The effect of non-steroidal anti-inflammatory drugs on benign prostatic hyperplasia

Lotta H Nygård[1], Kirsi Talala[2], Kimmo Taari[3], Teuvo LJ Tammela[1,4], Anssi Auvinen[5], Teemu J Murtola[1,4]

[1] University of Tampere, School of Medicine, Tampere, Finland

[2] Finnish Cancer Registry, Helsinki, Finland

[3] Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[4] Tampere University Hospital, Department of Urology, Tampere, Finland

[5] University of Tampere, School of Health Sciences, Tampere, Finland

Running head: NSAIDs and benign prostatic hyperplasia

Keywords: Benign prostatic hyperplasia; Cohort; Non-steroidal anti-inflammatory drugs; Risk

Correspondence: Teemu J Murtola, Tampere University Hospital, Department of Urology, M-building, 3rd floor, room 313, Teiskontie 35, PL 2000, 33521 Tampere, Finland. Tel. +358 3 311 65015. E-mail: teemu.murtola@uta.fi

ABSTRACT

Background: Inflammation may play a role in pathogenesis of benign prostatic hyperplasia (BPH). However, the role of non-steroidal anti-inflammatory drugs (NSAIDs) as BPH risk factor is unclear. The objective of this study was to examine risk of BPH by NSAID use in a population-based cohort.

Methods: A total of 74,754 Finnish men without previous BPH at baseline in 1996 - 1999 were linked to national medication reimbursement database for information on physician-prescribed NSAID purchases during 1995 - 2009. Information on BPH procedures and diagnoses was obtained from national Care Register for and Health Care. Cox regression with adjustment for age and use of cholesterol-lowering, antidiabetic and antihypertensive medication and NSAID use as time-dependent variable was used to analyse the risk of BPH surgery, medication use and recorded diagnosis.

Results: Of the subjects 57,707 men (77.2 %) used prescription NSAIDs. The risk of BPH was elevated among NSAID users compared to non-users: HR 2.04, 95 % CI 1.97-2.10 for BPH medication use, HR 1.59, 95 % CI 1.47 - 1.71 for recorded diagnosis and HR 1.61, 95 % CI 1.49 - 1.74 for surgery. The risk increase correlated with duration of NSAID usage, less with annual dosage. Nevertheless, the risk increase was observed already at short-term and low-dosage use.

Conclusions: NSAID use is associated with an increased risk of BPH. The association is affected by systematic differences by NSAID use as the risk increase was observed already at short-term use. Nevertheless, the association correlated with duration of use, suggesting that NSAID usage or the conditions indicating it may increase BPH risk.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most frequent medical conditions in aging men and one of the most common chronic diseases among the male population. BPH is progressive, as it evolves from asymptomatic tissue alterations to clinical disease with lower urinary tract symptoms (LUTS). These symptoms have an important effect on the quality of life and can lead to acute urinary retention if untreated [1]. Hence improvement in the prevention and clinical treatment of this condition would be beneficial.

Although the pathogenesis and etiology of BPH are not entirely understood, hormonal dysregulation seems to play an essential role as a shift in prostatic androgen metabolism occurs with aging. This causes abnormal accumulation of dihydrotestosterone, resulting in prostate enlargement [2]. Also local growth factors and complex inflammation appear to have an impact on BPH. BPH is often accompanied by metabolic syndrome, a condition characterized by systemic inflammation [2]. Thus, use of non-steroidal anti-inflammatory drugs (NSAIDs) may affect BPH by reducing inflammation. NSAIDs are prescribed for analgesia in various common conditions with pain and inflammation. Both BPH and NSAID usage are common in older men which highlights the importance of understanding their interrelationship.

Evidence regarding the role of inflammation in BPH has been accumulating and inflammatory pathways seem to play significant role in different phases of BPH. This has been indicated by histological studies reporting intraprostatic inflammation in 43 - 98 % of BPH tissue samples [3, 4]. High C-reactive protein concentration has also been associated with an increased BPH risk [5]. T-cell derived cytokines may contribute and enhance prostatic growth [6] as various interleukins increase the expression of cyclooxygenase 2 (COX-2), which is up-regulated on macrophages and epithelial cells in BPH [7]. Thus inhibition of inflammatory pathways by NSAIDs could decrease and inhibit the development of BPH. Such an effect has been reported *in vitro* [8].

The amount of research on this subject is scarce and results somewhat conflicting. One of the few studies reported a weak positive association between regular NSAID use and prevalent BPH/LUTS [9], whereas another study found a strong inverse association between daily NSAID use and incident BPH/LUTS [10]. Additionally, a systematic review and meta-analysis of randomized controlled trials on the subject concluded that NSAIDs improve lower urinary symptoms and urine flow [11]. Results from the Prostate Cancer Prevention Trial and from the Prostate, Lung, Colorectal, and Ovarian cancer screening trial provide no clear evidence that use of NSAIDs would reduce the BPH risk [12, 13]. More research on this subject is clearly needed to resolve the controversy.

