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ARTICLE

Incidence of erectile dysfunction treatment after radical prostatectomy by Statin use in Finnish Nationwide Cohort Study

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ABSTRACT

Background: Erectile dysfunction (ED) is common after radical prostatectomy (RP) due to cavernous nerve damage. Risk of ED is also affected by vascular function. Statins prevent vascular events but their association with post-prostatectomy ED is unclear. We explored the likelihood of starting ED treatment after RP by statin use at the population level.

Methods: The study cohort included 14,295 prostate cancer (PCa) patients with no ED treatment prior to diagnosis of PCa treated with RP in Finland during 1995–2013. Information on use of cholesterol-lowering drugs and ED medication during 1995–2014 and penile prosthesis implantation during 1996–2014 were gathered from national registries. Risk of ED treatment initiation after RP was analyzed by pre-diagnostic and post-diagnostic statin and non-statin cholesterol lowering (NSCL) drug use with Cox regression model.

Results: Pre-diagnostic statin use or NSCL drug use overall had no association with risk of ED treatment initiation after RP. Post-diagnostic statin use was associated with a slightly increased risk of initiation of any ED treatment (HR = 1.07; 95% CI = 1.01–1.14). Patients with the longest duration of post-diagnostic statin use had a significantly decreased risk of PDE5 inhibitor initiation compared to non-users (HR = 0.43; 95% CI = 0.20–0.94). Among patients with no cardiovascular comorbidities, pre-diagnostic statin users had a significantly increased risk of initiation of injectable ED drugs (HR = 1.27; 95% CI = 1.04–1.55), however, no association with risk of any other ED treatment was observed.

Conclusion: Statin users have a slightly increased risk of ED treatment initiation after RP, which probably reflects the effect of the underlying vascular insufficiency.

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Prostate cancer; Statin; radical prostatectomy; erectile dysfunction; PDE5 inhibitor; cohort study

Introduction

Erectile dysfunction (ED) is common among men older than 40 years, with an obvious impact on quality-of-life [1]. Age, diabetes mellitus, atherosclerosis, cardiovascular disease (CVD), metabolic syndrome, smoking, obesity, hyperlipidemia, depression, low testosterone levels and some medications are known risk factors of ED. Surgery or radiation therapy for prostate cancer (PCa) are known to cause ED due to damage to cavernous nerves [1–3].

Use of statins has been linked to improvement in erectile function (EF) in retrospective studies, which is thought to result from actions of statins on endothelial function [2,4,5]. Among men with CVD or cardiovascular risk factors statin use was not associated with new onset ED during statin therapy [6]. Some studies have linked statins to lower testosterone levels [7].

PSA-based early diagnosis of PCa has led to great increases in the number of new PCa diagnoses [8]. Radical prostatectomy (RP) for localized PCa is an effective treatment, however, it leads to sexual dysfunction [9]. Also other active PCa treatment modalities lead to high risk of ED after therapy [10]. Injury to the cavernous nerves or neuropraxia during RP causes post-operative prevalence of ED, ranging from 10–82% [11].

The possible association of statin use on ED after radical prostatectomy is unclear. Statins are used for secondary prevention of CVD, an established ED risk factor. Concordantly, statin users have been reported to have more ED before and after RP compared to non-users [12]. Interestingly, atorvastatin may aid in earlier recovery of EF among patients with normal EF before nerve-sparing retropubic prostatectomy [13]. However, in a planned *post hoc* analysis of our randomized placebo-controlled study, use of atorvastatin 80 mg/day for a median of 21 days did not have an effect on EF after RP compared to placebo [14]. Therefore, studies exploring the association of long-term statin use on EF after RP are needed.

The aim of this study was to explore if statin use before or after RP associates with the likelihood of starting ED treatment after RP in a large population-based cohort.

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Materials and methods

Study population

PCa patients primary treated with RP were identified from the Finnish Cancer Registry (FCR). Information on primary management was complemented using patient files and Care Registry of the Finnish Institute for Health and Welfare (FIHW) by using procedure codes for RP (according to Nordic classification of procedures codes (NCPC): KEC00 and KEC01). Age, date of diagnosis and TNM-stage were obtained from FCR. Dates and causes of deaths, gathered through mandatory notifications by Statistics Finland, were collected from FCR. All data was linked using personal identification number.

