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Published in:
International Journal of Cancer

DOI:
10.1002/ijc.31886

Publication date:
2019

Document version:
Accepted manuscript

Citation for pulished version (APA):
Kristensen, K. B., Jensen, P. H., Skriver, C., Friis, S., & Pottegård, A. (2019). Use of vitamin K antagonists and risk of prostate cancer: Meta–analysis and nationwide case–control study. *International Journal of Cancer*, *144*(7), 1522-1529. https://doi.org/10.1002/ijc.31886

Use of vitamin K antagonists and risk of prostate cancer: Meta–analysis and nationwide case–control study

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Keywords

Anticoagulant drugs, Warfarin, Prostate cancer, Risk Factors, Case–Control Studies

Novelty and Impact / What's New

Vitamin K antagonists potentially exert antineoplastic effects on prostate cancer cells and may reduce prostate cancer risk. However, findings from observational studies examining vitamin K antagonist use in patients are conflicting. In the present nationwide study of incident prostate cancers among men in Denmark from 2005–2015, the authors found no evidence linking long–term use of vitamin K antagonists, specifically warfarin and phenprocoumon, to prostate cancer risk. In a systematic review and meta-analysis, the authors reported a high degree of heterogeneity among existing studies. In conclusion, the available evidence did not support a major protective effect of vitamin K antagonists against prostate cancer.

ABSTRACT

Use of vitamin K antagonists (VKAs) has been suggested to reduce the risk of prostate cancer. We conducted a nested case–control study using Danish demographic and health data registries and summarized existing evidence in a meta-analysis. The case-control study included all Danish men aged 40–85 years with incident histologically verified prostate adenocarcinoma between 2005 and 2015 (cases). For each case, we selected 10 age–matched controls. We used conditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CI) for prostate cancer associated with long–term VKA use adjusted for concomitant drug use, medical history, and socioeconomic status. We included 38,832 prostate cancer cases of which 1,089 (2.8%) had used VKAs for 3 or more years compared to 10,803 (2.8%) controls yielding a crude OR of 1.01 (95% CI, 0.95–1.08). Multivariable adjustment for covariates had limited influence on the association (OR, 1.03; 95% CI, 0.97–1.10). We observed no dose–response relationship (e.g. OR for 5–10 years of use, 1.06 95% CI, 0.97–1.16). We included 8 studies in the meta–analysis reporting effect estimates from 0.51 (95% CI, 0.23–1.13) to 1.10 (95% CI, 0.94–1.40). Using random effect methods, a pooled effect estimate of 0.86 (95% CI, 0.70–1.05) was obtained; however, there was considerable across–study heterogeneity (I^2: 93.9%).

In conclusion, we did not observe a reduced risk of prostate cancer associated with VKA use in this nationwide study and, taken together with previous study findings, a major protective effect of VKAs against prostate cancer seems unlikely.

INTRODUCTION

Prostate cancer is the most common non–skin cancer among men in western countries and the incidence continues to rise.[1] The etiology of prostate cancer remains largely unknown and only non–modifiable risk factors have been firmly established (age, genetic factors, and ethnicity).[1,2] Consequently, identification of preventive factors for prostate cancer would have a huge impact on public health.

In 2000, a secondary analysis of a clinical trial sparked interest in a possible antineoplastic effect of vitamin K antagonists (VKAs) as the authors reported a lower incidence of urogenital cancers in patients treated with VKAs for 6 months compared to patients treated for 6 weeks.[3] This finding was followed by observational studies reporting 20–30% reductions in prostate cancer risk with VKA use[3–7] as well as studies reporting neutral associations.[8–10] In laboratory studies, VKAs have been demonstrated to inhibit Axl–receptor signaling involved in cell growth regulation and to reduce transcriptional activity of the androgen receptor in prostate cancer cells.[11,12]

Given the conflicting epidemiological findings and the potential implications for development of drugs for prevention or treatment of prostate cancer, we conducted a systematic review of the literature, examined the association between VKA use and prostate cancer risk in a nationwide nested case–control study, and pooled the risk estimates from previous and the present study in a meta–analysis.

