (25.4%)	
PCa deaths; n (% of the cases)	415 (12.0%)	202 (6.6%)		20 (7.8%)	
Yrs of follow-up from diagnosis (median; 95% range)	7.1 (1-14)	8 (2.3-14.6)		7.8 (1.9-14.6)	
Baseline laboratory values‡‡					
Total cholesterol; median, (IQR)	5.1 (4.5-5.7)	5.3 (4.5-6.1)	< 0.001	5.1 (4.1-6.3)	0.69
LDL; median, (IQR)	3.0 (2.5-3.5)	2.8 (2.1-3.5)	< 0.001	2.5 (1.9-3.1)	0.001
Triglycerides; median, (IQR)	1.2 (0.9-1.6)	1.5 (1.1-2.1)	< 0.001	1.7 (1.3-2.7)	< 0.001
Fasting blood glucose (mmol/l); median, (IQR)	5.7 (5.4-6.2)	5.9 (5.5-6.7)	< 0.001	6.2 (5.6-7.1)	0.004
GHbA1c (%); median, (IQR)	40 (38-43)	43 (40-48)	< 0.001	44 (40-51)	0.003
Tumor characteristics					
Stage at diagnosis:			<0.001		0.32
Localized†; n (%)	3,085 (89.6%)	2,860 (93.5%)		241 (94.1%)	
Metastatic‡; n (%)	272 (7.9%)	133 (4.3%)		10 (3.9%)	
Unknown	87 (2.5%)	66 (2.2%)		5 (2.0%)	
Gleason score:			<0.001		0.61
6 or less	1550 (45.0%)	1451 (47.4%)		129 (50.4%)	
7	785 (22.8%)	696 (22.8%)		52 (20.3%)	
8-10	449 (13.0%)	319 (10.4%)		31 (12.1%)	
Unknown	660 (19.2%)	593 (19.4%)		44 (17.2%)	

PSA at diagnosis; median (IQR)	9.3 (5.8-17.6)	8.5 (5.5-14.2)	< 0.001	8.8 (5.4-14.3)	0.23
EAU risk group					
Low/intermediate risk; n (%)	1765	1737		141	
High risk; n (%)	1679	1322		115	
Primary treatment:			<0.001		0.049
Expectant management; n (%)	589 (17.1%)	560 (18.3%)		37 (14.5%)	
Prostatectomy; n (%)	899 (26.1%)	747 (24.4%)		61 (23.8%)	
External beam radiation therapy; n (%)	1,142 (33.2%)	1,219 (39.8%)		111 (43.4%)	
-adjuvant therapy	16 (0.5%)	32 (1.0%)		1 (0.4%)	
Brachytherapy; n (%)	96 (2.8%)	73 (2.4%)		7 (2.7%)	
Androgen deprivation therapy; n (%)	1,430 (41.5%)	1,219 (39.8%)		104 (40.6%)	
-neoadjuvant therapy	544 (15.8%)	508 (16.6%)		46 (18.0)	
-adjuvant therapy	66 (1.9%)	76 (2.5%)		6 (2.3%)	
Use of other drug groups					
Antidiabetic drug use; n (%)	358 (10.4%)	903 (29.5%)	<0.001	111 (43.4%)	<0.001
Antihypertensive drug use; n (%)	2,043 (59.3%)	2,675 (87.4%)	<0.001	238 (93.0%)	<0.001
Aspirin use; n (%)	263 (7.6%)	620 (20.3%)	<0.001	66 (25.8%)	<0.001
NSAID use; n (%)	2,876 (83.5%)	2,729 (89.2%)	<0.001	235 (91.8%)	<0.001
5α-reductase inhibitor use; n (%)	454 (13.2%)	447 (14.6%)	<0.001	43 (16.8%)	<0.001
Alpha-blocker use; n (%)	1,537 (44.6%)	1,482 (48.4%)	<0.001	121 (47.3%)	<0.001
Socioeconomic characteristics					
Income level; n (% of men with data available)			0.035		NS
Lower 50% (less than 30,000 e/year)	385 (48.3%)	341 (53.6%)		36 (50%)	
Upper 50% (30,000 e/year or more)	412 (51.7%)	295 (46.4%)		36 (50%)	
Education; n (% of men with data available)			0.042		NS
Secondary level or lower	145 (33.9%)	140 (40.8%)		9 (32.1%)	
Tertiary level	283 (66.1%)	203 (59.2%)		19 (67.9%)	
Marital status; n (% of men with data available)					
Single	52 (6.9%)	44 (7.2%)		6 (8.7%)	
Married/registered partnership	479 (63.4%)	388 (63.9%)		45 (65.2%)	
Divorced	134 (17.7%)	121 (19.9%)		9 (13.0%)	
Widowed	90 (11.9%)	54 (8.9%)		9 (13.0%))	

