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ORIGINAL PAPER

Anticoagulants and cancer mortality in the Finnish randomized study of screening for prostate cancer

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Abstract

Purpose Anticoagulants may reduce mortality of cancer patients, though the evidence remains controversial. We studied the association between different anticoagulants and cancer death.

Methods All anticoagulant use during 1995–2015 was analyzed among 75,336 men in the Finnish Randomized Study of Screening for Prostate Cancer. Men with prevalent cancer were excluded. Multivariable Cox regression was performed to compare risk of death from any cancer and disease-specific death from 9 specific cancer types between (1) anticoagulant users overall and (2) warfarin users compared to anticoagulant non-users and (3) warfarin or (4) low-molecular-weight heparins (LMWH) compared to users of other anticoagulants. Medication use was analyzed as time-dependent variable to minimize immortal time bias. 1-, 2- and 3-year lag-time analyses were performed.

Results During a median follow-up of 17.2 years, a total of 27,233 men died of whom 8033 with cancer as the primary cause of death. In total, 32,628 men (43%) used anticoagulants. Any anticoagulant use was associated with an increased risk of cancer death (HR = 2.50, 95% CI 2.37–2.64) compared to non-users. Risk was similar independent of the amount, duration, or intensity of use. The risk increase was observed both among warfarin and LMWH users, although not as strong in warfarin users. Additionally, cancer-specific risks of death were similar to overall cancer mortality in all anticoagulant categories.

Conclusion Our study does not support reduced cancer mortality among anticoagulant users. Future studies on drug use and cancer mortality should be adjusted for anticoagulants as they are associated with significantly higher risk of cancer death.

Keywords Cancer mortality · Anticoagulant · Warfarin · Low-molecular weight heparins · Cohort

Introduction

Venous thromboembolism (VTE) is a clinically important complication among patients with malignancies, as the risk of VTE is five- to sevenfold in patients with cancer [1, 2]. However, especially tumors of pancreas, brain, liver, and

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lung are associated with even more risk of VTE and additionally the risk increases considerably with more advanced disease [3]. Cancer patients with deep VTE or pulmonary embolism have an eightfold risk of death compared to VTE in patients without cancer [4]. Prognosis for cancers patients with embolism is fairly poor: 1-year overall survival is only 38% [5].

The biological rationale of anticoagulants is against cancer progression rather than cancer initiation in experimental animal studies. Evidence against cancer development is limited. It has been reported that tissue factor pathway inhibition has been reported to be relevant in formation of certain brain tumors [6]. It has further been suggested that cancer cells may activate coagulation through increased expression of tissue factor increasing malignant phenotype of cancer cells [7].

Significantly more evidence is found on cancer progression and coagulation cascade as well as anticoagulants; infusion of small amounts of thrombin increases colon cancer metastases [8]. Hemophilic mice with Factor VIII deficiency are protected against experimentally induced cancer cell metastasis [9] and in heterozygous prothrombin-deficient mice, metastatic spread is considerably reduced [10]. In contrast, in hypercoagulable mice, risk of metastases is increased [11]. Concordantly, anticoagulants targeting Factor Xa and/or thrombin reduce metastases and increases survival in animal studies [12, 13]. Figure 1 illustrates aforementioned associations reported in the literature.

Vitamin K antagonists (VKA) such as warfarin have been promising in some experimental studies [14, 15], but a systematic review covering five randomized controlled trials (RCTs) (from 1984 to 1997) indicated no evidence for improved survival among cancer patients [16]. Results of RCTs on low-molecular weight heparins (LMWH) and cancer survival are inconsistent and considerable number of included patients had at least Stage III disease possibly affecting the generalizability to less advanced disease [17–20]. Due to improvements in contemporary cancer care since the 1990s, it is unclear whether the results from the warfarin RCTs are still applicable. Thus, the effect of anticoagulants on risk of cancer death is still under debate.

To date only three cohort/case–control studies of > 300 patients have assessed warfarin use and risk of cancer-specific death [21–23] and only one covers other anticoagulant drugs [23]. Due to paucity of studies on this topic, we explored the association between all types of anticoagulants during 1996–2015 and cancer mortality in the population of the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) [24].

Methods

Study cohort

FinRSPC includes 80,458 men aged 55–67 years at baseline. After exclusion of prevalent prostate cancer cases, the men were randomized during 1996–1999 either to prostate-specific antigen (PSA) screening at 4-year intervals or to no intervention. For this analysis, we further excluded 3,279 men with previous diagnoses of any other cancer types at baseline. In total, 75,336 men were included in the analysis. This is demonstrated in Supplementary Fig. 1. Information on baseline cancers was obtained from comprehensive Finnish cancer registry, which covers over 90% of cancer cases diagnosed in Finland. The follow-up started at randomization and continued until death, emigration from Finland or 1 January 2016, whichever occurred first.

Information on deaths was obtained from the national death certificate registry of Statistics Finland, which assigns official causes of death based on mandatory death certificates. The information included date and immediate,

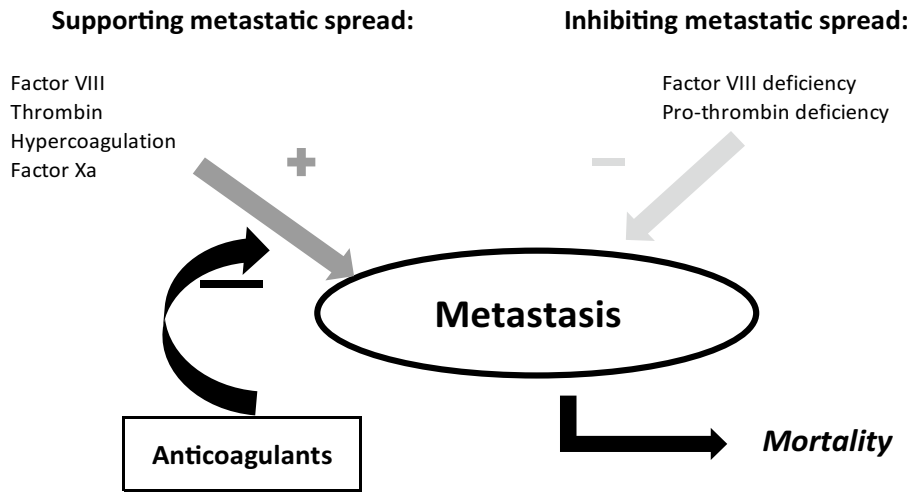

Fig. 1 Simplified illustration of relation between coagulation cascade and cancer metastasis and mortality in the literature. Additionally, antimetastatic effect of anticoagulant drugs reported in the literature that may decrease cancer mortality

primary, and contributory causes of death. Only deaths with cancer (ICD-10 codes C00-D48) listed as the primary cause of death were regarded as cancer deaths.

