SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 3, 221–226
https://doi.org/10.1080/21681805.2021.1916072

ARTICLE

Short-term ciprofloxacin prophylaxis for prostate biopsy and risk of aortic aneurysm. Nationwide, population-based cohort study

Karl-Johan Lundström[a], Hans Garmo[b,c,d], Rolf Gedeborg[e], Pär Stattin[d] and Johan Styrke[a]

[a]Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden; [b]Translational Oncology and Urology Research (TOUR), School of Cancer and Pharmaceutical Sciences, King's College London, Guy's Hospital, London, UK; [c]Regional Cancer Center Uppsala Örebro, Uppsala University Hospital, Uppsala, Sweden; [d]Department of Surgical Sciences, Urology, Uppsala University, Uppsala, Sweden; [e]Department of Surgical Sciences, Anesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden

ABSTRACT

Introduction: The use of quinolones has recently been questioned due to reports on side effects including an increased risk of aortic aneurysm. The aim of the study was to examine the risk of aortic aneurysm (AA) after short-term ciprofloxacin as prophylaxis for prostate biopsy.

Materials and Methods: We used the Prostate Cancer data Base Sweden and investigated 192,024 prostate biopsy exposures vs. 554,974 non-exposures for risk of AA.

Materials and Methods: Prostate biopsy was used as a proxy for quinolone use as short-term ciprofloxacin is the recommended and documented prophylaxis in Sweden for this procedure.

Materials and Methods: The outcome was the hazard ratio (HR) of AA in men who underwent a biopsy vs. those that did not.

Results: The absolute risk of AA was small, 39/10,000 person years for all AÁs and for ruptured AÁs 3.5/10,000 person years. In multivariate analyses, there were small, non-significant increases in risk of all AA's (adjusted HR = 1.13, 95% CI: 0.91 to 1.39) and ruptured AÁs (adjusted HR = 1.05, 95% CI: 0.52 to 2.15) in men who underwent biopsy. A significantly increased risk of AA was observed in men diagnosed with high-risk prostate cancer on biopsy (HR = 1.50, 95% CI: 1.15–2.21). The use of prostate biopsy as a proxy for exposure to ciprofloxacin was a limitation of the study.

Conclusions: Short-term ciprofloxacin was not associated with an increased risk of aortic aneurysm and the increased risk in men with high-risk prostate cancer was likely due detection bias caused by imaging more commonly performed in these men.

ARTICLE HISTORY
Received 7 December 2020
Revised 18 March 2021
Accepted 7 April 2021

KEYWORDS
Prostate biopsy; ciprofloxacin; aortic aneurysm; prophylaxis

Introduction

The use of quinolones has been associated with an increased risk of aortic dissection and aneurysm (AA) [1–3]. These studies have also shown an increased risk of ruptured AA. The mechanisms linking quinolone use to AA have been proposed to be an increase of degradation of extracellular matrix due to increased activity of mixed metalloproteinase [4] and the decrease of expression of collagen [5].

This, amongst other reasons, led the European Medicines Agency (EMA) to recommend a restriction of the use of quinolones [6]. However, many guidelines still recommend short term use of quinolone as a prophylactic agent in conjunction with prostate biopsy [7]. Ciprofloxacin, a quinolone, is the most common prophylaxis used in conjunction with prostate biopsy in Sweden and elsewhere [8]. In a recent survey, 87% of clinics in Sweden used short-term ciprofloxacin prophylaxis and specifically 69% used a single dose and 18% of the clinics multiple doses [9].

The aim of the study was to investigate the association between short-term ciprofloxacin prophylaxis and the risk of a diagnosis or rupture of an aortic aneurysm.

Materials and methods

Study population

In the Prostate Cancer data Base Sweden (PCBaSe) [10], the National Prostate Cancer Register (NPCR) of Sweden has been linked to other registries, including the Swedish Cancer Registry [11], the Cause of Death Registry [12], the Prescribed Drug Registry [13], the National Patient Registry [14], the Longitudinal integrated database for health insurance and labor market studies (LISA) [15] and the Multi-Generation Registry [16] using the unique Swedish Personal Identity Number (PIN) [17].