The aim of this study is to evaluate possible connections between NSAID usage and the BPH risk in a large population-based cohort.

MATERIALS AND METHODS

Study cohort and data sources

Study population consisted of men in the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) which is the largest component of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The Finnish Trial included 80,144 men born in 1929 - 1944 (aged 55, 59, 63 and 67 years at entry) resident in Tampere and Helsinki areas in 1996 - 1999. These men were randomized either to be invited to screening with PSA test at four-year intervals (screening arm) or to the control arm with no intervention, both groups followed via national health-care registries. In total, 32,000 men were randomized to the screening arm. Men over 71 years old were no longer invited for re-screening (men 67 years old at entry were screened twice, whereas those aged 55, 59 or 63 years three times). The follow-up continued until the end of 2013.

This study was limited to include men from the FinRSPC study population who didn't have any BPH medication purchases (finasteride or alpha-blockers, data available from 1995 onwards) and hadn't undergone BPH-related surgery before baseline, the year of FinRSPC randomization. A total of 74,754 men were included in our study cohort. The follow-up continued until the first BPH treatment, emigration, death or beginning of 2013, whichever occurred first. Three different definitions were used for BPH treatment: recorded BPH diagnosis in a hospital contact, use of BPH medication (finasteride, dutasteride, tamsulosin, alfuzosin) or surgical treatment (transurethral resection of the prostate (TURP), laser resection/enucleation or intracapsular prostatectomy, performed extra- or transvesically).

Detailed individual information on use of NSAIDs and other drugs (statins, antidiabetic drugs and antihypertensive drugs) was obtained from the reimbursement database of the Social Insurance Institution of Finland (SII). NSAIDs were identified using ATC-codes (Supplementary table 1). All

purchases of physician-prescribed drugs approved by the SII (most prescription drugs in clinical use) are recorded in the database. The database includes information on date, dosage, package size and number of obtained packages for each reimbursed purchase. The database does not record over-the-counter purchases or drugs administered during hospital inpatient periods. Information on over-the-counter NSAID use was collected with surveys mailed with the screening invitations on the third screening round, with 93 % response rate [14].

Yearly purchases of each NSAID were added together for total yearly mg amount of usage. Differences between drugs were standardized by dividing the yearly mg amount with amount corresponding to a Defined Daily Dose as listed by WHO [15]. Each year with registered NSAID purchases was regarded as a year of usage regardless of the purchased amount. Average yearly amount of NSAID usage was calculated by dividing the cumulative amount of use with the cumulative number of years with registered purchases.

The information on diagnoses and medical procedures recorded at outpatient visit and hospitalization episodes was obtained from the Care Register for and Health Care (HILMO) maintained by the National Institute for Health and Welfare (THL). The ICD-10 code N40 was used to identify BPH diagnoses. BPH procedures were identified using NCSP (Nordic Classification of Surgical Procedures) codes KED00, KED10, KED22, KED33, KED62, KED72, KED52 and KED76. Additionally, we identified common diagnoses for regular NSAID use arthrosis and rheumatoid arthritis based on ICD-10 codes M15-M19 and M05-M06, respectively.

Both registries cover all hospitals (whether public or private) and the entire population of Finland.

Statistical methods

Risk of BPH was compared by overall NSAID usage, previous or current usage and by length of usage as compared to non-users. For comparison, BPH risk was separately analyzed by aspirin and coxib usage.

The analysis was performed using Cox regression to calculate hazard ratios (HRs) and their 95 % confidence intervals (95 % CIs) for the three separate BPH outcomes defined earlier. Analysis was adjusted for age and use of other medications (statins, antidiabetic drugs and antihypertensive drugs).

NSAID usage was analyzed as a time-dependent variable, with usage status, as well as cumulative length of usage were updated for each year of follow-up based on yearly NSAID purchases. We performed separate analysis for NSAID ever-users, and an analysis of current users (men still using NSAIDs on a given follow-up year) and previous users (usage on previous years, but not on the observation year).

Users were stratified into quartiles according the total cumulative number of years with recorded NSAID purchases. To estimate the role of yearly amount of NSAID use, the users were stratified to those who used less than 100 DDDs/year and men who used 100 DDD/year or more. Like status on NSAID usage, these variables were updated separately for each year of follow-up according to medication purchases.

Additionally, one-year and three-year lag time analyses were performed to evaluate NSAIDs' long-term effects on BPH risk. In this analysis NSAID exposure was lagged forward in the follow-up time, for example in a three-year lag time analysis exposure in 1996 would affect the outcome on 1999.