The study cohort included 14,424 men who underwent RP in Finland during 1995–2013. A total of 129 men with records of ED treatment before diagnosis of PCa were excluded. The remaining 14,295 eligible men were included in the study cohort.

Information on medication use

The Social Insurance Institution of Finland (SII) maintains a database which registers purchases of physician-prescribed drugs. Patients purchasing drugs approved by SII for reimbursement are eligible for price discounted at each purchase. ATC-codes, date, dose, package size and number of packages of each purchase transaction are recorded in the database. The data of each participant drug use during 1995–2014 was collected from the prescription database of SII by linking it to the study cohort using personal identification number. The data of drug use contained phosphodiesterase 5 (PDE5) inhibitors, intracavernous prostaglandin E1 (PGE1), statins, non-statin cholesterol-lowering drugs (NSCL), androgen deprivation therapy (ADT), antidiabetic drugs, anti-hypertensive drugs and nitrates. Please see ATC-codes in Supplementary Table S1.

Information on diagnoses and procedures

The Care Registry of the FIHW maintains a registry of recorded diagnoses and performed procedures in Finnish health care units. Diagnoses are classified according to International Classification of Diagnoses 10 (ICD-10) and procedures according to NCSP. Diagnoses of cardiovascular comorbidities during 1996–2014 (arterial hypertension, type 1 and 2 diabetes mellitus, obesity and coronary artery disease) were collected from the registry. Penile prosthesis is a surgical option in the treatment of ED. Penile prosthesis implantations during 1996–2014 were identified based on recorded procedure code.

Information on used chemotherapy and radiation therapy as adjuvant or secondary therapy of PCa were collected from the care registry. To complete the information on ADT we collected the information on surgical castration during 1996–2014 by NCSP of orchiectomy.

Information on diagnoses and procedures were linked to data by using personal identification number. Diagnosis codes and procedure codes are listed in Supplementary Table S1.

Statistical analysis

Initiation of ED treatment was the measured outcome of this study. ED treatment was categorized into four groups: PDE5 inhibitors (sildenafil, tadalafil, vardenafil and alanafil), injectable ED drugs (alprostadil), penile prosthesis and any ED treatment. Patients were included in the group of any ED treatment if at least one of PDE5 inhibitors, injectable ED drugs or penile prothesis was recorded. ED treatment was considered to initiate at the year of the first ED treatment recorded. Endpoint of follow-up time was the initiation of ED treatment, death or end of 2014, whichever came first. Follow-up time was calculated separately for each category of ED treatment until the month of first record of the treatment.

Hazard ratios (HRs) with 95% confidence intervals (CIs) for initiation of each ED treatment group were evaluated with Cox regression method. Statin and NSCL drug users were compared to non-users. To evaluate the effects of statin use on initiation of ED treatment among patients without cardiovascular comorbidities we also performed our analysis of statin use restricted to patients with no known comorbidities. Population, tumor and cardiovascular comorbidity characteristics by statin and NSCL drug use were compared using chi-square test for categorical variables and Mann-Whitney U-test for continuous variables.

Medication on hypercholesterolemia was categorized into two groups: Statins and NSCL drugs (fibrates, bile acid sequestrants and ezetimibe). Drugs included in these categories are gathered in Supplementary Table S2. Total amount in milligrams (mg) for each purchase of each drug was calculated according to the number of packages, size of packages and dose. Total yearly amount was calculated by summarizing all purchases within a calendar year. Standardized amount (Defined Daily Doses (DDDs)) and intensity (DDDs/year) of each cholesterol-lowering drug usage were calculated as previously described [15,16].

The use of cholesterol-lowering drugs during the preceding year or before PCa diagnosis was defined as pre-diagnostic use and drug use during or after year of PCa diagnosis was defined as post-diagnostic use. Patients remained non-users until the year of first purchase of cholesterol-lowering drugs. Variables of pre-diagnostic and post-diagnostic doses, duration and intensity of use were formed for statins and NSCL drugs separately. To evaluate dose-dependence of effects the pre-diagnostic amount, duration and intensity were divided by median into two equal size groups and post-diagnostic use was divided according to tertiles into three equal size groups.