PCBaSe version 4.1 included men diagnosed with prostate cancer between 1998 and 2016 with follow up until 2017-12-31, and also a comparison cohort that consisted of five men randomly selected for each prostate cancer case from the general population, matched on birth year, county of

CONTACT Karl-Johan Lundström karl-johan.lundstrom@regionjh.se Östersunds Hospital, Kyrkgatan 16Östersund 83131, Sweden
Supplemental data for this article can be accessed here.
© 2021 Acta Chirurgica Scandinavica Society

residence and free of prostate cancer. Also, relatives to the index case, born before 1932, were included [10].

Exposure

We used a health care contact in the National Patient Registry indicating prostate biopsy (TKE00) or a biopsy registered in NPCR from 1 July 2006 through 31 December 2017 as a proxy for short term exposure to ciprofloxacin. The reason to use this proxy was that we did not have data on short-term exposure to ciprofloxacin as it is distributed directly to the patient in the clinic and not by a filled prescription. In a recent survey of the use of prophylactic antibiotics in Sweden between 2014 and 2016, short-term ciprofloxacin prophylaxis was used in 87% of the clinics. Preferably, a single dose at the time of biopsy was used [9]. The survey had a response rate of 90% (76/84) of clinics. A comparison was made to men in PCBaSe who had not undergone a biopsy and thus had not received ciprofloxacin. Three unique non-exposed men were randomly selected from all control men who were born the same year as the corresponding index man. The comparison men were matched to their respective case at the date of first biopsy, which defined a 'pseudo date' for biopsy for the comparison men. We allowed men to experience multiple biopsy events. If the case underwent another biopsy, he retained the same comparison men who received a new pseudo date for the repeat biopsy.

Outcomes

The outcome aortic aneurysm (AA) was defined as an International Classification of Diseases version 10 (ICD-10) diagnosis I71 in the National Patient Registry that occurred within 60 days from the date of biopsy. Ruptured aortic aneurysms were identified by use of the ICD-10 codes I71.1, I71.3, I71.5, I71.8. Deaths due to these diagnoses were also considered an aortic aneurysm event.

Covariates

Educational level was categorized as low: 9 years, medium: 12 years, and high: more than 12 years (university/college). Previous treatment with ciprofloxacin was detected up to one year prior to the prostate biopsy by use of data in the Prescribed Drug Registry. Hypertension was defined by use of the ICD-10 diagnoses I10-I15 in the National Patient Registry during a 10-year period preceding the biopsy, or at least one filled prescription of antihypertensive medication (ATC codes C02, C03, C07, C08, C09) during the year preceding the biopsy.

The Charlson Comorbidity Index (CCI) was calculated based on discharge diagnoses from hospitalizations and specialist outpatient visits, extracted from National Patient Registry and the Cancer Registry for the 10-year period preceding the start of follow-up, as were preexisting peripheral artery disease (ICD-10 codes I70, I73) and cardiovascular disease (ICD-10 codes I20-I25) [18].

Prostate cancer risk was categorized as low/intermediate-risk ($\leq$T2 or PSA $\leq$20 ng/ml or Gleason score ≤ 7 $(4+3)$ or high-risk ($>$T2 or PSA $>$20 ng/ml or Gleason score $7 > 4+3$ or metastases) using a modified version of National Comprehensive Cancer Network (NCCN) classification [19]. Calendar year was considered as a potential confounder and used as a covariate in the regression models.

Statistical methods

Follow-up started at the date of biopsy and ended at the date of an outcome event, repeat biopsy, emigration, death, or end of follow-up at 31 December 2017, whichever event occurred first.

For time to event analyses a repeated biopsy in the same man was considered as a new exposure and a robust sandwich estimator was applied to account for the within study subject variability.

For unexposed comparison men, the follow-up was also censored at the date of a filled prescription for ciprofloxacin or a prostate biopsy. Crude incidence rates were calculated for 60 and 180 days of follow-up.

Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated by use of multivariable Cox proportional hazard models. Adjustment was made for age as a continuous variable, calendar year for biopsy stratified as 2007–2009, 2010–2013, and 2014–2017, history of hypertension (IDC-10 diagnosis Yes/No), prescription of antihypertensive medication (Yes/No), history of peripheral arterial disease (Yes/No), history of cardiovascular disease (Yes/No), CCI (stratified 0/1/2/$\geq$3). A cumulative incidence plot was generated by considering ruptured and non-ruptured aortic aneurysms as competing risks, censoring for other events as specified above. The absolute risk at 60 days, with 95% confidence intervals, was extracted from the cumulative incidence curves.

Subgroup and sensitivity analyses

All analyses were also performed using a 180-day follow-up. A restricted analysis was made of men without previous exposure to ciprofloxacin, previous biopsy, or previous diagnosis of aortic aneurysm or dissection, with the aim to minimize confounding. To evaluate potential detection bias or misclassification of prevalent aneurysms at the time of the biopsy, we also performed an analysis of risk restricted to ruptured aortic aneurysm.

In a sensitivity analysis, the analysis set was restricted to biopsies performed in hospitals where use of single dose ciprofloxacin as prophylaxis had been verified in our recent survey [9].

Stratified analyses were performed based on the result of the biopsy; no cancer, low/intermediate-risk, or high-risk/metastatic prostate cancer. These analyses were performed in order to evaluate the potential influence of diagnostic procedures such as computed tomography or ultrasonography that we assumed would be more commonly used in men for whom the biopsy showed a cancer, especially a high-risk cancer.

The PCBaSe 4 project was approved in 2016 by the Regional Ethics Board in Umeå and this specific project

Table 1. Baseline characteristics in Prostate Cancer data Base of Sweden (PCBaSe) 4.1.

	Biopsy $n = 192\,024$ (139 166 men)		No biopsy $n = 554\,974$ (410 019 men)	
Age at biopsy median (Q1–Q3)	68	(63-74)	68	(63-74)
Year of biopsy, *n* (%)				
2006–2009	59,556	(31)	172,268	(31)
2010–2013	66,855	(35)	192,849	(35)
2014–2017	65,613	(34)	189,857	(34)
Prior aortic aneurysm[a], *n* (%)				
No	190989	(99)	550554	(99)
Yes	1035	(1)	4420	(1)
Hypertension[b], *n* (%)				
No	176,921	(92)	505,904	(91)
Yes	15,103	(8)	49,070	(9)
Ischemic heart disease[b], *n* (%)				
No	179,209	(93)	509,210	(92)
Yes	12,815	(7)	45,764	(8)
Peripheral arterial disease[b], *n* (%)				
No	191,289	(100)	551,475	(99)
Yes	735	(0)	3,499	(1)
Charlson Comorbidity Index[b], *n* (%)				
0	146,057	(76)	404,358	(73)
1	22,395	(12)	71,596	(13)
2	14,256	(7)	42,409	(8)
3+	9,316	(5)	36,611	(7)
Educational level[c], *n* (%)				
High	50,164	(26)	134,695	(24)
Middle	78,253	(41)	222,430	(40)
Low	62,419	(33)	191,069	(34)
Missing	1,188	(1)	6,780	(1)
Previous ciprofloxacin[a], *n* (%)				
No	155,805	(81)	532,324	(96)
Yes	36,219	(19)	22,650	(4)
Previous biopsy[b], *n* (%)				
No	130,853	(68)	554,974	(100)
Yes	61,171	(32)	–	–
Antibiotic regime according to survey, *n* (%)[d]				
Short-term ciprofloxacin	109800	(57)	–	–
Other antibiotics or no information in survey	82,224	(43)	554,974	(100)
Type of prostate cancer on biopsy[e], *n* (%)				
Low-/intermediate risk	59,565	(31)	–	–
High-risk	40,106	(21)	–	–
No prostate cancer	92,353	(48)	554,974	(100)

CCI: Charlson Comorbidity Index.
[a]According to filled prescription in Prescribed Drug Registry in the year prior to biopsy.
[b]According to the National Patient Registry.
[c]According to the Longitudinal integrated database for health insurance and labour market studies (LISA).
[d]Patients biopsied at clinic participating in survey.
[e]According to the National Prostate Cancer Register.

based on data in PCBaSe 4.1 was approved by the Research Ethics Authority in 2019.