The analyses were carried out using IBM SPSS Statistics 23 statistical software (Chicago, IL, USA).

RESULTS

Population characteristics

Of the 74,754 participants, 77.2 % were NSAID users (Table 1). The median age at baseline was 59 years in both NSAID users and non-users. The use of antidiabetic drugs, antihypertensive drugs and statins was more common among NSAID users.

BPH risk by NSAID usage

The risks for BPH-related hospital visits, starting BPH-medication and BPH surgery were elevated among NSAID users compared to non-users in multivariable-adjusted analyses both for over-the-counter and prescription usage (Table 2). The largest risk increase was observed for usage of BPH drugs, but also the risk of BPH surgery was increased compared to non-users. For prescription use, the risk was highest among men on NSAIDs, whereas in men who discontinued NSAIDs usage the risk elevation was reduced, but remained elevated compared to the non-users. The association was amplified with increasing years of NSAID usage. No clear risk trends were observed by annual amount of NSAID doses; the risk for each BPH endpoint was elevated in both men who had used less than 100 DDDs/year (85 % of users) and men who had used 100 DDDs/year or more (15 % of users). For BPH diagnosis and BPH surgery the risk elevations were slightly higher among those who used less than 100 DDDs/year.

BPH risk by use of aspirin and coxibs

Similar to NSAID usage, the use of coxibs was associated with a higher risk of each BPH endpoint (Table 3). The risk association was somewhat weaker for aspirin; only the risk of BPH medication use was elevated among ever-users of prescribed aspirin (HR, 1.19; 95 % CI, 1.13 - 1.26) and over-the-counter users (HR 1.11; 95 % CI 1.04 - 1.19). However, among current prescription users, also the risks of BPH-related hospital visits and BPH surgery were elevated. The results were also similar in an analysis where NSAIDs and coxibs were included together in the Cox regression model to take into account simultaneous use of multiple groups of NSAIDs.

Lag time analyses

The association between NSAIDs and BPH risk was weaker in both 1- and 3-year lag time analyses compared to the main analysis, but still remained statistically significant, consistent with a short-term effect (Table 4).

Subgroup analyses

Age, BMI or antidiabetic drug use did not modify the association between ever-use of NSAIDs and risk of BPH surgery (Figure 1). The risk was modified, however, by use of statins and antihypertensive drugs (p for interaction 0.045 and 0.001, respectively); the risk elevation was not as strong among men who had also used these drug groups.

Sensitivity analyses

Rheumatoid arthritis and arthrosis, which are common indications for NSAID use, were both associated with increased risk of starting BPH medication (HR 1.46, 95 % CI 1.13 - 1.89 and HR 1.76, 95 % CI 1.35 - 2.28). However, neither was associated with the risk of having recorded BPH diagnosis or surgery.

DISCUSSION

In our population-based cohort of Finnish men, NSAID users had a higher risk of BPH-related hospital visits, starting BPH medication and undergoing BPH surgery compared to non-users. The association was correlated with years of NSAIDs usage, and weakened after discontinuation, yet remaining significantly elevated compared to non-users. This shows that at population level, the risk association is opposite than would have been expected based on *in vitro* findings.

Aspirin did not have a similar association with BPH risk. The reason may lie in different indications for aspirin use. In Finland NSAIDs are prescribed for analgesia, whereas aspirin is prescribed in combination with dipyridamole mainly for secondary prevention of stroke and cerebral circulatory disorders. It should be noted that our register-based data on aspirin prescriptions is an underestimation of true prevalence of usage, as in Finland for cardiovascular disease prevention aspirin is typically purchased over-the-counter due to its cheaper price. This may have diluted the observed risk associations by aspirin use. Nevertheless, the risk associations were similar also in the subgroup of men with information on over-the-counter aspirin use.

The results show that either use of NSAIDs in itself or the conditions indicating their use increases the BPH risk and the probability of BPH progression to a stage requiring surgical management. The observed risk association is probably affected by both; strengthening risk association along with years of NSAID usage suggests direct effect of NSAIDs. On the other hand, the elevated risk observed even at low-dose usage and after discontinuation of usage suggests NSAID users differ in their BPH risk as a group from non-users. Overweight, which is associated with metabolic syndrome, and musculoskeletal disorders caused by it may be more common among NSAID users. Nevertheless, common indications for regular NSAID use were associated only with increased risk of BPH medication use, but not with risk of having recorded BPH diagnosis or surgery. Thus our results may not be entirely explained by confounding by indication, although indications for NSAID usage vary considerably and are hard to evaluate comprehensively even with our national register data.

Metabolic syndrome has been linked to systemic inflammation [16], which may also increase the BPH risk [5]. Concordantly, the risk association was modified by background use of cholesterol-lowering and antidiabetic drugs, suggesting that these conditions may have a role in the risk association.