We also obtained information on conditions that are major indications for anticoagulant use: pulmonary embolism (ICD-10: I26.0, I26.9), venous thromboembolism (ICD-10: I82.0-82.9), and atrial fibrillation (ICD-10: I48) from the national care register for health care (HILMO) maintained by the National Institute for Health and Welfare, which covers all hospitals in Finland and records all diagnoses for in- and out-patients visits during 1996–2014. Diagnoses from primary care are not covered. Additionally, Charlson Comorbidity Score [25] was calculated based on diagnoses recorded in the HILMO database during 1996–2015.

Information on anticoagulant usage

Information on anticoagulant drug purchases during 1996–2015 was obtained by linking the study cohort to a national medication reimbursement database maintained by the Finnish Social Insurance Institution (SII). The record linkage was based on the unique personal identification number assigned to all residents of Finland. Medication usage data were available for 75,336 men. As a part of the national health insurance that covers all Finnish citizens, SII provides reimbursements for purchases of physician-prescribed drugs. In Finland, anticoagulant drugs are available only through physicians' prescription. Therefore, the obtained data cover all anticoagulant reimbursements in outpatient setting. Drugs used during hospital inpatient periods are not covered.

All 14 anticoagulant drugs used in outpatient setting during the study period were identified based on their Anatomic Therapeutic Chemical (ATC) codes. These were warfarin (B01AA03) and fenindion (B01AA02) as VKAs, dalteparin (B01AB04), enoxaparin (B01AB06), and tinzaparin (B01AB10) as heparins, clopidogrel (B01AC04), dipyridamole (B01AC30), iloprost (B01AC11), and ticlopidine (B01AC05) as aggregation inhibitors, dabigatran (B01AE07) and ximelagatran (B01AE05) as direct thrombin inhibitors, as well as factor Xa inhibitors rivaroxaban (B01AX06), apixaban (B01AF02), and fondaparinux (B01AX05). Additionally, we obtained information on cholesterol-lowering drugs, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensive drugs, and antidiabetic drugs as these may influence survival [26–30].

Statistical analysis

Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for cancer death. The follow-up started at the FinRSPC randomization and continued until death or right censoring (emigration from Finland or 1 January 2016), whichever occurred first. Time metric was years and months since the baseline. Validity of proportional hazards assumption was tested with an interaction term between follow-up time and time-fixed variables. In each case, the interaction term was statistically non-significant, confirming the assumption. In addition to general cancer mortality, we explored cancer-specific mortality separately for the following cancer types: lung, gastric, colorectal, central nervous system (CNS), non-Hodgkin lymphoma, hepatic, pancreatic, renal, and bladder. Prostate cancer deaths are included in general cancer mortality; prostate cancer-specific mortality has been covered in detail in our previous study [23].

For each man in the study cohort, yearly medication purchases were summed to obtain the total annual amount. Differences in dosing between different anticoagulants were standardized by dividing the total annual milligram amount with the standard Defined Daily Dose (DDD) as listed by the WHO [31]. Each year with registered anticoagulant purchases was regarded as a year of usage regardless of the amount. Average yearly dosage (intensity of use) was estimated by dividing the number of annual doses with the number of years of usage. Intensity of use was also updated annually as a time-dependent variable.

Anticoagulant use after the FinRSPC randomization was analyzed as a time-dependent variable: medication use status and cumulative usage were updated for each year of follow-up based on annual drug purchases. Men were categorized as non-users until the year of the first anticoagulant purchase. The status was changed into a user after the first purchase and maintained as a user for each year with recorded purchases. Men who discontinued anticoagulant purchases during the follow-up were categorized as previous users. In ever-users, both current and previous users of anticoagulants were included. Similarly, cumulative amount, duration, and average yearly dose were updated for each follow-up year according to yearly anticoagulant purchases.

In the analysis comparing warfarin users with men using other anticoagulant drugs, the men were categorized as warfarin users each year with recorded warfarin purchases even if they had used other types of anticoagulants. Only for years with recorded anticoagulant purchases without warfarin use, men were considered warfarin non-users. Similar methodology was used for comparison between heparin users and men using non-heparin anticoagulants.

The main analysis was performed by adjusting Cox regression model for age (continuous variable), use of other medications (categorical variables), indications for anticoagulant usage (categorical variables), and Charlson Comorbidity Score (continuous variable) to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for cancer deaths. The analysis was performed separately for (1) all anticoagulants as a group, (2) warfarin users

compared to anticoagulant non-users, (3) warfarin users, and (4) LMWH users compared to users of other anticoagulant drugs.

In order to evaluate impact of timing of anticoagulant use, we performed a lag-time analysis, where anticoagulant exposure was lagged 1–3 years forward in follow-up time, i.e., outcome events were related to 1–3 years earlier.

Additionally, we performed subgroup analyses stratified by age at randomization, indication for anticoagulant drug use, Charlson Comorbidity Score divided into 3 groups (0 points, 1–2 points, and 3 or more points), and use of other drugs as listed earlier. We also stratified the subgroup analyses by Body Mass Index (BMI), which was available for 11,345 men of the study population. Statistical significance of the effect modification by background variables was tested by adding an interaction term between anticoagulant use and the tested variable in the Cox regression analysis to see whether it improved model fit. p value < 0.05 was considered statistically significant.

All statistical analyses were carried out using IBM SPSS Statistics 22.0. All statistical tests are two-sided.

Results

Population characteristics

During a median follow-up of 17.2 years, 27,233 men died, of whom 8,033 with cancer as the primary cause of death. Among men who died from cancer, the median follow-up was 11.3 years. A total of 48,103 men were followed up until 1 January 2016. In total, 32,628 men (43%) had used anticoagulants during 1995–2015. Distribution of cancer mortality, numbers of cancer-specific deaths, indications for anticoagulant usage, use of other medication, and other background variables stratified by anticoagulant user status are presented in Table 1.