* At least two 1st degree male relatives (father, brother or son) with prostate cancer

† Including lymph-node positive cases

‡ M1 cases

¶ as primary treatment, neo-adjuvant or adjuvant setting

§ Surgical or chemical castration as the only treatment, neoadjuvant or adjuvant setting

** NSCLA=non-statin cholesterol lowering agents. Any usage during 1995-2009

†† P value for difference compared to non-users. Only statistically significant p-values reported.

‡‡ First available measure, obtained for 1,646 (total cholesterol), 1,510 (LDL), 1,649 (triglycerides), 1,624 (fasting blood glucose) and 1,076 men (GHbA1c).

Table 2. Risk of prostate cancer death by amount, duration and intensity of statin use before prostate cancer diagnosis in a cohort of men in the Finnish Prostate Cancer Screening Trial during 1996-2012.

			Risk of PCa death			
			All cases		Low or medium risk	High risk
Statin use before prostate cancer diagnosis	n of men at risk	n of PCa deaths	HR (95% CI) age-adjusted	HR (95% CI) multivar. adjusted model 2†	HR (95% CI) multivar. adjusted model 2†	HR (95% CI) multivar. adjusted model 2†
None	*4,702*	*479*	Reference	Reference	Reference	Reference
Any use	*1,835*	*138*	*0.80 (0.66-0.96)*	*0.92 (0.75-1.12)*	*0.63 (0.36-1.10)*	*1.00 (0.81-1.23)*
Current users	*1,584*	*109*	*0.72 (0.58-0.89)*	*0.84 (0.68-1.04)*	*0.52 (0.34-0.81)*	*1.04 (0.80-1.37)*
Previous users	*251*	*29*	*1.30 (0.89-1.90)*	*1.37 (0.93-2.00)*	*1.23 (0.60-2.53)*	*1.42 (0.88-2.28)*
Amount of statin use (DDDs)						
14-930	*926*	*68*	*0.74 (0.57-0.95)*	*0.88 (0.68-1.14)*	*0.57 (0.27-1.19)*	*0.96 (0.73-1.27)*
931 or more	*909*	*70*	*0.87 (0.67-1.12)*	*0.95 (0.73-1.24)*	*0.70 (0.33-1.50)*	*1.03 (0.78-1.36)*
P for trend‡			*0.23*	*0.96*	*0.45*	*0.50*
Years of statin use						
1-4	*1,012*	*81*	*0.82 (0.65-1.04)*	*0.87 (0.69-1.11)*	*0.51 (0.24-1.07)*	*0.96 (0.74-1.24)*
5 years or longer	*823*	*57*	*0.76 (0.58-1.01)*	*0.99 (0.74-1.32)*	*0.83 (0.38-1.80)*	*1.06 (0.78-1.45)*
P for trend‡			*0.051*	*0.82*	*0.11*	*0.60*
Intensity of statin use (DDDs/year)						
14-249	*922*	*68*	*0.75 (0.58-0.96)*	*0.95 (0.73-1.23)*	*0.74 (0.37-1.47)*	*1.03 (0.77-1.36)*
250 or more	*913*	*70*	*0.85 (0.66-1.10)*	*0.89 (0.68-1.15)*	*0.50 (0.21-1.16)*	*0.97 (0.74-1.27)*
P for trend‡			*0.16*	*0.54*	*0.46*	*0.69*

† Calculated with Cox regression model adjusted for same variables as model 1, and additionally for tumor Gleason grade, M-stage and PSA level at diagnosis

‡ Calculated by including the categories of cumulative amount, years or intensity of pre-diagnostic statin use into logistic regression model as continuous variable

DDD = Defined Daily Dose

Table 3. Risk of prostate cancer death by cumulative amount, duration and intensity of post-diagnostic statin use in a cohort of prostate cancer cases diagnosed among men participating in the Finnish Prostate Cancer Screening Trial during 1996-2012.