All analyses of pre-diagnostic and post-diagnostic use were performed separately with age-adjusted and multivariable adjusted models. The multivariable adjusted model included age, arterial hypertension, coronary artery disease, type 1 and 2 diabetes mellitus, obesity, ADT initiated before ED treatment, radiation therapy, chemotherapy and tumor

stage. Variables of cardiovascular comorbidities in multivariable adjusted model were formed by combining drug purchases and recorded diagnoses to a comprehensive combination variable.

IBM SPSS statistics 26 software was used to carry out analyses (Chicago, IL). All *p*-values are two-sided and *p*-values less than 0.05 were considered statistically significant.

Finnish Institute of Health and Welfare approved the study protocol (THL/490/5.05.00/2016).

Results

Population characteristics

Median follow-up after prostatectomy was 2.8 years (IQR = 1.1–7.7 years). Median age at diagnosis was 62 years (IQR = 58–66 years) for statin users and non-users.

Proportion of participants dying due to PCa or any other cause was lower among statin users than non-users (Table 1). Patients with post-diagnostic statin use had more likely local PCa than non-users (Table 1). All cardiovascular comorbidities were more common among statin users. Statin users before diagnosis of PCa were less likely to start ADT but more likely to undergo radiation therapy after prostatectomy. The study population included 252 patients with pre-diagnostic NSCL drug use and 448 patients with post-diagnostic drug use. Characteristics of the NSCL drug group were similar to the statin group.

Risk of ED treatment initiation by use of statins and NSCL drugs before diagnosis of PCa

The proportion of PDE5 inhibitor usage or ED treatment overall was lower among pre-diagnostic statin users than non-users (Table 1).

Generally, pre-diagnostic statin or NSCL drug use was not associated with risk of ED treatment initiation in a multivariable adjusted model compared to non-users (Table 2, Supplementary Table S3). When compared to non-users, high-intensity (298 DDDs/year or more) statin users had a statistically significant reduction in risk of initiation of PDE5 inhibitors in age-adjusted analysis but in multivariable-adjusted analysis the observed association was no longer significant (Table 2, Supplementary Table S4). However, pre-diagnostic statin users had an increased risk of initiation of injectable ED drugs in multivariable adjusted analysis (HR = 1.15, 95% CI = 1.01–1.30).

Table 1. Population characteristics. Pre-diagnostic and post-diagnostic statin use compared to participants with no cholesterol-lowering drug use.

	Statin use		No cholesterol-lowering drug use	
	Pre-diagnostic	Post-diagnostic	Pre-diagnostic	Post-diagnostic
Number of men	3,403	6,660	10,345	7,591
Age at diagnosis				
Median (years) [IQR]	63 [59–66]	62 [58–66]	61 [57–66]	62 [57–66]
p for difference	<0.001	<0.001	ref	ref
PCa death	51 (1.5%)	139 (2.1%)	296 (2.9%)	280 (3.7%)
p for difference	<0.001	<0.001	ref	ref
Death	203 (6.0%)	600 (9.0%)	1,104 (10.7%)	941 (12.4%)
p for difference	<0.001	<0.001	ref	ref
Median of follow up time (years) [IQR]	2.5 [1.1–5.6]	3.0 [1.1–8.6]	2.8 [1.1–7.9]	2.8 [1.1–6.8]
Local PCa	2,345 (68.9%)	4,787 (71.9%)	7,380 (71.3%)	5,317 (70.0%)
p for difference	<0.001	<0.001	ref	ref
ED treatment				
Any treatment of ED	1,336 (39.3%)	3,003 (45.1%)	4,642 (44.8%)	3,155 (41.6%)
p for difference	<0.001	<0.001	ref	ref
PDE5 inhibitor	1,075 (31.6%)	2,454 (36.8%)	3,898 (37.7%)	2,616 (34.5%)
p for difference	<0.001	0.003	ref	ref
Injectable ED drugs	705 (20.7%)	1,552 (23.3%)	2,228 (21.5%)	1,508 (19.9%)
p for difference	0.29	<0.001	ref	ref
Penile prothesis	3 (0.09%)	13 (0.2%)	21 (0.2%)	15 (0.2%)
p for difference	0.17	0.99	ref	ref
Comorbidities				
Diabetes*	946 (27.8%)	1,812 (27.2%)	1,391 (13.4%)	639 (8.4%)
Obesity**	52 (1.5%)	86 (1.3%)	89 (0.9%)	61 (0.8%)
p for difference	<0.001	0.004	ref	ref
Hypertension*	2,763 (81.1%)	5,545 (83.3%)	6,528 (63.1%)	4,185 (55.1%)
Coronary artery disease*	1,156 (33.9%)	2,476 (37.2%)	1,966 (19.0%)	904 (11.9%)
Additional treatments after prostatectomy				
Chemotherapy	9 (0.3%)	24 (0.4%)	47 (0.5%)	35 (0.5%)
p for difference	0.12	0.36	ref	ref
Radiation therapy	179 (5.3%)	243 (3.6%)	381 (3.7%)	320 (4.2%)
p for difference	<0.001	0.08	ref	ref
ADT	498 (14.6%)	1,323 (19.9%)	2,041 (19.7%)	1,490 (19.6%)
p for difference	<0.001	0.76	ref	ref
ADT before initiation of treatment on ED	94 (2.8%)	259 (3.9%)	395 (3.8%)	263 (3.5%)
p for difference	0.003	0.21	ref	ref