METHODS

Systematic review and meta–analysis

We conducted a systematic review to summarize existing evidence on use of vitamin K antagonists (VKAs) and risk of prostate cancer. We searched PubMed, Embase, and the Cochrane Library from inception until April 2018 with no restrictions on language or publication date. We combined keywords and thesaurus terms related to prostate cancer and VKA treatment. Appendix B provides a detailed description of the applied search strategy. Eligible studies included human participants, presented empirical data on VKA use, and reported associations between VKA use and prostate cancer. Titles and abstracts were screened for relevance by 2 medical doctors (KBK and PHJ) independently and any disagreements were resolved by consensus. We cross–reference searched all publications selected for full–text screening. Data was extracted by KBK and PHJ independently using a pre-defined data extraction sheet with information on author, year of publication, study design, study setting, study size, exposure definition, confounders, statistical methods, and effect estimates with 95% confidence intervals. For studies reporting effect estimates for several categories of cumulative VKA exposure, we reported those closest to 3 or more years of VKA use corresponding to the main exposure of the present case–control study. For the meta–analysis, we pooled the adjusted effect estimates from the studies identified in the systematic review and the present study using DerSimonian and Laird random effects methods and assessed heterogeneity using Cochran's Q and the I^2 statistic.[13] Besides presenting an overall pooled effect estimate, we stratified the

studies by the reported effect estimate. Thus, we analyzed studies reporting risk ratios (RR) or odds ratios (OR) and studies reporting hazard ratios (HR) or incidence rate ratios (IRR) separately. Because the present study partially included the same population as a previous study on VKA use and risk of selected cancers in Denmark,[5] the previous study was omitted from the meta–analysis. Further, we carried out a *post hoc* sensitivity analysis excluding a study with high risk of immortal time bias.[4,14,15]

Case–control study

We conducted a nationwide case–control study comparing use of VKAs in patients with incident prostate cancer (cases) to use in men in the general population without cancer (population controls). Using conditional logistic regression, we estimated ORs for prostate cancer associated with VKA use.

Data Sources

We retrieved data from the Danish National Prescription Registry,[16] Danish Cancer Registry,[17] Danish National Patient Registry,[18] Danish Civil Registration System,[19] and Statistics Denmark.[20] Appendix C provides a detailed description of these registries. The registries were linked individually by the unique Danish Civil Registration Number assigned to all Danish residents.[19] The Danish National Health Care System guarantees free access to medical care and partial reimbursement of prescribed drugs, and this system allows for practically complete identification of individual–level demographic and health registry data for the entire Danish population.

Study population

We sampled our study participants from a nationwide cohort of all Danish men aged 40–85 years. We further required that participants were without previous cancer (except non–melanoma skin cancer) and had resided continuously in Denmark 10 years preceding enrollment. Using the Danish Cancer Registry,[17] we identified all incident, histologically verified prostate cancer cases during Jan 1, 2005 – Dec 31, 2015. For each case, we randomly selected 10 age–matched controls on the date of diagnosis (index date). Participants were eligible for sampling as controls before they became cases. Thereby, the calculated ORs are estimates of the IRRs from a cohort study of the underlying source population.[21]

Exposure

Assessment of VKA use was based on filled prescriptions of warfarin and phenprocoumon recorded in the Danish National Prescription Registry.[16] Our *a priori* main exposure was 3 or more years of VKA use. Furthermore, we modelled exposure as ever–use (at least 1 filled VKA prescription) and, to evaluate any dose–response relationship, as an ordinal variable according to cumulative duration of use (< 1, 1–3, 3–5, 5–10, and >10 years). To define the duration assigned to each prescription fill, we fitted a reverse waiting time distribution (rWTD) model for warfarin and phenprocoumon prescriptions filled in 2005 adjusting for age and number of pills redeemed (100, 200, 300+).[22] If the next prescription for VKAs occurred within the duration defined by the

rWTD model, we assumed that the treatment episode had continued. If it occurred later, we assumed that treatment had been paused. Similarly, the duration assigned to a single prescription and the last prescription was the estimated duration for that given age and package size in the rWTD model. Hereafter, we cumulated the duration of all VKA treatment episodes for each individual. We disregarded all VKA use 2 years prior to the index date (i.e. applied a lag–time of 2 years) to avoid reverse causation bias.[23]