Risk of cancer death by use of any anticoagulants

Ever-use of any anticoagulant was associated with an increased risk of cancer death (HR = 2.50, 95% CI 2.37–2.64). The risk was increased for both current (HR = 2.20, 95% CI 2.06–2.35) and previous users (HR = 2.81, 95% CI 2.64–2.99). The risk increase was similar regardless of the amount or intensity of use. The increased risk was most pronounced in high-intensity (more than 207 DDD/year) usage (HR = 3.09, 95% CI 2.87–3.34). When exploring cancer-specific risk of death, the risk was elevated for all cancer types, being lowest for hepatic cancer and highest for bladder cancer (Table 3).

Risk of cancer death in relation to warfarin use

Compared to other anticoagulants, use of warfarin was associated with a significantly lower risk of cancer death (HR = 0.45, 95% CI 0.41–0.50). This was observed regardless of the amount, duration, or intensity of use (Table 2), the risk decrease being most apparent in high-dose (cumulative use greater than 1,200 DDD, HR = 0.36, 95% CI 0.31–0.43) and high-intensity (more than 193 DDD/year, HR = 0.31, 95% CI 0.27–0.37) use of warfarin. The risk of cancer-specific death was significantly lower among warfarin users compared to users of other anticoagulants in all cancer types (Table 3).

When using anticoagulant non-users as the reference instead of men using other types of anticoagulants, risk for cancer death was significantly increased also among warfarin users (HR = 2.34, 95% CI 2.20–2.48). The risk increase was considerably elevated for previous users (HR = 3.01, 95% CI 2.83–3.21) and moderately increased among current warfarin users compared to anticoagulant non-users (HR = 1.31, 95% CI 1.19–1.43). Warfarin use was associated with an elevated risk of cancer death compared to anticoagulant non-users regardless of amounts, duration, or intensity of use (Table 2). Risk of cancer-specific death was elevated for all cancer types (Table 3).

Risk of cancer death related to heparin use

In total, 12,326 men used LMWH during the study period (69% had used 80 DDD or less). LMWH users compared to non-LMWH anticoagulant users were at significantly higher risk of cancer death (HR 2.04, 95% CI 1.90–2.20) (Table 2). Risk increase was especially high for high dose (more than 80 DDD), use for 2 year or longer, and high-intensity (more than 60 DDD/year) usage. Low dose (40 DDD or less) was not associated with increased risk of cancer death. Conversely, in 3-year lag-time the risk association was reversed to be lower in LMWH users compared to users of other anticoagulant drugs (HR = 0.86, 95% CI 0.77–0.95). Cancer mortality was significantly elevated for all examined cancer types with the exception of central nervous system cancers, where the risk increase was statistically non-significant (Table 3). The most pronounced risk increase was observed for pancreatic and colorectal cancer death.

Lag-time analysis

Any use of anticoagulants compared to non-users was associated with an increased risk of cancer death in 1-year, 2-year, and 3-year lag-time analyses. The risk slightly attenuated with longer lag-time but remained elevated. Risk of cancer-specific death remained elevated in 3-year lag-time for all cancer types (Table 3).

Table 1 Characteristics of the study population stratified by anticoagulant user status

	Anticoagulant user status					
	No anticoagulation	Warfarin[a]	LMWH[a]	Non-warfarin or LMWH anticoagulants	Total n of deaths	Median age at death
n of men in the study population	42.708	17.826	12.326	8.595		
Overall cancer mortality/10,000 person years	75	54	81	46		
n of cancer deaths						
Overall	**4,766 (11.2%)**	1,549 (8.7%)	**1,733 (14.1%)**	**654 (7.6%)**	**8.033**	**72**
Lung cancer	1,404 (3.3%)	380 (2.1%)	351 (2.8%)	213 (2.5%)	1.739	71
Gastric cancer	203 (0.7%)	52 (0.3%)	76 (0.6%)	24 (0.3%)	327	71
Colorectal cancer	414 (1.0%)	144 (0.8%)	233 (1.9%)	49 (0.6%)	764	72
Central nervous system cancers	112 (0.3%)	32 (0.2%)	27 (0.2%)	21 (0.2%)	182	69
Non-Hodgkin lymphomas	125 (0.3%)	64 (0.4%)	65 (0.5%)	18 (0.2%)	244	74
Hepatic cancer	292 (0.7%)	79 (0.4%)	67 (0.5%)	34 (0.4%)	441	71
Pancreatic cancer	432(1.0%)	118 (0.7%)	195 (1.6%)	45 (0.5%)	733	71
Renal cancer	124 (0.3%)	51 (0.3%)	72 (0.6%)	20 (0.2%)	239	72
Bladder cancer	87 (0.2%)	52 (0.3%)	66 (0.5%)	18 (0.2%)	195	73
Recorded diagnoses of						
Pulmonary embolisms	112 (0.3%)	661 (3.7%)	634 (5.1%)	59 (0.7%)		
Venous thromboembolism	23 (0.1%)	205 (1.2%)	233 (1.9%)	12 (0.1%)		
Atrial fibrillation	953 (2.2%)	9,174 (51.5%)	3,833 (31.1%)	508 (0.6%)		
Charlson Comorbidity Score						
0 points	24,979 (58.5%)	6,354 (35.6%)	4,133 (33.5%)	3,879 (45.1%)		
1–2 points	12,669 (29.7%)	6,226 (34.9%)	4,566 (37.0%)	3,020 (35.1%)		
3 or more points	5,060 (11.8%)	5,246 (29.4%)	3,627 (29.4%)	1,696 (19.7%)		
Use of other medication						
Statin users	16,307 (38.2%)	11,613 (65.1%)	7,827 (63.5%)	7,060 (82.1%)		
Aspirin users	4,218 (9.9%)	3,666 (20.6%)	2,542 (20.6%)	4,266 (49.6%)		
NSAID users	34,574 (80.1%)	16,016 (89.8%)	11,865 (96.3%)	7,883 (91.7%)		
Antihypertensive drug users	27,860 (65.2%)	17,055 (95.7%)	10,698 (86.8%)	7,835 (91.2%)		
Antidiabetic drug users	6,300 (14.8%)	4,237 (23.8%)	3,154 (25.6%)	2,215 (25.8%)		
Body Mass Index (BMI)[b]						
<27.6	3,442 (8.1%)	1,078 (6.0%)	958 (7.8%)	604 (7.0%)		
≥ 27.6	2,780 (6.5%)	1,603 (9.0%)	1,265 (10.3%)	700 (8.1%)		

NSAID non-steroidal anti-inflammatory drug

[a]Warfarin and LMWH user status not mutually exclusive. 6,119 men used both warfarin and LMWH during the study period

[b]Information on BMI was available only for 11,345 men. Value 27.6 was the median and was used to divide into two groups of equal size

When comparing warfarin users to anticoagulant non-users, the risk remained elevated although slightly attenuated over all lag times up to 3 years (Table 3).