*All *p*-values < 0.001.
**Recorded diagnosis of obesity.

Table 2. Risk of initiation of ED treatment among PCa patients with pre-diagnostic statin use compared to non-users. Multivariable adjusted analysis.

	Risk of initiation of any ED treatment Multivariable adjusted model	Risk of initiation of PDE5 inhibitor Multivariable adjusted model	Risk of initiation of injectable ED drugs Multivariable adjusted model
Pre-diagnostic Statin use	HR (95% CIs)	HR (95% CIs)	HR (95% CIs)
Any use	1.00 (0.94–1.07)	0.99 (0.92–1.06)	1.07 (0.98–1.17)
Amount (DDDs)			
1,157 or less	0.99 (0.91–1.08)	0.96 (0.88–1.05)	1.06 (0.95–1.19)
1,157 or more	1.01 (0.93–1.11)	1.02 (0.93–1.12)	1.08 (0.96–1.21)
Duration (years)			
4 or less	0.97 (0.89–1.04)	0.94 (0.86–1.03)	1.02 (0.92–1.14)
4 or more	1.06 (0.97–1.16)	1.05 (0.95–1.16)	1.15 (1.01–1.30)
Intensity (DDDs/year)			
298 or less	1.01 (0.93–1.09)	1.01 (0.92–1.10)	1.04 (0.92–1.16)
298 or more	1.00 (0.92–1.09)	0.96 (0.88–1.06)	1.11 (0.92–1.25)

Due to the low number of cases and weak statistical power, risk estimates for penile prosthesis implantation are not shown.
Results of age-adjusted analysis are shown in Supplementary Table S4.

Table 3. Risk of initiation of ED treatment among post-diagnostic statin users compared to non-users. Multivariable adjusted analysis.

	Risk of initiation of any ED treatment Multivariable adjusted model	Risk of initiation of PDE5 inhibitor Multivariable adjusted model	Risk of initiation of injectable ED drugs Multivariable adjusted model
Post-diagnostic statin use	HR (95% CIs)	HR (95% CIs)	HR (95% CIs)
Any use	1.07 (1.01–1.14)	1.06 (0.99–1.13)	1.13 (1.04–1.22)
Amount (DDDs)			
1,470 or less	1.08 (1.01–1.15)	1.08 (1.01–1.16)	1.12 (1.03–1.22)
1,470–4,187	1.04 (0.89–1.22)	0.94 (0.79–1.11)	1.17 (0.97–1.41)
4,187 or more	0.64 (0.40–1.03)	0.81 (0.53–1.23)	0.66 (0.37–1.17)
Duration (years)			
3 or less	1.08 (1.02–1.15)	1.08 (1.00–1.15)	1.13 (1.03–1.23)
3–7	1.02 (0.82–1.26)	1.01 (0.82–1.24)	0.96 (0.73–1.26)
7 or more	0.61 (0.31–1.23)	0.43 (0.20–0.94)	1.12 (0.60–2.09)
Intensity (DDDs/year)			
327 or less	1.10 (1.01–1.19)	1.08 (0.99–1.18)	1.14 (1.02–1.27)
327–641	1.09 (0.99–1.16)	1.10 (0.99–1.21)	1.08 (0.95–1.22)
641 or more	0.99 (0.88–1.13)	0.94 (0.82–1.09)	1.11 (0.94–1.31)