Covariates

Potential confounders included (i) age and calendar time (inherent adjustment by study design); (ii) use of drugs with suggested preventive effect against prostate cancer including 5α–reductase inhibitors, α–blocking agents, statins, aspirin and other non–steroidal anti–inflammatory drugs (NSAIDs), angiotensin–converting enzyme inhibitors, and angiotensin II receptor blockers;[24–26] (iii) history of type 2 diabetes, ischemic heart disease, congestive heart disease, or chronic obstructive pulmonary disease;[27] (iv) history of conditions with relative contraindication for VKA use including moderate/severe liver disease, moderate/severe kidney failure, heavy alcohol use, gastrointestinal bleeding and intracranial hemorrhage; and, lastly, (v) highest achieved education as a measure of socioeconomic status. Exposure to potential confounding drugs was defined as having filled 2 or more prescriptions on separate dates. A history of potential confounding conditions was based on primary or secondary discharge/ambulatory diagnoses and/or filled prescriptions of drugs used primarily for these conditions (Appendix D). For all covariates, we introduced a 2–year lag–time as for the primary exposure variable.

Data analysis

We used conditional logistic regression to estimate ORs for prostate cancer associated with VKA use compared to never–use. We evaluated presence of a dose–response relationship by including duration of treatment as an ordinal variable in conditional regression analyses and modelling duration of treatment as a continuous variable in unconditional logistic regression analyses. In the latter analysis, we estimated the incremental OR from each 1–year increase in duration of use. We adjusted for age and calendar time in the unconditional logistic regression analysis as the matching was broken.

Supplementary and sensitivity analyses

Our main exposure was use of any VKA, i.e. warfarin or phenprocoumon. We carried out analyses for warfarin and phenprocoumon separately in sensitivity analyses. In order to evaluate potential effect measure modification, we stratified the main analyses according to age, calendar time, clinical stage based on the TNM classification (Appendix D),[28] and modified Charlson Comorbidity Index scores (excluding cancer diagnoses).[29] To examine whether the association varied by the presumed primary indication for anticoagulant therapy, we defined a combined exposure measure of VKA use and a diagnosis of atrial fibrillation/atrial flutter or venous thromboembolism. Further, we applied a new–user design by excluding all study subjects having filled a

prescription for VKAs during 1995–1996 from our base population. Finally, we varied the length of the lag–time (i.e., the period prior to index date disregarded in the VKA exposure assessment) from 0 to 60 months.

Other

All analyses were performed using STATA Release 14.2 (StataCorp, College Station, TX, USA). The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study. According to Danish law, ethical approval is not required for registry–based studies.

RESULTS

Case–control study

We included 38,832 prostate cancer cases and 388,320 population controls (Figure 1). Characteristics were largely similar between cases and controls (Table 1). Among cases, 1,089 (2.8%) were long–term users of VKAs compared to 10,803 (2.8%) among controls, yielding a crude OR of 1.01 (95% CI: 0.95–1.08) (Table 2). Multivariable adjustment for covariates had limited influence on the association (OR, 1.03; 95% CI: 0.97–1.10). We observed no apparent dose–response relationship with ORs of 1.08 (95% CI: 1.02–1.15) for less than 1 year of use and 1.06 (95% CI: 0.97–1.16) for 5 to 10 years of use (Table 2). Likewise, modelling VKA use as a continuous variable resulted in an adjusted incremental OR for each 1–year increase in cumulative use of 1.00 (95% CI: 0.99–1.01, p–value for trend 0.98).

We identified no apparent effect measure modification by age, modified Charlson Comorbidity Index score, or clinical stage (Table 3). ORs seemed to differ slightly with calendar time ranging from 0.93 (95% CI: 0.82–1.06) for 2005–2008 and 1.11 (95% CI: 1.01–1.22) for 2012–2015.

The analyses combining VKA use with diagnoses of either atrial fibrillation/flutter (OR, 1.04; 95% CI: 0.96–1.12) or venous thromboembolism (OR, 1.11; 95% CI: 0.95–1.30) yielded neutral associations (Appendix A). The new–user analysis yielded an OR of 1.04 (95% CI: 0.97–1.12) and varying the lag–time from zero months to 60 months did not influence the observed associations (Appendix A).