Results

The study population consisted of 139,166 men exposed to 192,024 biopsies, and 410,019 unexposed comparison men with 554,974 pseudo-biopsies (Table 1). Median age at biopsy was 68 years (inter quartile range 63–74) and 32% of the biopsies were repeat biopsies. Characteristics for men who underwent biopsy were similar to men who did not undergo biopsy, apart from a notably higher proportion of previous ciprofloxacin exposure in the biopsy group. 113 in the biopsy group and 340 men in the comparison group had a diagnosis of AA within 60 days, corresponding to an absolute risk of 64 per 100,000 men in both groups (95% CI: 52 to 76, and 57 to 71 per 100,000 men), and an incidence rate of 39 per 10,000 person years. Ruptured AA within 60 days was diagnosed amongst 10 men in the biopsy group and 30 in the comparison group, corresponding to absolute risks of 6 per 100,000 men in both groups (95% CI: 2 to 9, and 4 to 8 per 100,000 men) and an incidence rate of 35 per 100,000 person years.

After adjustment for potential confounding there was a small increase in the risk of AA in men who had undergone a biopsy, adjusted hazard ratio (HR) of 1.13 (95% CI: 0.91 to 1.39) (Table 2). The incidence rate ranged from 25 to 88 events per 10,000 person-years in the different subsets studied.

In a separate analysis with ruptured AA as outcome event, the increase was even smaller (Figure 1(A)), with an adjusted HR of 1.05 (95% CI: 0.52 to 2.15) (Table 3).

When stratifying the analysis according to prostate cancer risk category, men diagnosed with a high-risk prostate cancer at biopsy had a notably increased risk, adjusted HR 1.60 (95% CI: 1.15 to 2.21) (Figure 1(C)) (Table 2), whereas there was a reduced risk in men not diagnosed with prostate cancer, adjusted HR 0.85 (95% CI: 0.59 to 1.24) and in men diagnosed with a low/intermediate-risk prostate cancer, adjusted HR 0.93 (95% CI: 0.60 to 1.44) (Figure 1(B)) (Table 2). Extending the follow-up to 180 days slightly decreased the risk estimates (Supplementary Table 1).

In a restricted analysis of men without previous exposure to ciprofloxacin, previous biopsy, or previous diagnosis of aortic aneurysm or dissection, the risk estimates did not significantly differ between the cases and controls, adjusted HR 1.21 (95%CI: 0.92 to 1.59). Restricting the analysis to men subjected to one or more previous biopsies did not alter the association, adjusted HR 1.08, 95% CI: 0.68 to 1.70) (Supplementary Table 2). In a sensitivity analysis restricted to hospitals where short-term ciprofloxacin was used according to our survey, risk estimates were similar as for all men (Table 2).

Due to the limited number of ruptured aneurysms, we did not calculate adjusted HRs for this outcome in all subsets (Table 3). Extending the observation period to 180 days resulted in a further reduced risk for ruptured aneurysm in the biopsy group (Supplementary Table 3).

Discussion

In this nationwide, population-based register study, prostate biopsy as a proxy for short-term ciprofloxacin was not associated with an increased risk of aortic aneurysm (AA). We interpret the increased risk of AA in men with high-risk prostate cancer as due to detection bias caused by imaging more commonly performed in these men. In support of this interpretation, there was no increase in the risk of ruptured aneurysms after biopsy.

In contrast to our study, two other post authorization safety studies based on drug registries in Sweden and Canada have reported an increased relative risk of 1.6 to 2.2

Table 2. Hazard ratio of aortic aneurysm or death due to aortic aneurysm 60 days after prostate biopsy.