Due to the low number of cases and weak statistical power, risk estimates for penile prosthesis implantation are not shown.
Results of age-adjusted analysis are shown in Supplementary Table S4.

Risk of ED treatment initiation by use of statins and NSCL drugs after diagnosis of PCa

The proportions of men starting ED treatments, except penile prosthesis implantation, were higher among post-diagnostic cholesterol-lowering drug users (Table 1).

In multivariable-adjusted analysis, post-diagnostic statin use overall was associated with slightly increased risk of initiation of any ED treatment (HR = 1.07; 95% CI = 1.01–1.14) (Table 3). Post-diagnostic statin use with the lowest intensity (327 or less DDDs/year) was associated with a slightly increased risk of any ED treatment (HR = 1.10; 95% CI = 1.01–1.19). By increasing the amount and duration of statin use the risk estimates tended more toward reduced risk of ED treatment initiation, however, in multivariable adjusted analysis the findings were not statistically significant (Table 3).

At separate analysis, the association between low amount and duration of post-diagnostic statin use and increased risk of initiation of ED drugs was observed for PDE5 inhibitors separately (Table 3). However, the risk association was reversed with increasing duration of statin use; risk of PDE5 inhibitor initiation was lowered compared to non-users when usage had lasted for 7 or more years (HR = 0.43; 95% CI = 0.20–0.94). For injectable ED treatment, post-diagnostic statin users had an increased risk of starting the treatment (HR = 1.13; 95% CI = 1.04–1.22). The risk increase remained, regardless of intensity of use (Table 3).

Post-diagnostic use of NSCL drugs had no association with risk of ED treatment initiation and no dose-dependency was observed (Supplementary Table S3).

Results of age-adjusted analysis are shown in Supplementary Table S4.

Risk of ED treatment initiation by use of statins before and after diagnosis of PCa among patients with no cardiovascular comorbidity

In analysis restricted to patients with no known cardiovascular comorbidities (arterial hypertension, diabetes mellitus, coronary artery disease or obesity) recorded during the follow-up, pre-diagnostic statin use in general was not associated with risk of ED treatment (Table 4). Increased risk of any ED treatment was observed among the group with the highest duration of pre-diagnostic statin use (HR = 1.30; 95% CIs = 1.06–1.61), however, no clear dose-dependency was found (Table 4). When considering ED treatment by type of medication, pre-diagnostic statin usage had no association with risk of initiation of PDE5 inhibitors, but increased risk of starting alprostadin injections for ED treatment (HR = 1.27; 95% CI = 1.04–1.55).

Post-diagnostic statin use was not statistically significantly associated with risk of initiation of ED treatments. However, risk estimates were tending toward slightly increased risk