Risk decrease for overall cancer death observed in the main analysis disappeared in the lag-time analyses comparing warfarin users to users of other anticoagulants (Table 2). The same was observed for cancer-specific risks of death, and the risk decrease remained statistically significant for only non-Hodgkin lymphomas in 1- and 2-year lag-time models (Table 3).

Subgroup analysis

Among all anticoagulant users, significant effect modification was observed for age at randomization, indication for anticoagulant use (excluding atrial fibrillation), for use of statins or antidiabetic drugs, and Charlson Comorbidity Score ($p < 0.001$ for each). Also BMI modified the effect statistically significantly ($p = 0.010$). The effect modification was most pronounced for VTE diagnosis, the risk

Table 2 Multivariable and lag-time hazard ratios (95% CI) related to cancer-specific deaths

	n of deaths	Multivariable-adjusted	1-year lag-time	2-year lag-time	3-year lag-time
Any anticoagulant compared to anticoagulant non-users					
None	4.766	Ref.	Ref.	Ref.	Ref.
Ever-users	3.267	**2.50 (2.37–2.64)**	**2.20 (2.08–2.32)**	**1.73 (1.64–1.83)**	**1.67 (1.57–1.77)**
Amount of anticoagulant use					
≤200 DDD	1.348	**2.28 (2.14–2.43)**	**1.94 (1.82–2.08)**	**1.52 (1.42–1.64)**	**1.54 (1.43–1.66)**
200–1,100 DDD	1.046	**2.74 (2.54–2.96)**	**2.41 (2.23–2.61)**	**1.90 (1.74–2.06)**	**1.77 (1.62–1.93)**
> 1,100 DDD	873	**2.84 (2.62–3.09)**	**2.64 (2.42–2.87)**	**2.06 (1.88–2.26)**	**1.87 (1.69–2.07)**
Duration of anticoagulant use					
≤2 year	1.867	**2.47 (2.33–2.62)**	**2.12 (1.99–2.25)**	**1.61 (1.51–1.72)**	**1.57 (1.47–1.68)**
3–5 years	663	**2.64 (2.42–2.89)**	**2.38 (2.17–2.61)**	**1.91 (1.73–2.11)**	**1.78 (1.60–1.98)**
6 or more years	737	**2.50 (2.29–2.74)**	**2.34 (2.13–2.56)**	**1.99 (1.80–2.19)**	**1.91 (1.72–2.11)**
Intensity of anticoagulant use					
≤100 DDD/year	1.234	**2.23 (2.09–2.38)**	**1.91 (1.78–2.05)**	**2.53 (1.42–1.65)**	**1.52 (1.40–1.64)**
97–207 DDD/year	929	**2.50 (2.31–2.70)**	**2.16 (1.99–2.35)**	**1.78 (1.63–1.94)**	**1.78 (1.63–1.95)**
> 207 DDD/year	1.104	**3.09 (2.87–3.34)**	**2.84 (2.62–3.06)**	**2.07 (1.90–2.25)**	**1.83 (1.67–2.01)**
Warfarin compared to anticoagulant non-users					
None	4.766	Ref.	Ref.	Ref.	Ref.
Ever-users	1.549	**2.34 (2.20–2.48)**	**2.06 (1.94–2.19)**	**1.73 (1.63–1.85)**	**1.66 (1.55–1.77)**
Amount of warfarin use					
≤307 DDD	713	**2.61 (2.39–2.84)**	**2.25 (2.06–2.46)**	**1.74 (1.58–1.91)**	**1.71 (1.55–1.89)**
307–1200 DDD	482	**2.29 (2.07–2.55)**	**2.19 (1.97–2.44)**	**1.85 (1.66–2.07)**	**1.76 (1.57–1.98)**
> 1200 DDD	354	**2.04 (1.81–2.30)**	**2.07 (1.84–2.33)**	**1.81 (1.60–2.05)**	**1.70 (1.49–1.95)**
Duration of warfarin use					
≤2 year	720	**2.45 (2.25–2.67)**	**2.18 (1.99–2.38)**	**1.70 (1.55–1.87)**	**1.67 (1.51–1.84)**
3–7 years	504	**2.37 (2.14–2.63)**	**2.23 (2.00–2.47)**	**1.83 (1.63–2.04)**	**1.67 (1.48–1.87)**
8 or more years	325	**2.21 (1.95–2.50)**	**2.17 (1.91–2.46)**	**1.96 (1.72–2.24)**	**2.00 (1.74–2.30)**
Intensity of warfarin use					
≤120 DDD/year	701	**2.34 (2.14–2.55)**	**2.09 (1.90–2.29)**	**1.68 (1.52–1.87)**	**1.65 (1.49–1.84)**
120–193 DDD/year	446	**1.75 (1.58–1.95)**	**1.77 (1.59–1.98)**	**1.56 (1.39–1.75)**	**1.58 (1.40–1.78)**
> 193 DDD/year	402	**1.53 (1.37–1.70)**	**1.75 (1.58–1.95)**	**1.71 (1.54–1.91)**	**1.66 (1.48–1.86)**
Warfarin compared to other anticoagulant drugs					
Non-warfarin anticoagulant users	1.718	Ref.	Ref.	Ref.	Ref.
Warfarin users	1.549	**0.45 (0.41–0.50)**	1.00 (0.91–1.09)	1.09 (0.99–1.21)	1.03 (0.92–1.14)
Amount of warfarin use					
≤307 DDD	713	**0.68 (0.59–0.78)**	**1.23 (1.07–1.40)**	1.12 (0.96–1.31)	1.13 (0.96–1.33)
307–1200 DDD	482	**0.39 (0.33–0.45)**	0.94 (0.83–1.07)	1.10 (0.96–1.26)	0.99 (0.86–1.15)
> 1200 DDD	354	**0.36 (0.31–0.43)**	0.88 (0.77–1.01)	1.07 (0.92–1.24)	0.98 (0.83–1.15)
Duration of warfarin use					
≤2 year	720	**0.58 (0.50–0.66)**	**1.17 (1.03–1.33)**	1.11 (0.96–1.28)	1.09 (0.93–1.27)
3–7 years	504	**0.40 (0.34–0.46)**	0.92 (0.81–1.04)	1.05 (0.92–1.20)	0.90 (0.78–1.04)
8 or more years	325	**0.40 (0.34–0.47)**	0.92 (0.79–1.06)	1.14 (0.98–1.33)	1.17 (0.99–1.39)
Intensity of warfarin use					
≤120 DDD/year	701	**0.71 (0.62–0.81)**	**1.23 (1.07–1.40)**	1.14 (0.98–1.33)	1.04 (0.88–1.24)
120–193 DDD/year	446	**0.42 (0.36–0.49)**	0.99 (0.86–1.13)	1.05 (0.91–1.22)	0.99 (0.84–1.17)
> 193 DDD/year	402	**0.31 (0.27–0.37)**	**0.86 (0.76–0.98)**	1.09 (0.96–1.25)	1.04 (0.91–1.20)
LMWH compared to other anticoagulant drugs					
Non-LMWH anticoagulant users	1.534	Ref.	Ref.	Ref.	Ref.
LMWH users	1.733	**2.04 (1.90–2.20)**	**1.57 (1.45–1.70)**	1.02 (0.93–1.12)	**0.86 (0.77–0.95)**
Amount of warfarin use					
≤40 DDD	497	1.09 (0.98–1.20)	0.99 (0.89–1.11)	**0.81 (0.72–0.91)**	**0.73 (0.63–0.83)**