Our result differs from secondary analyses of previously published randomized controlled trials, which reported no association with BPH risk. Contrary to this study, randomized trials often use highly selected study populations, which may lead to poor generalizability. Our study population was a population-based cohort with minimal exclusions due to background variables apart from having BPH at baseline. This is probably why the results of this study differ from those of previous randomized trials. This study proves that NSAID use does not decrease the number of BPH diagnoses nor the harmful effects of the condition at the population level.

The findings of this study differ from some previous epidemiological studies. A population-based cohort study of 2,447 men reported that daily use of NSAIDs was associated with improved urinary symptoms, increased urine flow rate, and decreased prostate volume and prostate-specific antigen levels, i.e. indications of decreased prostatic volume [10]. In contrast to our study, NSAID use in that study was ascertained by a structured interview at baseline and by a questionnaire during the follow-up, meaning that possible changes in NSAID use over time were not thoroughly examined. Additionally, definition for BPH was somewhat different. In addition to BPH treatment (surgery or BPH medications), acute urinary retention, moderate/severe urinary symptoms (as assessed by the AUASI), time to low maximum urinary flow rate (<12 ml/second), prostate volume >30 ml and serum PSA level >1.4 ng/ml were examined as endpoints.

In another cohort study of 4,964 men NSAIDs were not associated with the BPH risk [12]. The main difference between that and our study is the size of the study population. Also, the data on current NSAID use was collected by interviewing the participants at baseline and at each follow-up contact, and BPH was defined as either surgery, medical treatment or sustained, clinically significant BPH symptoms. Only the initiation of NSAID use was taken into consideration, therefore the continuation was assumed. Also the information on dose wasn’t captured. Another difference

between our study and these two previous studies is the source of information on NSAID exposure; information collected through surveys likely catches over-the-counter usage for mild and transient need, whereas our study mainly included prescription usage. Thus in our study NSAID users likely had a condition for which prescription use was needed, and as a result the NSAID users as a group could differ between our study and the previous studies.

Similar to our study, another study with a large study population, 34,694 participants, reported a modest excess risk for BPH among NSAID users [9]. In that study, the information on BPH was obtained by questionnaires where history of BPH (enlarged prostate or BPH told by a physician) or surgical treatment (TURP) was asked. The same questionnaires included the information on NSAID use, defined as regular use of aspirin or ibuprofen in last year.

Our study has several strengths. A principal strength is the extensive and detailed data on prescribed NSAID use, as well as several information sources on BPH diagnoses and treatments. These made it possible to assess BPH on multiple levels, from medical treatment to surgery. In addition, the large study population and the long follow-up time increase the validity of this study.

The limited information on the over-the-counter use of NSAIDs is one the limitations. It’s more than likely that some men who didn’t have NSAID prescriptions nevertheless had over-the-counter usage, causing exposure misclassification diluting the observed risk differences. Furthermore, detailed information on indications for NSAID use was not available, along with the knowledge of whether prescribed drugs were actually taken. Our information on BPH came from national health care registers, and the BPH cases in our study population represent men whose condition was severe enough to warrant medication use, health care contact or surgical treatment. We could not evaluate milder or non-symptomatic forms of BPH.

CONCLUSIONS

The use of NSAIDs does not lower the risk of BPH at population level. On the contrary, the risk is higher compared to NSAID non-users.

CONFLICTS OF INTEREST

TJ Murtola has received consultation fee from Astellas, Janssen-Cilag and speakers' honorarium from Abbvie, Astellas, Janssen-Cilag and MSD.

K Taari has received consultation fee from Abbvie and lecture fee from GSK and has participated in an international meeting with Astellas and Orion. Taari has received research funding from Medivation.

FUNDING

Funded by competitive research grant from Pirkanmaa Hospital District, memorial fund of Seppo Nieminen, grant number 150617

REFERENCES

1. Fitzpatrick JM. The natural history of benign prostatic hyperplasia. *BJU Int* 2006;97 (Suppl. 2):3-6; discussion 21-2
2. Dobrek Ł, Thor PJ. Benign prostatic hyperplasia – progress in pathophysiology and management. *Pol Merkur Lekarski* 2015 Nov;39(233):263-7
3. Di Silverio F, Gentile V, De Matteis A, Mariotti G, Giuseppe V, Luigi PA, Sciarra A. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. *Eur Urol* 2003;43:164-75
4. Kohnen PW, Drach GW. Patterns of inflammation in prostatic hyperplasia: a histologic and bacteriologic study. *J Urol* 1979;121:755-60
5. Schenk JM, Kristal AR, Neuhouser ML, Tangen CM, White E, Lin DW, Kratz M, Thompson M. Biomarkers of systemic inflammation and risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *Am J Epidemiol* 2010;171:571-82
6. Steiner GE, Newman ME, Paikl D, Stix U, Memaran-Dagda N, Lee C, Marberger MJ. Expression and function of pro-inflammatory interleukin IL-17 and IL-17 receptor in normal, benign hyperplastic, and malignant prostate. *Prostate* 2003;56:171-82
7. Wang W, Bergh A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. *Prostate* 2004;61:60-72
8. Minnery CH, Getzenberg RH. Benign prostatic hyperplasia cell line viability and modulation of jm-27 by doxazosin and Ibuprofen. J Urol 2005;174:375-9
9. Kang D, Andriole GL, Van De Vooren RC, Crawford D, Chia D, Urban DA, Reding D, Huang WY, Hayes RB. Risk behaviours and benign prostatic hyperplasia. *BJU Int* 2004;93:1241-1245