		Incidence rate within 60 days (per 10,000 person-years)	Crude analysis		Adjusted	
			HR	(95% CI)	HR	(95% CI)
All men	No biopsy	39	1.00	Ref	1.00	Ref
	Biopsy	39	1.00	(0.81–1.24)	1.13	(0.91–1.39)
Short-term ciprofloxacin[a]	No biopsy	38	1.00	Ref	1.00	Ref
	Biopsy	44	1.15	(0.86–1.53)	1.27	(0.95–1.69)
No prostate cancer on biopsy[b]	No biopsy	35	1.00	Ref	1.00	Ref
	Biopsy	25	0.73	(0.50–1.06)	0.85	(0.59–1.24)
Low-/intermediate-risk prostate cancer on biopsy[b]	No biopsy	34	1.00	Ref	1.00	Ref
	Biopsy	27	0.81	(0.52–1.25)	0.93	(0.60–1.44)
High-risk prostate cancer on biopsy[b]	No biopsy	56	1.00	Ref	1.00	Ref
	Biopsy	88	1.55	(1.12–2.16)	1.60	(1.15–2.21)

[a]Patients who underwent prostate biopsy at a clinic where short-term ciprofloxacin was used according to survey [9].
[b]According to the National Prostate Cancer Register.

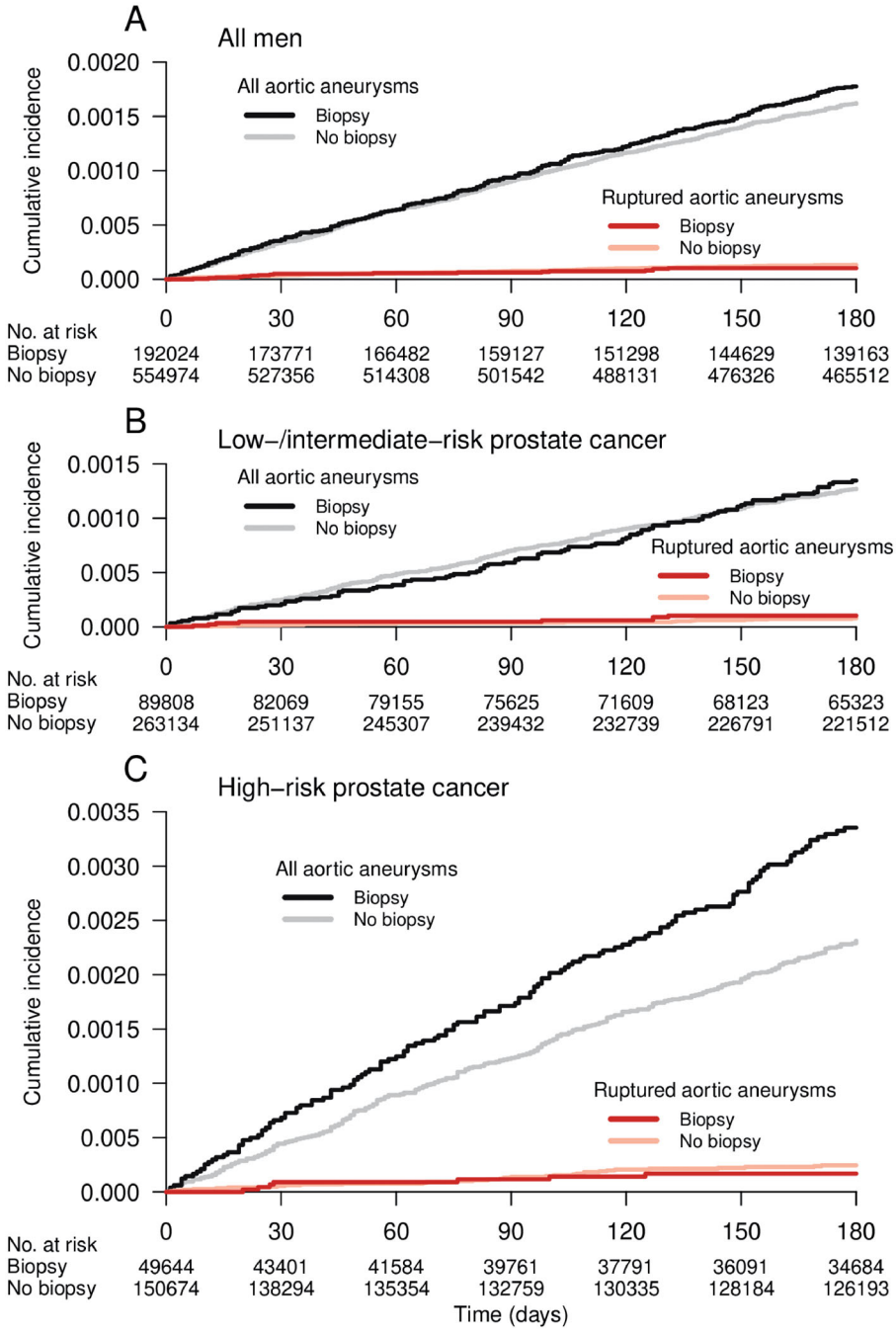

Figure 1. Cumulative incidence of aortic aneurysms.

Table 3. Hazard ratio of aortic aneurysm or death due to *ruptured* aortic aneurysm 60 days after prostate biopsy.

		Incidence rate within 60 days (per 10,000 person-years)	Crude analysis		Adjusted	
			HR	(95% CI)	HR	(95% CI)
All men	No biopsy	3.5	1.00	Ref	1.00	Ref
	Biopsy	3.5	1.00	(0.49–2.05)	1.05	(0.52–2.15)
Short-term ciprofloxacin[b]	No biopsy	3.6	1.00	Ref		NA[a]
	Biopsy	4.7	1.82	(0.60–5.57)		
No prostate cancer on biopsy	No biopsy	2.5	1.00	Ref		
	Biopsy	2.2	0.87	(0.24–3.18)		
Low-/intermediate-risk prostate cancer on biopsy[c]	No biopsy	3.2	1.00	Ref		
	Biopsy	3.3	1.02	(0.28–3.77)		
High-risk prostatecancer on biopsy[c]	No biopsy	5.7	1.00	Ref	1.00	Ref
	Biopsy	6.5	1.12	(0.36–3.53)	1.14	(0.36–3.58)