			Risk of prostate cancer death			
			Full FinRSPC cohort		Low/medium risk	High risk
Statin use after prostate cancer diagnosis	n of men at risk	n of PCa deaths	HR_1 (95% CI)	HR_2 (95% CI)	HR_3 (95% CI)	HR_3 (95% CI)
None	*3,616*	*430*	*Reference*	*Reference*	*Reference*	*Reference*
Any statin use	*2,921*	*187*	*0.71 (0.58-0.87)*	*0.80 (0.65-0.98)*	*0.49 (0.27-0.89)*	*0.88 (0.71-1.10)*
Amount of statin use						
1st tertile (14-784 DDD)	*995*	*78*	*0.72 (0.55-0.94)*	*0.81 (0.62-1.07)*	*0.65 (0.28-1.52)*	*0.87 (0.65-1.16)*
2nd tertile (785-1,876 DDD)	*934*	*65*	*0.79 (0.58-1.08)*	*0.89 (0.64-1.22)*	*0.70 (0.30-1.63)*	*0.94 (0.67-1.33)*
3rd tertile (1,876 DDD or more)	*992*	*44*	*0.58 (0.37-0.91)*	*0.63 (0.40-0.99)*	*0.11 (0.02-0.82)*	*0.81 (0.51-1.30)*
P for trend*			*0.054*	*0.102*	*0.267*	*0.021*
Duration of statin use						
2 years or less	*1,021*	*82*	*0.71 (0.55-0.94)*	*0.81 (0.61-1.07)*	*0.71 (0,30-1.66)*	*0.86 (0.64-1.15)*
3-5 years	*1,079*	*61*	*0.72 (0.52-0.98)*	*0.84 (0.61-1.15)*	*0.56 (0.24-1.32)*	*0.92 (0.65-1.30)*
6 years or longer	*821*	*44*	*0.68 (0.43-1.09)*	*0.69 (0.43-1.11)*	*0.13 (0.02-0.97)*	*0.89 (0.54-1.46)*
P for trend*			*0.047*	*0.080*	*0.266*	*0.018*
Intensity of statin use (DDDs/year)						
14-240	*861*	*76*	*0.84 (0.63-1.12)*	*0.94 (0.70-1.26)*	*0.47 (0.17-1.29)*	*1.07 (0.79-1.46)*
241-400	*950*	*52*	*0.66 (0.48-0.92)*	*0.74 (0.53-1.04)*	*0.73 (0.31-1.70)*	*0.76 (0.53-1.10)*
over 400	*1,108*	*59*	*0.62 (0.43-0.88)*	*0.69 (0.48-0.98)*	*0.30 (0.10-0.97)*	*0.79 (0.54-1.15)*
P for trend*			*0.023*	*0.066*	*0.635*	*0.031*

HR_1 Cox regression model adjusted for age only; HR_2 additional model adjustment for use of other drugs (aspirin, NSAIDs, antidiabetic drugs, antihypertensive drugs, alpha-blockers or 5α-reductase inhibitors) and for the screening trial arm and tumor stage, grade and pre-diagnostic PSA.

* Calculated by adding tertiles of cumulative amount, duration or intensity of post-Dx statin usage into Cox regression model as continuous variable.

DDD = Defined Daily Dose

Table 4. Prostate cancer mortality by pre- and post-diagnostic statin use compared to non-users. Prostate cancer cases stratified by baseline variables.