10. St Sauver JL, Jacobson DJ, McGree ME, Lieber MM, Jacobsen SJ. Protective association between nonsteroidal antiinlammatory drug use and measures of benign prostatic hyperplasia. *Am J Epidemiol* 2006;164:760-768
11. Kahokehr A, Vather R, Nixon A, Hill AG. Non-steroidal anti-inflammatory drugs for lower urinary tract symptoms in benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials. *BJU Int* 2013;111:304-311
12. Schenk JM, Calip GS, Tangen CM, Goodman P, Parsons JK, Thompson IM, Kristal AR. Indications For and Use of Nonsteroidal Antiinflammatory Drugs and the Risk of Incident, Symptomatic Benign Prostatic Hyperplasia: Results From the Prostate Cancer Prevention Trial. *American Journal of Epidemiology* 2012;176(2):156-163
13. Sutcliffe S, Grubb III RL, Platz EA, Ragard LR, Riley TL, Kazin SS, Hayes RB, Hsing AW, Andriole GL; Urologic Diseases in America Project. Non-steroidal anti-inflammatory drug use and the risk of benign prostatic hyperplasia-related outcomes and nocturia in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *BJU Int* 2012;110(7):1050-1059
14. Sarre S, Määttänen L, Tammela TL, Auvinen A, Murtola TJ. Postscreening follow-up of the Finnish Prostate Cancer Screening Trial on putative prostate cancer risk factors: vitamin and mineral use, male pattern baldness, pubertal development and non-steroidal anti-inflammatory drug use. *Scand J Urol.* 2016;50(4):267-73.
15. WHO ATC/DDD Index 2017. Available at https://www.whocc.no/atc_ddd_index/ [Accessed 16 Jan. 2017]
16. Marsland AL, McCaffery JM, Muldoon MF, Manuck SB. Systemic Inflammation and the Metabolic Syndrome among Middle-aged Community Volunteers. *Metabolism: clinical and experimental* 2010;59(12):1801-1808

Table 1. Population characteristics. Study cohort of 74,754 men without benign prostatic hyperplasia at baseline from the Finnish Randomized Study of Screening for Prostate Cancer.

	NSAID usage	
	Yes	No
n (%) of men	57,707 (77.2 %)	17,047 (22.8 %)
median age at baseline (IQR)	59.00 (55.00 - 63.00)	59.00 (55.00 - 63.00)
median BMI (IQR)*	26.47 (24.39 - 29.07)	25.62 (23.67 - 28.33)
BPH end-points occurring during follow-up:		
Initiation of BPH medication use; n (%)	17,822 (30.9 %)	2,552 (15.0 %)
Median (IQR) follow-up until BPH medication	12.00 (10.00 - 13.00)	12.00 (11.00 - 13.00)
Recorded BPH diagnosis; n (%)	3,034 (5.3 %)	523 (3.1 %)
Median (IQR) follow-up until BPH diagnosis	12.00 (11.00 - 13.00)	12.00 (11.00 - 14.00)
BPH surgery; n (%)	2,959 (5.1 %)	490 (2.9 %)
Median (IQR) follow-up until BPH surgery	12.00 (11.00 - 13.00)	12.00 (11.00 - 14.00)
Use of other medications:		
n (%) of antidiabetic drug users	12,325 (21.4 %)	2,700 (15.8 %)
n (%) of antihypertensive drug users	40,484 (70.2 %)	9,449 (55.4 %)
n (%) of statin users	25,927 (44.9 %)	5,045 (29.6 %)

BPH = benign prostatic hyperplasia, NSAID = non-steroidal anti-inflammatory drugs

* Available for 11,220 men

Table 2. Risk of benign prostatic hyperplasia by NSAID usage. Study cohort of 74,754 men without benign prostatic hyperplasia at baseline from the Finnish Randomized Study of Screening for Prostate Cancer.