Systematic review and meta–analysis

We screened 2,389 titles and abstracts and selected 29 studies for full–text screening (Appendix B). Of these, 6 studies were included.[4–9] We excluded 18 studies that did not report original data, e.g. reviews, comments, or conference proceedings, 4 studies that reported outcomes unrelated to prostate cancer risk, e.g. prostate cancer survival, and 1 study that reported a composite outcome of urogenital malignancies but not prostate cancer specifically.[30] We identified 2 eligible studies from cross–referencing[3,10] resulting in a total of 8 included studies; 7 observational studies[4–10] and 1 secondary analysis of clinical trial data.[3] In the secondary analysis of the clinical trial, patients were assigned to either 6 weeks (n=419) or 6 months (n=435) of VKA therapy after first

occurrence of venous thromboembolic disease and followed for occurrence of cancer for a mean of 8.1 years from recruitment.[3] In the 6 week arm, 17 patients were diagnosed with prostate cancer during follow–up compared to 9 patients in the 6 month arm yielding a RR of 0.51 (95% CI, 0.23–1.13). The observational studies comprised 4 cohort studies and 3 case–control studies. The studies varied substantially regarding patient selection, exposure definition, covariate adjustment, and outcome ascertainment. Key features of the included studies are described in Appendix B.

After exclusion of a study with a population partly shared by the present study,[5] a total of 8 studies were included in the meta-analysis. The reported effect estimates ranged from 0.51 (95% CI, 0.23–1.13) to 1.10 (95% CI, 0.94–1.40) with considerable across–study heterogeneity (I^2: 93.9%) (Figure 2). The pooled effect estimate using random effect methods was 0.86 (95% CI, 0.70–1.05). When stratifying by type of effect estimate, heterogeneity was smaller for studies reporting ORs or RRs (I^2: 64.2%) compared to studies reporting HRs or IRRs (I^2: 93.0%). The *post hoc* sensitivity analysis that excluded a study with high risk of immortal time bias[4] showed less heterogeneity for studies reporting rate ratios (I^2: 66.8%) as well as less overall heterogeneity (I^2: 58.4%) (Appendix B). The pooled effect estimate of this analysis was 0.94 (95% CI, 0.83–1.07).

DISCUSSION

We aimed to summarize existing evidence on the association between VKA use and prostate cancer risk and to examine whether VKA use was associated with prostate cancer risk in a nested case–control study including all Danish incident prostate cancer cases during 2005–2015. In our nested case–control study, we did not observe an association between VKA use and prostate cancer risk and we identified no apparent dose–response relationship in analyses with up to 10 or more years of VKA use. Overall, the reported associations between VKA use and prostate cancer risk remain conflicting and are derived from studies with a high degree of heterogeneity in several key features, including study design, exposure definition, confounder adjustment, and outcome assessment.

Strengths of this study include the nationwide approach using validated registry data which allowed for identification of virtually all men diagnosed with prostate cancer in the study period and a well–defined base population. Prostate cancer diagnoses were based on the Danish Cancer Registry known to have high accuracy and completeness with histological verification of all cases further enhancing case validity.[17] Furthermore, the use of the patient and prescription registries allowed us to account for several potential confounding factors and a minimum of ten years of exposure and covariate data was available for all study subjects.[16,18] Limitations include lack of information on lifestyle factors. However, only non–modifiable risk factors for prostate cancer (age, ethnicity, genetic predisposition) have been firmly established.[31] Assessment of drug use by prescription data is associated with some misclassification as in–hospital treatment is not available and non–compliance cannot be quantified. However, the primary care setting accounted for 98.2% of the total sales of VKAs in Denmark during 1996–2015.[32]