Table 2 (continued)

	n of deaths	Multivariable-adjusted	1-year lag-time	2-year lag-time	3-year lag-time
40–80 DDD	276	**1.59 (1.40–1.82)**	**1.28 (1.10–1.48)**	0.95 (0.79–1.13)	0.90 (0.74–1.10)
> 80 DDD	960	**4.73 (4.34–5.15)**	**3.38 (3.06–3.74)**	**1.70 (1.48–1.96)**	**1.23 (1.02–1.47)**
Duration of warfarin use					
≤ 1 year	1.173	**1.80 (1.66–1.94)**	**1.46 (1.34–1.59)**	0.96 (0.87–1.06)	**0.83 (0.74–0.93)**
2 or more years	560	**3.00 (2.71–3.32)**	**2.00 (1.77–2.27)**	**1.29 (1.09–1.52)**	0.98 (0.79–1.21)
Intensity of warfarin use					
≤ 40 DDD/year	580	**1.12 (1.01–1.23)**	1.01 (0.91–1.11)	**0.82 (0.73–0.92)**	**0.75 (0.65–0.85)**
40–60 DDD/year	198	**1.66 (1.43–1.93)**	**1.35 (1.14–1.61)**	1.07 (0.87–1.32)	0.97 (0.77–1.23)
> 60 DDD/year	955	**4.83 (4.43–5.26)**	**3.40 (3.07–3.75)**	**1.62 (1.41–1.87)**	1.15 (0.96–1.38)

increase being strongest among those who had recorded diagnosis of VTE (Fig. 2).

When comparing warfarin to other types of anticoagulants, effect modification was observed for indication of anticoagulant use, Charlson Comorbidity Score and for NSAID, antihypertensive and antidiabetic drug use. Otherwise, the risk of overall death was similar independent of background variables (Fig. 3).

Among LMWH users compared to use of other anticoagulant drugs, effect modification was observed for VTE, atrial fibrillation, Charlson Comorbidity Score, and use of antihypertensive drugs (Supplementary Fig. 2)

Sensitivity analysis

Since the data included cancer deaths but not cancer diagnoses, we performed a sensitivity analysis comparing crude median survival times to end of year 2014 for the studied cancer types for anticoagulant non-user, anticoagulant users, and users of warfarin only and LMWH only. Median follow-up ranged from 0 to 4.5 years, being lowest for lung and hepatic cancer and highest for renal and bladder cancer and non-Hodgkin lymphomas. These data are provided in Supplementary Table.

Discussion

Anticoagulant use was associated with an increased risk of overall and cancer-specific cancer death independent of duration, amounts, or intensity of use. The risk increase prevailed although slightly attenuated in all lag-time analyses. The risk association was modified by indications of usage and by comorbidities; especially diagnosis of VTE greatly modified the risk association, although number of recorded VTE diagnoses was relatively low. For specific cancer types, the risk of cancer-specific death was increased for all cancer types, especially for bladder cancer.

The risk associations were similar when comparing users of warfarin to anticoagulant non-users for both overall and cancer-specific risk of death. When comparing warfarin users to users of other anticoagulant drugs, the risk was considerably lower in the non-lagged analysis but in the lag-time analyses the risk associations were similar. The same was observed for the risk of cancer-specific death. Thus, the timing of warfarin use modified the risk associations, especially when comparing to anticoagulant non-users. Strongest effect modification was observed by diagnosis of atrial fibrillation, Charlson Comorbidity Score, and use of antihypertensive drugs.

All anticoagulant sub-types were associated with an increased risk of cancer death. However, risk of cancer death among warfarin users compared to other anticoagulants was much lower but still elevated compared to non-users although warfarin is not recommended for treatment of cancer-induced thrombi. A possible explanation for the lower risk among users of warfarin compared to other anticoagulants in the non-lagged analysis is most likely due to an increased risk associated with indication of anticoagulant use, especially LMWH use which was associated with significantly high risk of overall cancer death and cancer-specific death in the non-lagged analysis. LMWH is recommended for management of VTE in patients with cancer, as the likelihood of VTE recurrence may be lower when using this drug group in cancer patients [32]. Current Finnish guidelines for thromboprophylaxis in cancer patients recommend treatment with LMWH for 3–12 months or permanently. The vast majority (69%) of the LMWH users in our study cohort used less than 80 DDD of LMWH, equaling a duration of use for less than 3 months.