Table 4. Analysis restricted to patients with no known comorbidities.*

	Risk of initiation of any ED treatment Multivariable adjusted model	Risk of initiation of PDE5 inhibitor Multivariable adjusted model	Risk of initiation of injectable ED drugs Multivariable adjusted model
Pre-diagnostic statin use	HR (95% CIs)	HR (95% CIs)	HR (95% CIs)
Any use	1.07 (0.92–1.23)	1.02 (0.87–1.19)	1.27 (1.04–1.55)
Amount (DDDs)			
1,157 or less	0.96 (0.79–1.17)	0.91 (0.74–1.13)	1.22 (0.94–1.59)
1,157 or more	1.21 (0.99–1.48)	1.16 (0.93–1.45)	1.33 (1.00–1.77)
Duration (years)			
4 or less	0.93 (0.77–1.12)	0.90 (0.73–1.10)	1.14 (0.88–1.48)
4 or more	1.30 (1.06–1.61)	1.23 (0.98–1.55)	1.47 (1.10–1.96)
Intensity (DDDs/year)			
298 or less	1.03 (0.85–1.25)	0.98 (0.79–1.21)	1.27 (0.97–1.65)
298 or more	1.11 (0.90–1.36)	1.06 (0.85–1.32)	1.27 (0.96–1.68)
Post-diagnostic statin use			
Any use	1.12 (0.97–1.28)	1.06 (0.92–1.24)	1.17 (0.96–1.42)
Amount (DDDS)			
1,470 or less	1.09 (0.94–1.26)	1.02 (0.87–1.20)	1.13 (0.92–1.40)
1,470–4,187	1.29 (0.88–1.90)	1.39 (0.96–2.01)	1.17 (0.69–2.00)
4,187 or more	0.77 (0.19–3.08)	0.37 (0.05–2.65)	1.36 (0.34–5.49)
Duration (years)			
3 or less	1.11 (0.96–1.28)	1.05 (0.89–1.22)	1.15 (0.94–1.42)
3–7	1.22 (0.71–2.07)	1.39 (0.86–2.23)	0.95 (0.44–2.06)
7 or more	—	0.76 (0.10–5.63)	—
Intensity (DDDs/year)			
327 or less	1.13 (0.94–1.38)	1.06 (0.86–1.31)	1.05 (0.79–1.40)
327–641	1.05 (0.84–1.32)	1.08 (0.85–1.36)	1.07 (0.78–1.48)
641 or more	1.16 (0.85–1.59)	1.08 (0.77–1.53)	1.48 (0.99–2.23)

The risk of initiation of ED treatment among pre-diagnostic and post-diagnostic statin users compared to non-users. Multivariable adjusted analysis.
*Comorbidities = Arterial hypertension, diabetes mellitus, coronary heart disease and obesity.
Due to the low number of cases and weak statistical power, risk estimates for penile prosthesis implantation are not shown.
Results of age-adjuster analysis are shown in Supplementary Table S5.

compared to non-users with no clear dose-dependence (Table 4).

Results of age-adjusted analysis are shown in Supplementary Table S5.

Discussion

Pre-diagnostic statin or NSCL drug use had no clear association with risk of ED treatment initiation. Slightly increased risk estimates were observed among pre-diagnostic statin users with no known comorbidities. Results are likely reflecting effects of hypercholesterolemia and a possible underlying CVD that indicated statin use, as CVDs are known to be associated with ED *via* atherosclerosis, which impedes blood flow in the corpora cavernosa [17,18]. Lack of cardiovascular comorbidities predict less strict target values of lipids, thus subjects are less likely to be statin users and to use the drugs with lower intensity.

Use of atorvastatin has previously been reported to associate with increased risk of ED among patients with hypercholesterolemia. In that study participants had no other cardiovascular risk factors and their PCa status was unknown [19]. Prevalence of ED before and after surgery is elevated among PCa patients who use statins [12], which is concordant with our finding of increased likelihood of ED by statin use. This association is likely not caused by statin use directly, but rather reflects the underlying conditions indicating statin use; in a previous study 6 months treatment with simvastatin use did not have an impact on EF among men with untreated ED [20]. Furthermore, in our previous randomized placebo-controlled study short-term high-dose atorvastatin use (80 mg) before RP did not have an impact on post-operative EF [14].

Post-diagnostic statin use was associated with slightly increased risk of ED treatment initiation. However, slightly decreased risk of ED treatment initiation was observed among statin users with longer duration of use. RP can cause physical damages leading to ED instantly after surgery and recovery of EF can occur up to 4 years after prostatectomy [10]. Protective association with long-term use may be caused by statin users having improved control of risk factors of ED and CVD, decreased sexual motivation, worse EF at baseline and hesitance to use ED drugs later or, alternatively, by better preservation of vascular function by long-term statin use.