	Prostate cancer mortality	
	Current pre-Dx use	Current post-Dx use
	HR (95% CI)*	HR (95% CI)†
Disease characteristics		
Tumor Gleason score		
6 or less	0.87 (0.53-1.41)	0.89 (0.57-1.40)
7	0.80 (0.52-1.25)	0.73 (0.47-1.13)
8-10	0.96 (0.71-1.29)	0.88 (0.64-1.19)
Tumor stage		
Local or lymph-node involvement only	0.86 (0.59-1.26)	0.54 (0.35-0.83)
Metastatic	1.07 (0.80-1.44)	0.97 (0.71-1.32)
PSA at diagnosis		
below the median (7.31 ng/ml or lower)	0.92 (0.61-1.40)	0.83 (0.54-1.28)
median or above (7.32 ng/ml or higher)	0.92 (0.73-1.17)	0.84 (0.66-1.06)
Primary treatment		
Expectant management	0.67 (0.18-2.54)	1.00 (0.31-3.22)
Radical prostatectomy	1.32 (0.64-2.73)	0.95 (0.46-1.96)
External beam radiation therapy	1.04 (0.72-1.51)	0.88 (0.60-1.29)
Hormone therapy	0.86 (0.69-1.07)	0.74 (0.59-0.94)
Patient characteristics		
Age at diagnosis		
below the median (66 or younger)	0.97 (0.69-1.37)	0.91 (0.65-1.27)
median or above (67 or older)	0.89 (0.70-1.14)	0.73 (0.56-0.95)
FinRSPC study arm		
Screening	0.95 (0.67-1.35)	0.84 (0.66-1.08)
Control	0.90 (0.71-1.14)	0.70 (0.49-1.01)
Prediagnostic statin use		
Yes	-	0.81 (0.60-1.08)
No	-	0.80 (0.55-1.18)
Usage of other drug groups		

Aspirin (by prescription and over-the-counter use)	1.30 (0.74-2.27)	0.72 (0.40-1.28)
NSAIDs (by prescription and over-the-counter use)	0.97 (0.78-1.19)	0.83 (0.67-1.02)
Antidiabetic drugs	1.30 (0.90-1.90)	0.86 (0.59-1.25)
Antihypertensive drugs	0.96 (0.78-1.19)	0.85 (0.68-1.05)
5α-reductase inhibitors	1.08 (0.63-1.84)	0.83 (0.45-1.53)
Alpha-blockers	0.90 (0.68-1.18)	0.87 (0.66-1.16)
Comorbitidies		
Ischemic heart disease	0.49 (0.20-1.16)	0.81 (0.35-1.85)
Type 2 diabetes	1.64 (0.54-4.98)	1.69 (0.57-4.98)
Hypertension w/wo complications	0.93 (0.42-2.06)	1.07 (0.46-2.50)
Socioeconomic status		
Income level		
Lower 50% (less than 30,000 e/year)	0.73 (0.36-1.50)	0.75 (0.36-1.54)
Upper 50% (30,000 e/year or more)	0.73 (0.33-1.64)	0.80 (0.39-1.67)
Education		
Secondary level or lower	0.48 (0.14-1.68)	0.55 (0.18-1.68)
Tertiary level	0.35 (0.08-1.59)	1.01 (0.36-2.81)
Marital status		
Married/registered partnership	0.93 (0.46-1.91)	0.84 (0.42-1.69)
Divorced	0.71 (0.22-2.30)	1.35 (0.45-4.00)
Metabolic syndrome resemblance		
No	0.92 (0.75-1.12)	0.80 (0.65-0.98)
Yes	1.00 (0.086-11.62)	1.00 (0.087-11.54)

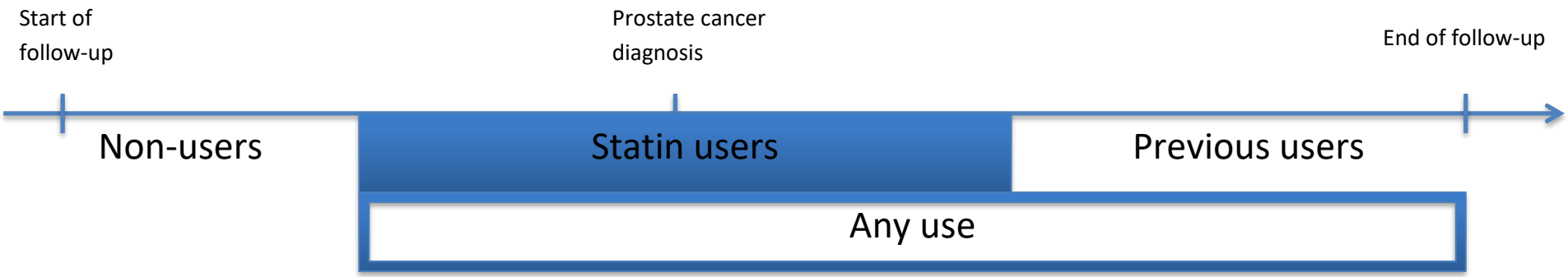
* Calculated with logistic regression model adjusted for age, use of other drugs (aspirin, NSAIDs, antidiabetic drugs, antihypertensive drugs, alpha-blockers or 5α-reductase inhibitors) and for FinRSPC study arm