	BPH medication use		Recorded BPH diagnosis		BPH surgery	
	$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*	$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*	$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*
Over-the-counter NSAID use						
None	Ref	Ref	Ref	Ref	Ref	Ref
Any	1.29 (1.19 - 1.40)	1.26 (1.16 - 1.37)	1.27 (1.03 - 1.58)	1.26 (1.02 - 1.57)	1.23 (0.99 - 1.53)	1.22 (0.98 - 1.51)
Prescription NSAID use						
None	Ref	Ref	Ref	Ref	Ref	Ref
Any	2.14 (2.07 - 2.20)	2.04 (1.97 - 2.10)	1.64 (1.53 - 1.77)	1.59 (1.47 - 1.71)	1.67 (1.55 - 1.80)	1.61 (1.49 - 1.74)
Active users	2.99 (2.89 - 3.10)	2.83 (2.73 - 2.93)	2.25 (2.07 - 2.45)	2.17 (1.20 - 2.37)	2.34 (2.15 - 2.55)	2.25 (2.07 - 2.46)
Previous users	1.62 (1.56 - 1.67)	1.56 (1.50 - 1.62)	1.28 (1.18 - 1.39)	1.25 (1.15 - 1.36)	1.28 (1.18 - 1.40)	1.25 (1.14 - 1.36)

Years of use						
1 year	1.75 (1.68 - 1.82)	1.71 (1.64 - 1.77)	1.36 (1.24 - 1.49)	1.34 (1.22 - 1.47)	1.36 (1.24 - 1.50)	1.34 (1.22 - 1.48)
2-3 years	2.15 (2.07 - 2.24)	2.07 (1.99 - 2.15)	1.64 (1.50 - 1.80)	1.60 (1.46 - 1.76)	1.68 (1.53 - 1.85)	1.64 (1.49 - 1.80)
4-5 years	2.47 (2.35 - 2.60)	2.34 (2.23 - 2.47)	1.80 (1.59 - 2.03)	1.73 (1.54 - 1.96)	1.91 (1.69 - 2.15)	1.84 (1.63 - 2.08)
6 years or longer	2.96 (2.80 - 3.14)	2.78 (2.62 - 2.95)	1.91 (1.67 - 2.17)	1.83 (1.60 - 2.08)	1.88 (1.65 - 2.15)	1.80 (1.58 - 2.06)
Average number of DDDs per year						
less than 100 DDD/year	2.14 (2.07 - 2.20)	2.03 (1.97 - 2.10)	1.67 (1.55 - 1.81)	1.62 (1.50 - 1.75)	1.70 (1.57 - 1.84)	1.64 (1.52 - 1.78)
100 DDD/year or more	2.14 (2.04 - 2.25)	2.04 (1.94 - 2.14)	1.48 (1.31 - 1.67)	1.42 (1.25 - 1.60)	1.52 (1.34 - 1.72)	1.46 (1.29 - 1.65)

BPH = benign prostatic hyperplasia, DDD = Defined Daily Dose, NSAID = non-steroidal anti-inflammatory drugs

* From Cox regression model with adjustment for baseline age and antidiabetic-, antihypertensive- and cholesterol-lowering drug

Table 3. Risk of BPH by use of aspirin and coxibs. Study cohort of 74,754 men without benign prostatic hyperplasia at baseline from the Finnish Randomized Study of Screening for Prostate Cancer.

		BPH medication use		Recorded BPH diagnosis		BPH surgery	
		$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*	$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*	$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*
ASA usage	Over-the-counter use						
	None	Ref	Ref	Ref	Ref	Ref	Ref
	Any	1.15 (1.08 - 1.24)	1.11 (1.04 - 1.19)	1.08 (0.90 - 1.29)	1.06 (0.88 - 1.27)	1.08 (0.89 - 1.29)	1.06 (0.88 - 1.27)
	Prescription use						
	None	Ref	Ref	Ref	Ref	Ref	Ref
	Any	1.37 (1.30 - 1.45)	1.19 (1.13 - 1.26)	1.13 (0.99 - 1.29)	1.04 (0.91 - 1.18)	1.12 (0.98 - 1.28)	1.03 (0.90 - 1.17)
	Active users	1.87 (1.72 - 2.04)	1.63 (1.49 - 1.77)	1.62 (1.33 - 1.97)	1.49 (1.22 - 1.82)	1.53 (1.24 - 1.88)	1.40 (1.13 - 1.72)
	Previous users	1.17 (1.09 - 1.25)	1.02 (0.95 - 1.09)	0.93 (0.79 - 1.10)	0.86 (0.72 - 1.01)	0.96 (0.81 - 1.13)	0.88 (0.74 - 1.04)