[a]Model not applicable due to no events in the group exposed to history of peripheral arterial disease.
[b]Patients who underwent prostate biopsy at a clinic where short-term ciprofloxacin was used according to survey [9].
[c]According to the National Prostate Cancer Register.

of AA in persons with a filled prescription for 7–14 days of treatment with a quinolone [1,2]. In our study, exposure to ciprofloxacin was much shorter as one single dose was the most common prophylaxis in conjunction with prostate biopsy in our survey [9]. The estimated absolute risk of a diagnosis of AA within 60 days was 64 per 100,000 men both for men who had undergone a prostate biopsy and those in the comparison group. This incidence rate (39 per 10,000 person years) is twice as high as in a previous study in Sweden of men and women who had filled a prescription for a quinolone (incidence 19 per 10,000 person-years for men above 65) [1]. While the median age was around 68 years in both studies, and the calendar period for the study was quite similar, our study population consisted exclusively of men who had undergone prostate biopsy as a proxy for short -term ciprofloxacin as prophylaxis. The previous study investigated any use of any quinolone, in two propensity matched cohorts consequently creating a study population that differed substantially from ours. The difference between the studies in absolute incidence of aortic aneurysm is not unexpected.

The only quinolone used as prophylaxis for prostate biopsy in Sweden is ciprofloxacin and it was also the most commonly used quinolone in the other Swedish (80%) and in the Canadian study (50%).