Patients treated with VKAs are monitored routinely and may be more likely to undergo screening for prostate cancer than non–users. This may lead to underestimation of a potential protective effect of VKAs against prostate cancer. We did not have data on prostate-specific antigen (PSA) measurements to account for screening frequency directly. However, when stratifying by clinical stage we found that ORs for VKA use associated with prostate cancer were similar for localized and advanced disease. Two previous studies included data on screening frequency and/or cancer grade. A Canadian case–control study reported that VKA users were screened more frequently in the 5 years prior to index date than non–users (60.8 % of VKA–users screened 4 times or more vs 39.2% among non–users).[9] However, adjusting for screening frequency did not lower the effect estimates for prostate cancer risk associated with VKA use compared to the unadjusted analyses. Further, ORs for ever–use of VKA was 0.80 (95% CI, 0.50–1.28) for low grade prostate cancer and 0.70 (95% CI, 0.37–1.34) for high grade prostate cancer similar to the OR for all cancers of 0.76 (95% CI, 0.50–1.16). In a cohort study of men randomized to screening with PSA measurements in 4 year intervals or to no intervention, the HRs associating current VKA use with prostate cancer was 1.01 (95% CI, 0.87–1.17) for men in the screening arm and 1.15 (95% CI, 1.02–1.30) for men in the control arm.[8] However, adjusting for screening arm in the multivariate analyses did not lower the HR compared to the age–adjusted HR. Similar HRs were reported for 2–5 years of VKA use associated with overall prostate cancer (1.05, 95% CI 0.90–1.22), high–grade cancer (1.10, 95% CI 0.88–1.37), and metastasized cancer 1.03 (95% CI, 0.56–1.89).

Another possible source of bias was confounding by indication, however, ORs were similar when we examined VKA use with atrial fibrillation/flutter as presumed indication compared to patients with thromboembolic disease as presumed indication. We addressed reverse causation bias (anticoagulant therapy prescribed for thromboembolic disease caused by a cancer not yet diagnosed) by introducing a lag–time of 2 years. In sensitivity analyses, varying the lag–time from 0 to 60 months did not alter the obtained ORs, indicating that reverse causation bias probably did not play a major role in this study.

We identified 8 studies in our systematic review of which 1 was a secondary analysis of clinical trial data.[3] As a randomized controlled trial, known and unknown confounders were initially accounted for by design. However, this balance likely deviated over the post–intervention follow–up period. Moreover, the study was not powered to detect differences in cancer incidence as reflected in the wide confidence interval (RR 0.51, 95% CI, 0.23–1.13). In 2007, a nested case–control study including 455 exposed prostate cancer cases reported an OR for ever–use of VKAs of 0.94 (95% CI: 0.85–1.03) and an OR for 4 years of use of 0.80 (95% CI: 0.65–0.99).[7] In a Danish case–control study from 2000–2009 including 463 exposed prostate cancer cases, we observed an OR for 3 or more years of VKA use of 0.86 (95% CI: 0.78–0.95).[5] The reduced risk estimate in the previous study could, at least partly, be due to changes in clinical diagnoses of prostate cancer and/or VKA use over time, as we did observe a tendency towards increasing ORs with time when stratifying by calendar period. In 2016, a cohort study with 1,210 exposed cases reported a HR of 1.18 (95% CI: 1.08–1.30) for current VKA use and 1.12 (95% CI: 0.96–1.31) for 2 to 5 years of use.[8] Most recently, a cohort study including 1,699 exposed cases reported an IRR of 0.69 (95% CI: 0.65–0.72) for 6 or more months of VKA use.[4] However, this study was prone to

immortal time bias as the exposure definition seemed to be dependent on future cancer status.[14,15] Because of the risk of bias pertaining specifically to this study,[4] we decided to perform a *post hoc* sensitivity analysis where this study was excluded from the meta–analysis.

We included 8 studies in the meta–analysis and found a pooled effect estimate of 0.86 (95% CI, 0.70–1.05). A major limitation of our meta–analysis was the considerable heterogeneity between studies. Some of this heterogeneity was explained by inherent differences between ORs, RRs– and rate–ratios but also by differences in study design, study populations, covariate adjustment, exposure definition, and outcome ascertainment. We used a random effects model to obtain a pooled estimate, however, the pooled estimate should be interpreted with caution given the considerable degree of heterogeneity.

In conclusion, evidence on VKA use and prostate cancer risk is conflicting. The available evidence does not indicate any major protective effect of VKA use against prostate cancer and we found no evidence of a reduced risk of prostate cancer associated with VKA use in our nationwide study on incident prostate cancers in Denmark 2005–2015. Several biological mechanisms for VKAs compatible with anti–neoplastic properties against prostate cancer have been proposed. However, given previous findings and the findings of the current study, it does not appear that these observations translate into any major protective effect of VKA use against prostate cancer in a clinical setting.