Despite promising results in experimental animal studies [6–13], we found no decreased risk of cancer death associated with either warfarin or other anticoagulant drugs. On the contrary, the risk of cancer death is significantly increased. Out of previous epidemiological studies, our study is only comparable to O'Rorke et al. [20], as the other two studies [19, 21] covered only prostate cancer

Table 3 Multivariable and lag-time hazard ratios (95% CI) related to cancer-specific deaths

	n of deaths	Multivariable-adjusted	1-year lag-time	2-year lag-time	3-year lag-time
Any anticoagulant compared to anticoagulant non-users					
All cancers					
Non-user	4.766	Ref.	Ref.	Ref.	Ref.
Ever-user	3.267	**2.50 (2.37–2.64)**	**2.20 (2.08–2.32)**	**1.73 (1.64–1.83)**	**1.67 (1–57–1.77)**
Cancer type					
Lung cancer	799/1,404[a]	**2.19 (1.97–2.42)**	**1.89 (1.70–2.10)**	**1.55 (1.39–1.74)**	**1.53 (1.36–1.71)**
Gastric cancer	124/203[a]	**3.03 (2.33–3.96)**	**2.93 (2.24–3.85)**	**2.13 (2.60–2.84)**	**2.00 (1.48–2.70)**
Colorectal cancer	350/414[a]	**3.51 (2.96–4.16)**	**3.01 (2.53–3.58)**	**2.15 (1.80–2.58)**	**1.80 (1.49–2.18)**
Central nervous system cancers	70/112[a]	**3.23 (2.25–4.64)**	**3.02 (2.09–4.36)**	**1.59 (1.06–2.39)**	**1.28 (0.83–1.99)**
Non-Hodgkin lymphomas	119/125[a]	**2.91 (2.16–3.93)**	**2.53 (1.87–3.42)**	**1.97 (1.44–2.68)**	**1.69 (1.23–2.33)**
Hepatic cancer	149/292[a]	**1.64 (1.30–2.06)**	**1.43 (1.13–1.82)**	**1.32 (1.03–1.69)**	**1.37 (1.06–1.78)**
Pancreatic cancer	301/431[a]	**2.90 (2.44–3.46)**	**2.10 (1.75–2.52)**	**1.48 (1.22–1.80)**	**1.51 (1.23–1.84)**
Kidney cancer	115/124[a]	**3.08 (2.28–4.17)**	**2.35 (1.73–3.19)**	**1.75 (1.27–2.41)**	**1.75 (1.26–2.43)**
Bladder cancer	108/87[a]	**4.99 (3.58–6.96)**	**4.44 (3.19–6.20)**	**2.87 (2.04–4.04)**	**2.67 (1.89–3.77)**
Warfarin compared to anticoagulant non-users					
All cancers					
No anticoagulant use	4.766	Ref.	Ref.	Ref.	Ref.
Warfarin ever-use	1.549	**2.34 (2.20–2.48)**	**2.06 (1.94–2.19)**	**1.73 (1.63–1.85)**	**1.66 (1.55–1.77)**
Cancer type					
Lung cancer	380/1,404[b]	**2.01 (1.79–2.26)**	**1.74 (1.54–1.97)**	**1.51 (1.33–1.72)**	**1.40 (1.22–1.60)**
Gastric cancer	52/203[b]	**2.89 (2.14–3.90)**	**2.56 (1.87–3.51)**	**2.02 (1.45–2.82)**	**1.85 (1.30–2.63)**
Colorectal cancer	144/414[b]	**3.10 (2.56–3.76)**	**2.68 (2.20–3.26)**	**2.03 (1.65–2.49)**	**1.82 (1.47–2.25)**
Central nervous system cancers	32/112[b]	**2.68 (1.77–4.05)**	**2.43 (1.58–3.74)**	1.39 (0.87–2.23)	1.02 (0.61–1.73)
Non-Hodgkin lymphomas	64/125[b]	**2.73 (1.96–3.81)**	**2.48 (1.78–3.46)**	**2.04 (1.45–2.86)**	**1.88 (1.32–2.67)**
Hepatic cancer	79/292[b]	**1.47 (1.13–1.91)**	**1.51 (1.16–1.96)**	**1.42 (1.08–1.87)**	**1.53 (1.15–2.02)**
Pancreatic cancer	118/431[b]	**2.47 (2.02–3.01)**	**1.80 (1.46–2.22)**	**1.55 (1.25–1.93)**	**1.54 (1.22–1.93)**
Renal cancer	51/124[b]	**2.73 (1.95–3.83)**	**2.12 (1.50–2.99)**	**1.57 (1.09–2.25)**	1.40 (0.95–2.06)
Bladder cancer	52/87[b]	**5.29 (3.69–7.60)**	**4.45 (3.09–6.40)**	**2.91 (2.00–4.24)**	**2.62 (1.78–3.88)**
Warfarin compared to other anticoagulant drugs					
All cancers					
Non-warfarin anticoagulant users	1.718	Ref.	Ref.	Ref.	Ref.
Warfarin users	1.549	**0.45 (0.41–0.50)**	1.00 (0.91–1.09)	1.09 (0.99–1.21)	1.03 (0.92–1.14)
Cancer type					
Lung cancer	380/419[c]	**0.63 (0.52–0.75)**	1.09 (0.91–1.30)	1.13 (0.93–1.38)	1.00 (0.81–1.24)
Gastric cancer	52/72[c]	**0.35 (0.20–0.61)**	1.11 (0.70–1.77)	1.29 (0.78–2.12)	0.86 (0.49–1.51)
Colorectal cancer	144/206[c]	**0.37 (0.27–0.51)**	0.86 (0.65–1.15)	1.02 (0.74–1.40)	1.10 (0.77–1.56)
Central nervous system cancers	32/38[c]	**0.43 (0.23–0.83)**	1.40 (0.77–2.55)	1.08 (0.52–2.26)	1.00 (0.44–2.27)
Non-Hodgkin lymphomas	64/55[c]	**0.48 (0.29–0.78)**	**1.79 (1.14–2.82)**	**1.75 (1.07–2.87)**	1.64 (0.96–2.81)
Hepatic cancer	70/79[c]	**0.45 (0.29–0.69)**	0.82 (0.53–1.25)	0.97 (0.62–1.53)	1.06 (0.65–1.71)
Pancreatic cancer	118/183[c]	**0.34 (0.23–0.48)**	0.79 (0.57–1.10)	1.26 (0.88–1.80)	1.16 (0.79–1.69)
Renal cancer	51/64[c]	**0.31 (0.18–0.56)**	0.71 (0.43–1.18)	0.77 (0.43–1.36)	0.60 (0.32–1.14)
Bladder cancer	52/56[c]	**0.41 (0.23–0.72)**	0.98 (0.59–1.63)	1.16 (0.66–2.03)	1.40 (0.79–2.51)
LMWH compared to other anticoagulants					
All cancers					
Non-LMWH anticoagulants	1.534	Ref.	Ref.	Ref.	Ref.
LMWH	1.733	**2.04 (1.90–2.20)**	**1.57 (1.45–1.70)**	1.02 (0.93–1.12)	**0.86 (0.77–0.95)**
Cancer type					
Lung cancer	351/448[d]	**1.46 (1.26–1.69)**	1.10 (0.93–1.30)	**0.67 (0.54–0.82)**	0.61 (0.48–0.77)
Gastric cancer	48/76[d]	**3.39 (2.30–4.98)**	**3.19 (2.14–4.75)**	1.31 (0.82–2.09)	1.16 (0.69–1.96)
Colorectal cancer	233/117[d]	**3.60 (2.84–4.56)**	**2.75 (2.15–3.50)**	**1.70 (1.29–2.23)**	1.06 (0.77–1.45)