As the definition of ED in our study is based on purchases of ED drugs, our results reflect the association between statin use and sexual bother rather than erectile function directly. Our results on ED treatment initiation are not comparable with results of studies measuring statins' effects on EF recovery or impairment of EF during ED therapy. However, previously it has been reported that statin use might improve the response to PDE5 inhibitors [21]. Also, among PCa patients who underwent bilateral nerve sparing radical retropubic prostatectomy, atorvastatin (10 mg) administration for 90 days after prostatectomy was linked to improvement in International Index of Erectile Function 5 (IIEF5) score. However, no difference in reaching sufficient EF without PDE5 inhibitors was observed between statin users and non-users [13].

Based on our results we suggest that statin use have no protective effects on EF among PCa patients undergoing RP. On the contrary, statin users are slightly more likely to use

any ED treatment after prostatectomy. However, we are highlighting that cholesterol-lowering drugs are established treatment in primary and secondary prevention of CVD [22,23]. Further studies on effects of long-term statin use on EF recovery among surgically treated PCa patients with and without ED treatment are required, preferably with randomized controlled study design and information available on CVD and cholesterol-levels as well as EF measurements, e.g. IIEF5 questionnaire, at multiple time points before and after ED treatment.

Currently prostate MRI is commonly performed before radical prostatectomy. This likely leads to improved possibilities of nerve sparing as tumors can be localized more accurately pre-operatively. Thus, functional results regarding EF may differ in contemporary cohorts compared to our study population which was operated on an era preceding adoption of pre-operative MRI. However, this likely concerns both statin users and non-users, without any systematic difference between the groups. Thus, the association between ED and statin use probably is not changed even by more accurate diagnostics.

The strengths of our study are the large nationwide study population and comprehensive register-based data of medication use not liable to recall bias. Measured outcome included all medical possibilities of ED treatment. In this study patients undergoing any ED therapy had an ED with certain impaired quality-of-life.

The main limitations of our study are the lack of information on Gleason score, severity of ED, blood lipid values, sexual activity and mental factors affecting sexual activity and, thus, the likelihood of using ED therapy. We also had no information on lifestyle factors such as physical activity, smoking or drinking habits. Cardiovascular comorbidities were included in the multivariable adjusted model to control for possible selection bias. In addition, post-diagnostic analyses were done using time-dependent variables to avoid immortal time bias. Due to the low number of cases, statistical power was weak in all analyses of risk of penile prosthesis implantation. The extent of nerve-sparing in prostatectomies was unknown, however, this is unlikely to differ by statin use and thus is not expected to bias our results. Information on chemotherapy and radiation therapy in national registries is not as comprehensive as data on medication purchases, limiting our ability to adjust for them.

We were unable to categorize patients by date of prostatectomy as the date was not available. Instead we categorized by date of PCa diagnosis, which we assume to be close to the date of prostatectomy. This may not hold true, however, for patients who underwent active surveillance before radical prostatectomy. However, active surveillance was not as common during the study era as it is today and we estimate the proportion of such men to be low. In any case, any bias arising from this inaccuracy is not likely to differ by statin use.

We had no information on untreated ED. EF status before diagnosis was based on recorded ED treatment and there might be some patients with untreated ED included, thus, there is a possibility of selection bias. Further, we had no information on how relevant sexual activity was to study participants. Furthermore, in this study the first prostatectomies were performed in 1995 and in Europe marketing authorization for the first PDE5 inhibitor was granted in September 1998. Availability of PDE5 inhibitors activated more men to seek medical help for ED [24], thus, the possibility of untreated ED among subjects of this study is higher during the first 4 years of our study period and might cause some bias.

Conclusion

Statin users have slightly increased risk of ED treatment initiation after RP, which probably reflects the effect of the underlying vascular insufficiency among statin users. The association of pre-diagnostic statin use on risk of ED treatment initiation gets stronger among patients with no known cardiovascular comorbidities. This suggests that, besides cavernous nerve damage, also vascular factors have a role as risk factor of post-prostatectomy ED. Our results do not suggest that statin use could directly reduce EF. Further studies on how long-term statin use might affect ED recovery after RP are needed.

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Disclosure statement

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Data availability statement

Data used in this study is available from the authors by request.

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