Coxibs usage	None	Ref					
	Any	1.85 (1.78 - 1.92)	1.76 (1.70 - 1.83)	1.45 (1.33 - 1.59)	1.41 (1.29 - 1.54)	1.45 (1.32 - 1.59)	1.41 (1.28 - 1.54)
	Active users	2.09 (1.97 - 2.22)	1.99 (1.88 - 2.12)	1.52 (1.30 - 1.77)	1.48 (1.27 - 1.72)	1.44 (1.22 - 1.69)	1.40 (1.19 - 1.64)
	Previous users	1.74 (1.66 - 1.83)	1.66 (1.58 - 1.75)	1.45 (1.30 - 1.61)	1.40 (1.26 - 1.57)	1.46 (1.31 - 1.62)	1.41 (1.27 - 1.57)

BPH = benign prostatic hyperplasia, NSAID = non-steroidal anti-inflammatory drugs

* From Cox regression model with adjustment for baseline age and antidiabetic-, antihypertensive- and cholesterol-lowering drug

Table 4. Risk of BPH by NSAID usage in lag-time analysis. Study cohort of 74,754 men without benign prostatic hyperplasia at baseline from the Finnish Randomized Study of Screening for Prostate Cancer.

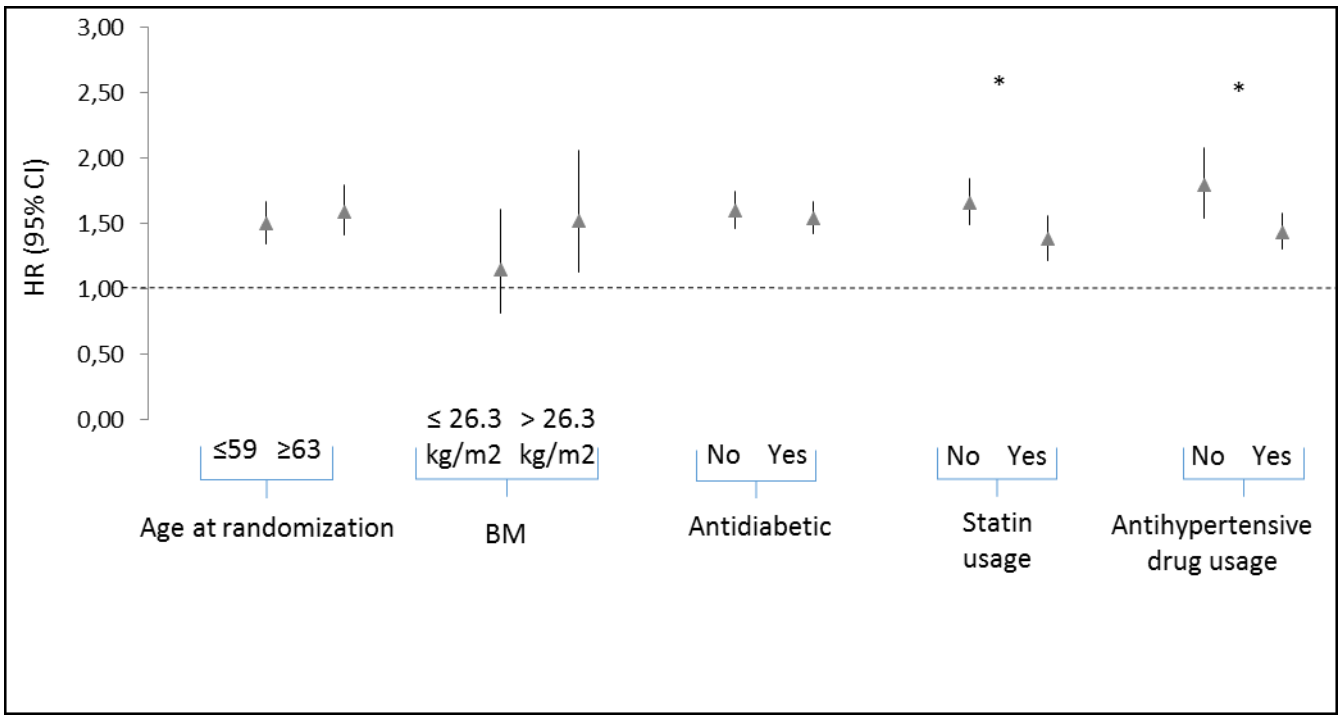
		BPH medication use		Recorded BPH diagnosis		BPH surgery	
NSAID usage		$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*	$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*	$HR_{age\text{-}adjusted}$ (95% CI)	$HR_{multivar.\text{-}adjusted}$ (95% CI)*
1-year lag time	None	Ref					
	Any	1.61 (1.56 - 1.65)	1.52 (1.47 - 1.56)	1.39 (1.30 - 1.49)	1.34 (1.25 - 1.44)	1.43 (1.33 - 1.53)	1.37 (1.27 - 1.48)
3-year lag time	None	Ref					
	Any	1.50 (1.46 - 1.55)	1.42 (1.38 - 1.47)	1.27 (1.19 - 1.36)	1.23 (1.14 - 1.31)	1.29 (1.20 - 1.38)	1.24 (1.15 - 1.33)