† Calculated with Cox regression model adjusted for age, tumor stage and grade, pre-diagnostic PSA, use of other drugs (aspirin, NSAIDs, antidiabetic drugs, antihypertensive drugs, alpha-blockers or 5α-reductase inhibitors) and for the FinRSPC trial arm.

DDD = Defined Daily Dose

Table 5. Risk of prostate cancer death by post-diagnostic statin use. Lag time analysis excluding 1-8 years of statin use from the end of follow-up.

				Years of statin use excluded from the end of follow-up			
	Full follow-up			1 year	3 years	5 years	8 years
Statin use after PCa diagnosis	No. of men at risk/PCa 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	HR (95% CI) multivar. adjusted
Non-users	3,616/430	Reference	Reference	Reference	Reference	Reference	Reference
Current users	2,229/73	0.52 (0.41-0.66)	0.55 (0.43-0.70)	0.57 (0.50-0.76)	0.52 (0.41-0.68)	0.46 (0.34-0.61)	0.60 (0.43-0.83)
Previous users	692/114	3.42 (2.48-4.72)	3.12 (2.25-4.31)	0.39 (0.17-0.87)	0.49 (0.22-1.09)	1.16 (0.52-2.59)	1.27 (0.60-2.71)


Start of follow-up
Prostate cancer diagnosis
End of follow-up
Non-users
Statin users
Previous users
Any use

Supplementary Table 1. Prostate cancer survival post-diagnostic statin users stratified by propensity of statin usage.

Propensity score for statin usage after PCa diagnosis*	n of men (post Dx statin users/non-users)	n of PCa deaths (exposed/non-exposed)	Prostate cancer survival, current post-Dx users HR (95% CI) †
1st tertile	439/1,763	161	0.56 (0.29-1.07)
2nd tertile	734/1,403	209	1.26 (0.83-1.89)
3rd tertile	1,748/450	247	0.77 (0.58-1.01)

***** Calculated with logistic regression model with statin usage after prostate cancer diagnosis as the dependent variable and age at diagnosis, BMI, statin usage before the diagnosis, usage of other drug groups (aspirin, NSAIDs, antidiabetic drugs, antihypertensive drugs, 5α-reductase inhibitors and alpha-blockers), tumor grade, stage and primary treatment as the independent variables

† Calculated with Cox regression model adjusted for age; tumor grade, stage and PSA level at diagnosis; use of other drugs (aspirin, NSAIDs, antidiabetic drugs, antihypertensive drugs, alpha-blockers or 5α-reductase inhibitors) and screening trial arm.

Supplementary Table 2. All-cause mortality by statin usage before and after the diagnosis among prostate cancer cases from the Finnish Prostate Cancer Screening Trial