The median age in the Canadian study was slightly younger than in the Swedish studies, 65 years [1,2]. Our study only included men, whereas the two other studies had a fairly equal gender distribution. In the Canadian study follow-up was 30 days and the incidence was 35/10.000 person years, i.e. quite similar to the incidence in our study. Thus, the main difference between our study and these two others was the much shorter duration of exposure in our study. In addition, ciprofloxacin was exclusively used as prophylaxis in conjunction with prostate biopsy, whereas the other two studies included use of any quinolone.

Our results are in accordance with a nested case control study in Taiwan that reported no increase in risk of AA in subjects treated with quinolone for less than 3 days, whereas there was an increased risk for subjects treated more than three days [3].

Aortic aneurysms are often detected incidentally due to screening or a general high vigilance. We argue that the increased risk of AA in men with high-risk prostate cancer was due to the fact that these men, according to The Swedish Prostate Care program, underwent an imaging procedure before a therapeutic decision. Likely, AA was incidentally found in a proportion of these investigations [20]. Supporting this view, no significant increase in risk of AA was observed for men who underwent a biopsy without a subsequent diagnosis of prostate cancer or in men with a low to intermediate-risk cancer, for whom there are no recommendations for imaging. The outcome of a ruptured or surgically repaired aneurysm is less likely to be affected by such bias. In our study there was no increased risk of ruptured aneurysms. In the other Swedish study, with longer treatment duration, there was an increased risk of hospital admission for AA and AA as the cause of death [1].

Strengths of our study include the population-based design, large cohort size, use of comprehensive data from high quality health care registers on exposures including prostate cancer risk category, socioeconomic status, comorbidity, and previous use of ciprofloxacin. The overall validity of ICD codes in the National Patient Registry has been shown to be high [14], and specifically the ICD codes for AA has been shown to be valid [21].

Limitations of our study include the use of prostate biopsy as a proxy for short-term exposure to ciprofloxacin. We had to use this proxy as a single dose ciprofloxacin is generally distributed in person to the patient immediately before biopsy at the out-patient department, and not by use of a prescription. In support of the use of this proxy, our recent survey showed that ciprofloxacin was used as prophylaxis in 87% of clinics in Sweden, in accordance with a previous survey [9,22]. Furthermore, despite the very large number of participants, there was still a limited number of AA and in particular, ruptured AA, which meant the confidence intervals of our risk estimates were fairly wide.

The European Medicines Agency has restricted the use of quinolones due to a number of adverse reactions [6]. This led the European Association of Urology, section of Infections in Urology (ESIU) to recommend to refrain from use of quinolones as prophylaxis prior to transrectal prostate biopsies [23,24], even though the guidelines still recommend that ciprofloxacin can be used in countries where it is permitted [7] . Our results with no increased risk of AA in men who underwent a prostate biopsy provide no support for the

view that urologists should refrain from ciprofloxacin as prophylaxis in conjunction with prostate biopsy.

Conclusions

Prostate biopsy as proxy for short-term exposure to ciprofloxacin was not associated with an increased risk of aortic aneurysm in this large population-based study. These data do not support a ban of ciprofloxacin as prophylaxis in conjunction with prostate biopsy.

Acknowledgements

This project was made possible by the continuous work of the National Prostate Cancer Register of Sweden (NPCR) steering group: Pär Stattin (chairman), Ingela Franck Lissbrant (co-chair), Camilla Thellenberg, Eva Johansson, Lennart Åström, Magnus Törnblom, Stefan Carlsson, Marie Hjälm Eriksson, David Robinson, Mats Andén, Ola Bratt, Jonas Hugosson, Maria Nyberg, Per Fransson, Johan Styrke, Hampus Nugin, Olof Ståhl, Thomas Jiborn, Olof Akre, Johan Stranne, Eva Johansson, Fredrik Jäderling, Fredrik Sandin, Karin Hellström, Gert Malmberg and Hans Joelsson.

Disclosure statement

None declared. Rolf Gedeborg is also employed by the Medical Products Agency (MPA) in Sweden. The MPA is a Swedish Government Agency. The views expressed in this article may not represent the views of the MPA.