BPH = benign prostatic hyperplasia

* From Cox regression model with adjustment for baseline age and antidiabetic-, antihypertensive- and cholesterol-lowering drug

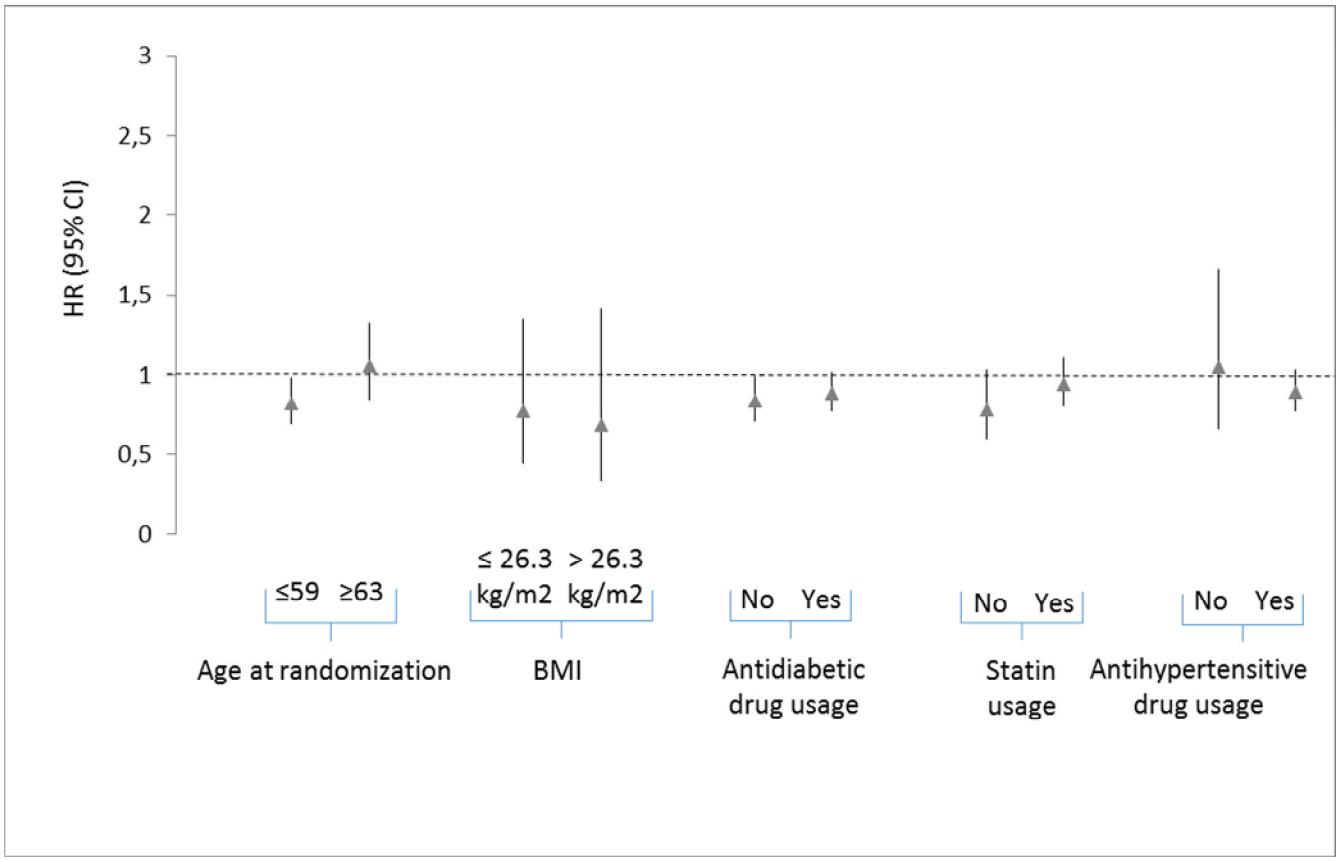
Figure 1. Risk of BPH surgery by NSAID usage in subgroup analyses. Study cohort of 74,754 men without benign prostatic hyperplasia at baseline from the Finnish Randomized Study of Screening for Prostate Cancer.

a) All NSAIDs



* P for interaction ≤0.05

b) Aspirin


HR (95% CI)
3
2,5
2
1,5
1
0,5
0
≤59
≥63
Age at randomization
≤ 26.3 kg/m2
> 26.3 kg/m2
BMI
No
Yes
Antidiabetic drug usage
No
Yes
Statin usage
No
Yes
Antihypertensitive drug usage