Table 3 (continued)

	n of deaths	Multivariable-adjusted	1-year lag-time	2-year lag-time	3-year lag-time
Central nervous system cancers	27/43[d]	1.10 (0.66–1.84)	0.73 (0.41–1.31)	0.65 (0.30–1.40)	0.76 (0.32–1.79)
Non-Hodgkin lymphomas	65/54[d]	**2.38 (1.62–3.50)**	**2.17 (1.44–3.26)**	**1.87 (1.20–2.94)**	**1.79 (1.09–2.93)**
Hepatic cancer	67/82[d]	**1.46 (1.04–2.05)**	0.84 (0.56–1.25)	**0.43 (0.25–0.73)**	**0.45 (0.25–0.80)**
Pancreatic cancer	195/106[d]	**3.57 (2.78–4.58)**	**1.91 (1.46–2.50)**	1.05 (0.76–1.46)	0.81 (0.56–1.18)
Renal cancer	72/43[d]	**3.21 (2.14–4.81)**	**2.81 (1.83–4.32)**	**1.72 (1.07–2.77)**	1.46 (0.87–2.44)
Bladder cancer	66/42[d]	**2.80 (1.85–4.25)**	**1.78 (1.16–2.73)**	0.95 (0.57–1.59)	0.67 (0.37–1.21)

Comparison between (1) anticoagulant users and non-users, (2) warfarin users and anticoagulant non-users, (3) warfarin users and users of other anticoagulants, and (4) LMWH users and user of other anticoagulants

Statistically significant results are bolded

[a]Deaths among anticoagulant users/deaths among non-users

[b]Deaths among warfarin users/deaths among anticoagulant non-users

[c]Deaths among warfarin users/deaths among users of other anticoagulants

[d]Deaths among LMWH users/death among users of other anticoagulants

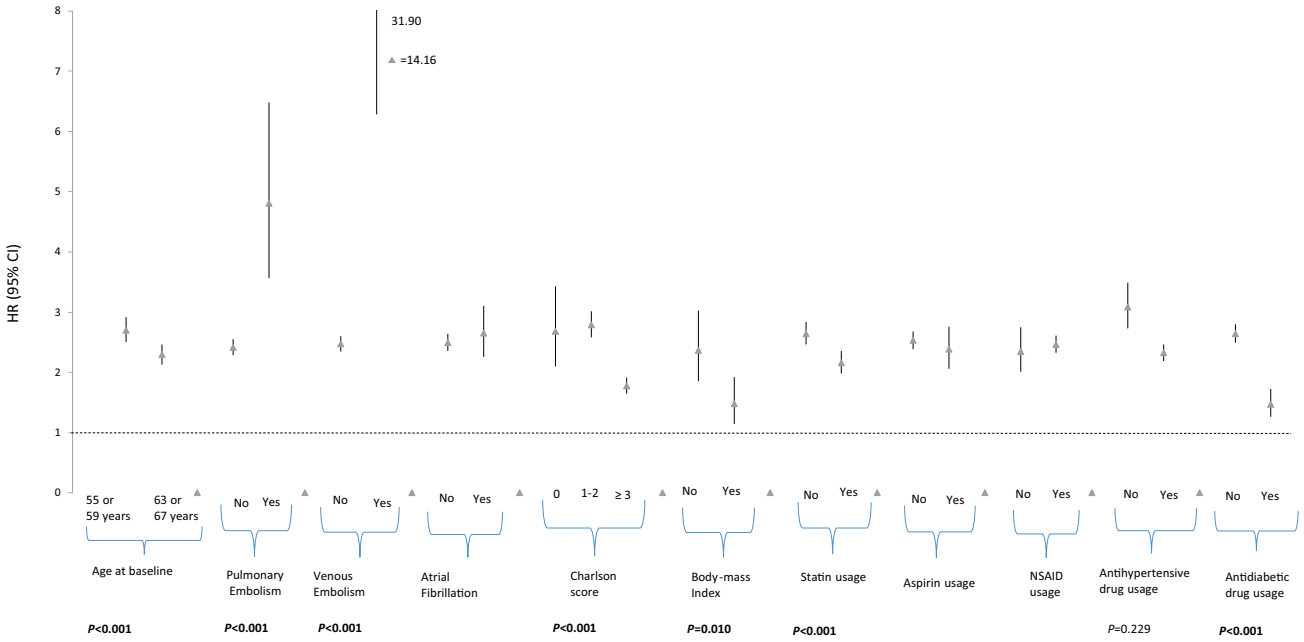

Fig. 2 Subgroup analysis between anticoagulant users and non-users for non-specific cancer death. *p* for interaction is given under the variable if effect modification was considered possible. Statistically significant *p* values are bolded. *NSAID* non-steroidal anti-inflammatory drugs

deaths. O'Rorke et al. additionally included lung, colorectal, and breast cancer-specific deaths. They reported increased risk of lung cancer death for pre-diagnostic but no risk increase for post-diagnostic warfarin use. For colorectal cancer, an increased risk of death was associated with post-diagnostic, but not with pre-diagnostic use. Our results for lung and colorectal cancer death and warfarin use are similar. Since we did not have sufficient data to divide anticoagulant use into pre- and post-diagnostic use, our results are not completely comparable, but both studies suggest that among lung and colorectal cancer patients, warfarin use is not associated with decreased mortality.