A study protocol was prepared before data collection but not registered before analysis

Funding

The study was supported by grants from Västernorrland County Council and the Swedish Research Council [2017-00847].

ORCID

Hans Garmo http://orcid.org/0000-0001-7181-7083

Data availability statement

Data used in the present study was extracted from the Prostate Cancer data Base Sweden 4.1. For information on data access and code used contact the corresponding author.

References

[1] Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ. 2018;360:678.

[2] Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open. 2015;5(11):1–9.

[3] Lee C-C, Lee M-tG, Chen Y-S, et al. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Internal Med. 2015;175(11):1839–1847.

[4] Corps AN, Harrall RL, Curry VA, et al. Ciprofloxacin enhances the stimulation of matrix metalloproteinase 3 expression by interleukin-1β in human tendon-derived cells. Arthritis Rheumatol. 2002;46(11):3034–3040.

[5] Chang H-N, Pang J-HS, Chen CPC, et al. The effect of aging on migration, proliferation, and collagen expression of tenocytes in response to ciprofloxacin. J Orthop Res. 2012;30(5):764–768.

[6] Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. Quinolone and fluoroquinolone Article-31 referral. European Medicines Agency; 2019.

[7] European Association of Urololgy Guidelines. Urological infections 2020. [cited 2020 0204].

[8] Yang L, Gao L, Chen Y, et al. Prophylactic antibiotics in prostate biopsy: a meta-analysis based on randomized controlled trials. Surg Infect. 2015;16(6):733–747.

[9] Styrke J, Resare S, Lundström K, et al. Current routines for antibiotic prophylaxis prior to transrectal prostate biopsy: a national survey to all urology clinics in Sweden. F1000research. 2020;9:58.

[10] Van Hemelrijck M, Wigertz A, Sandin F, et al. Cohort Profile: the National Prostate Cancer register of sweden and prostate cancer data base sweden 2.0. Int J Epidemiol. 2013;42(4):956–967.

[11] Barlow L, KW, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27–33. eng.

[12] Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765–773.

[13] Wallerstedt SM, Wettermark B, Hoffmann M. The first decade with the Swedish prescribed drug register – a systematic review of the output in the scientific literature. Basic Clin Pharmacol Toxicol. 2016;119(5):464–469.

[14] Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

[15] Statistics Sweden. Longitudinal integrated database for health insurance and labour market studies (LISA) 2019. [cited 2019 2019-12-13]. Available from: https://www.scb.se/en/services/guidance-for-researchers-and-universities/vilka-mikrodata-finns/longitudinella-register/longitudinal-integrated-database-for-health-insurance-and-labour-market-studies-lisa/

[16] Ekbom A. The Swedish multi-generation register. Methods Mol Biol. 2011;675:615–620.

[17] Hagel E, Garmo H, Bill-Axelson A, et al. PCBaSe Sweden: a register-based resource for prostate cancer research. Scand J Urol Nephrol. 2009;43(5):342–349.

[18] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130–1139.

[19] James LM, Andrew JA, Robert RB, et al. Prostate cancer, version 1.2016. J Natl Compr Canc Netw. 2016;14(1):19–30.

[20] Nationellt Vårdprogram Prostatcancer. In: Centre RC, editor. 2020.

[21] Landenhed M, Engström G, Gottsäter A, et al. Risk profiles for aortic dissection and ruptured or surgically treated aneurysms: a prospective cohort study. J Am Heart Assoc. 2015;4(1):e001513.

[22] Carlsson S, Bratt O, Stattin P, et al. Current routines for transrectal ultrasound-guided prostate biopsy: a web-based survey by the Swedish Urology Network. Scand J Urol Nephrol. 2012;46(6):405–410.

[23] Bonkat G, Pilatz A, Wagenlehner F. Time to adapt our practice? the european commission has restricted the use of fluoroquinolones since march 2019. Eur Urol. 2019;76(3):273–275.

[24] Bonkat G, Wagenlehner F. In the line of fire: should urologists stop prescribing fluoroquinolones as default? Eur Urol. 2019;75(2):205–207.