	All-cause mortality					
	Entire FinPCST cohort				FinPCST screening arm	FinPCST control arm
Statin use after PCa diagnosis	**n of men at risk**	**n of deaths**	**HR (95% CI) age-adjusted**	**HR (95% CI) multivar. adjusted***	**HR (95% CI) multivar. adjusted***	**HR (95% CI) multivar. adjusted***
None	3,616	1192	Reference	Reference	Reference	Reference
Current	2,229	289	0.67 (0.60-0.76)	0.60 (0.53-0.68)	0.69 (0.55-0.86)	0.56 (0.47-0.66)
Previous	692	380	2.16 (1.73-2.69)	2.01 (1.61-2.51)	2.12 (1.46-3.07)	2.15 (1.61-2.86)
Any	2,921	669	0.79 (0.70-0.88)	0.75 (0.66-0.84)	0.76 (0.63-0.90)	0.67 (0.58-0.78)
Intensity of statin use (DDDs/year)						
14-240	861	246	0.96 (0.81-1.15)	0.93 (0.78-1.11)	0.90 (0.68-1.20)	0.95 (0.75-1.19)
241-400	950	211	0.76 (0.62-0.93)	0.70 (0.57-0.85)	0.83 (0.61-1.11)	0.61 (0.46-0.82)
over 400	1108	212	0.71 (0.57-0.88)	0.65 (0.52-0.81)	0.67 (0.47-0.95)	0.63 (0.48-0.85)
Statin use before PCa diagnosis	**n of PCa cases**	**n of deaths**	**HR (95% CI) age-adjusted**	**HR (95% CI) multivar. adjusted***	**HR (95% CI) multivar. adjusted***	**HR (95% CI) multivar. adjusted***
None	4,702	842	Reference	Reference	Reference	Reference
Current	1,584	207	0.84 (0.75-0.94)	0.77 (0.68-0.87)	0.76 (0.62-0.92)	0.78 (0.67-0.90)
Previous	251	50	1.19 (0.95-1.50)	1.11 (0.88-1.40)	1.10 (0.76-1.58)	1.13 (0.84-1.53)
Any	1,835	257	0.89 (0.79-0.99)	0.81 (0.73-0.91)	0.80 (0.67-0.97)	0.82 (0.71-0.94)
Intensity of statin use (DDDs/year)						
14-249	922	245	0.91 (0.79-1.04)	0.84 (0.73-0.96)	0.74 (0.58-0.94)	0.90 (0.75-1.07)
250 or more	913	204	0.86 (0.74-0.99)	0.78 (0.67-0.91)	0.88 (0.69-1.12)	0.73 (0.60-0.89)

* Calculated with Cox regression model adjusted for age, use of other drugs (aspirin, NSAIDs, antidiabetic drugs, antihypertensive drugs, alpha-blockers or 5α-reductase inhibitors) and for FPCST trial arm.

Supplementary Table 3. Prostate cancer survival by current use of separate statins and non-statin cholesterol-lowering drugs before and after prostate cancer diagnosis. Cohort of men participating in the Finnish Prostate Cancer Screening Trial during 1996-2009.

	Prostate cancer survival	
	Pre-Dx use	Post-Dx use
Statin	HR (95% CI)*	HR (95% CI)*
Simvastatin	0.99 (0.78-1.25)	0.75 (0.59-0.96)
Atorvastatin	0.91 (0.69-1.22)	0.75 (0.54-1.05)
Fluvastatin	1.19 (0.80-1.78)	0.95 (0.53-1.69)
Non-statin cholesterol-lowering drugs†	1.29 (0.78-2.12)	1.00 (0.41-2.41)

* Calculated with Cox regression model adjusted for age, use of other drugs (aspirin, NSAIDs, antidiabetic drugs, antihypertensive drugs, alpha-blockers or 5α-reductase inhibitors) and for FPCST trial arm (analysis of prostate cancer mortality). Analyses on post-diagnostic usage additionally adjusted for tumor Gleason grade, tumor stage and PSA level at diagnosis.

† Includes users of fibric acid-derivatives (bezafibrate, clofibrate, fenofibrate gemfibrozil), bile acid-binding resins (cholestipol and cholestyramin), acipimox and ezetimibe

Supplementary Table 4. Risk of prostate cancer death calculated by using univariate adjustment.

	Postdiagnostic statin users	Prediagnostic statin use
	HR (95% CI)	HR (95% CI)
Use of aspirin	0.73 (0.55-0.96)	0.71 (0.54-0.93)
Use of NSAIDs	1.07 (0.83-1.37)	1.07 (0.83-1.37)
Use of 5α-reductase inhibitors	0.91 (0.70-1.18)	0.91 (0.70-1.18)
Use of alphablockers	1.31 (1.11-1.55)	1.31 (1.10-1.54)
Use of antihypertensive drugs	0.89 (0.73-1.08)	0.88 (0.73-1.06)
Use of antidiabetic drugs	1.08 (0.89-1.33)	1.07 (0.87-1.30)
Randomization group	1.10 (0.91-1.32)	1.12 (0.93-1.35)
Grade of PCa	3.89 (3.16-4.80)	3.81 (3.09-4.71)
Metastasis status	11.40 (9.56-13.64)	11.63 (9.74-13.89)
PSA (dichotomous)	1.70 (1.38-2.10)	1.73 (1.40-2.14)