This study has several strengths: a large population-based cohort with a median follow-up of 17.2 years and detailed register-based information on anticoagulant use preventing recall bias. We were able to stratify use of anticoagulants by amounts (DDD), duration, and intensity of use, and to compare anticoagulant users with non-users, as well as warfarin users to users of other anticoagulants in addition to anticoagulant non-users. We also compared LMWH users to users

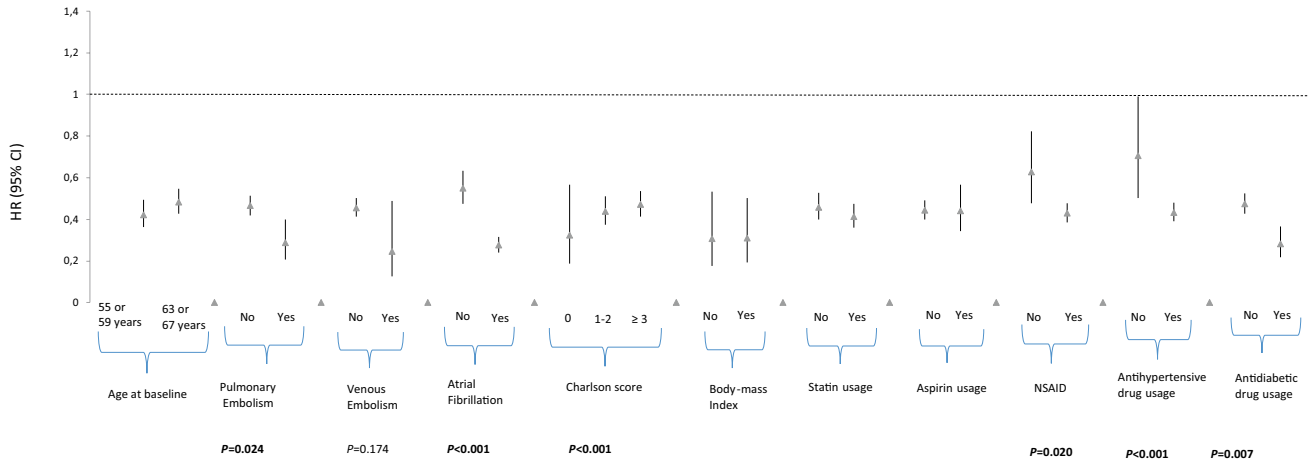

Fig. 3 Subgroup analysis between warfarin users and users of other types of anticoagulants for non-specific cancer death. *p* for interaction is given under the variable if effect modification was considered possible. Statistically significant *p* values are bolded. *NSAID* non-steroidal anti-inflammatory drugs

of other anticoagulant drugs. Additionally, we were able to perform lag-time analyses to estimate the impact of timing of anticoagulant use. We were also able to study several cancer types to evaluate cancer-specific risk of death. For several cancer types, risk of cancer-specific death among anticoagulant users has not been reported earlier in epidemiological studies. Most published clinical trials on this topic have involved breast cancer and lung cancer patients. Prostate cancer was not separately analyzed in this study, as we have previously covered it in detail [21]. In that study, we reported that post-diagnostic use of anticoagulants was associated with 1.6-fold and use of warfarin 1.5-fold risk of prostate cancer death when compared to anticoagulant non-users.

This study also has certain limitations. For many cancer types, the number of deaths was relatively low. We had limited information on BMI, only for 11,345 men (15%), which may influence cancer mortality and cause confounding [33]. BMI was assessed only in the subgroup analysis. Additionally, we did not have information on smoking, which has been associated with increased risk of death in many cancer types [34]. However, we were able to adjust for Charlson Comorbidity Score. We did not have information on dietary factors and physical activity which are linked to cancer prognosis [35]. Misclassification in cause of death on death certificates has been reported which could bias the association away from null [36]. Another limitation is that drug use during hospital inpatient periods is not covered. However, if a person has had a clear indication for anticoagulant usage, i.e., not only prophylaxis, the drug use is continued after hospitalization and is visible in the data used in this study. Furthermore, our study was not randomized and hence the comparability of the users and non-users was uncertain, with potential for confounding by indication. Additionally, our results might not be applicable to younger population, women, or non-Caucasian ethnicities, as this cohort covered only Finnish men aged 55–67 at baseline.

In a population-based setting, use of anticoagulants is associated with an increased risk of cancer death. The risk increase is likely caused by increased likelihood of thrombosis in cancer patients and the resulting treatment. In warfarin users, the risk increase was smaller compared to users of LMWH, but the risk was nevertheless increased compared to non-users of anticoagulants.

Conclusion

Anticoagulants as a group are associated with an increased risk of cancer death. Our study does not support reduced cancer mortality among anticoagulant drug users. For future studies exploring use of any drug group and cancer mortality, we recommend adjusting for use of anticoagulant drugs as this drug group is rarely adjusted for and is associated with significantly higher risk of cancer death. Additionally, we recommend exploring new oral anticoagulants and cancer mortality as they have now been in use for several years, but epidemiological studies on the topic are virtually non-existing.

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Data availability Permission to use the entire data has been granted personally for this specific study, and thus we are not allowed to make the entire data publicly available without permission. Limited data (i.e., variables used for the analyses) can be obtained upon reasonable request. Each Administrator and Information Commissioner of the used registries processed our request to use the data and granted a personal permission. If desired, similar permissions can be applied from the Finnish Social Insurance Institution (available at http://www.kela.fi/web/en/research) and the National Institute for Health and Welfare (available at https://www.thl.fi/en/web/thlfi-en/statistics/information-for-researchers).

Compliance with ethical standards

Competing interests We declare the following competing interests—PTT Kinnunen and K Talala: no competing interests. TJ Murtola: paid consultant for Astellas and Janssen-Cilag, and lecture fees from Astellas, Janssen-Cilag, Abbvie, and MSD. K Taari: research funding from Medivation, Astellas, Pfizer, and Orion, and travel support from Astellas. TLJ Tammela: paid consultant for Astellas, Orion Pharma, and Janssen-Cilag. A Auvinen: lecture fee from MSD, and paid consultant for Epid Research Inc.

Ethics approval The study has been approved by the Ethical Committee of Pirkanmaa Hospital District (Committee's reference number R10167). This study is based on register data collected routinely for other purposes. Thus, no informed consent is needed based on international practices.

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