Declaration of interests

The authors report no conflicts of interest.

Author's contributions

Conception of the work: AP, KBK, SF
Literature search: KBK, PHJ
Data analysis: KBK, AP
Drafting the article: KBK, AP
Critical revision of the article: All authors
Final approval of the version to be published: All authors

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Figure legends

Figure 1: Selection of prostate cancer cases

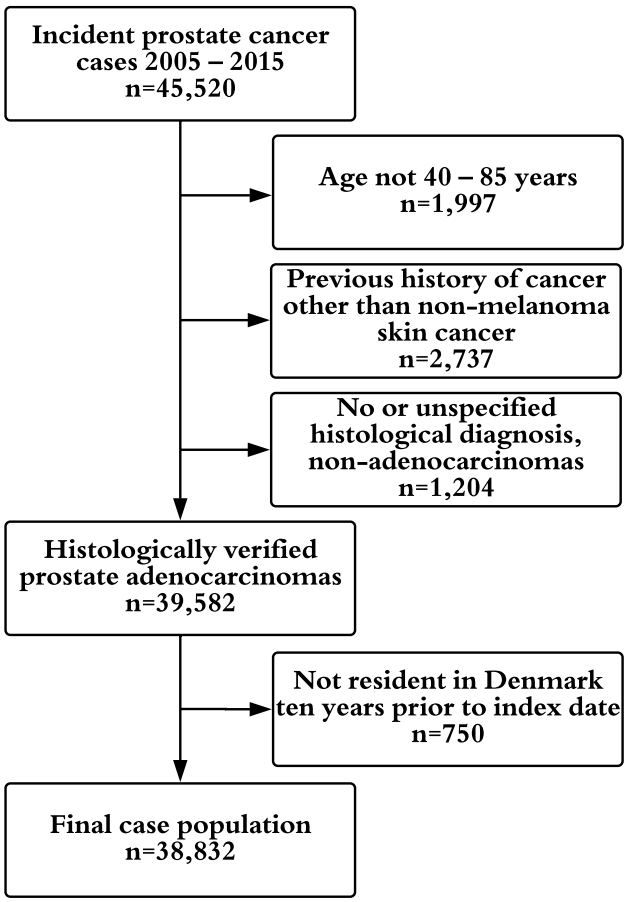
Figure 2: Forest plot of effect estimates with 95% confidence intervals for vitamin K antagonist use associated with prostate cancer stratified according to odds/risk ratios and hazard/incidence rate ratios

Table legends

Table 1: Characteristics of prostate cancer cases and controls

Table 2: Odds ratios for prostate cancer associated with vitamin K antagonist (VKA) use compared with non-use

Table 3: Odds ratios for prostate cancer associated with 3 or more years of vitamin K antagonist use compared with non-use specified by patient subgroups


Incident prostate cancer cases 2005 – 2015 n=45,520
Age not 40 – 85 years n=1,997
Previous history of cancer other than non-melanoma skin cancer n=2,737
No or unspecified histological diagnosis, non-adenocarcinomas n=1,204
Histologically verified prostate adenocarcinomas n=39,582
Not resident in Denmark ten years prior to index date n=750
Final case population n=38,832

Author (year)	Effect estimate (95% CI)	Weight
Odds/risk ratios		
Schulman (2000)	0.51 (0.23, 1.13)	4.6%
Tagalakis (2007)	0.80 (0.65, 0.99)	14.3%
Blanc-lapierre (2014)	0.80 (0.42, 1.52)	6.2%
Kristensen (2018)	1.03 (0.97, 1.10)	16.6%
Subtotal (I^2 = 64.2%, p = 0.039)	0.87 (0.69, 1.10)	41.8%
Hazard/incidence rate ratios		
Pengo (2011)	0.69 (0.50, 0.97)	11.6%
Ahern (2011)	1.10 (0.94, 1.40)	14.5%
Kinnunen (2016)	1.05 (0.90, 1.22)	15.4%
Haaland (2017)	0.69 (0.65, 0.72)	16.7%
Subtotal (I^2 = 93.0%, p = 0.000)	0.87 (0.65, 1.15)	58.3%
Overall (I^2 = 93.9%, p = 0.000)	0.86 (0.70, 1.05)	100%

Note: Weights are from random effects analysis

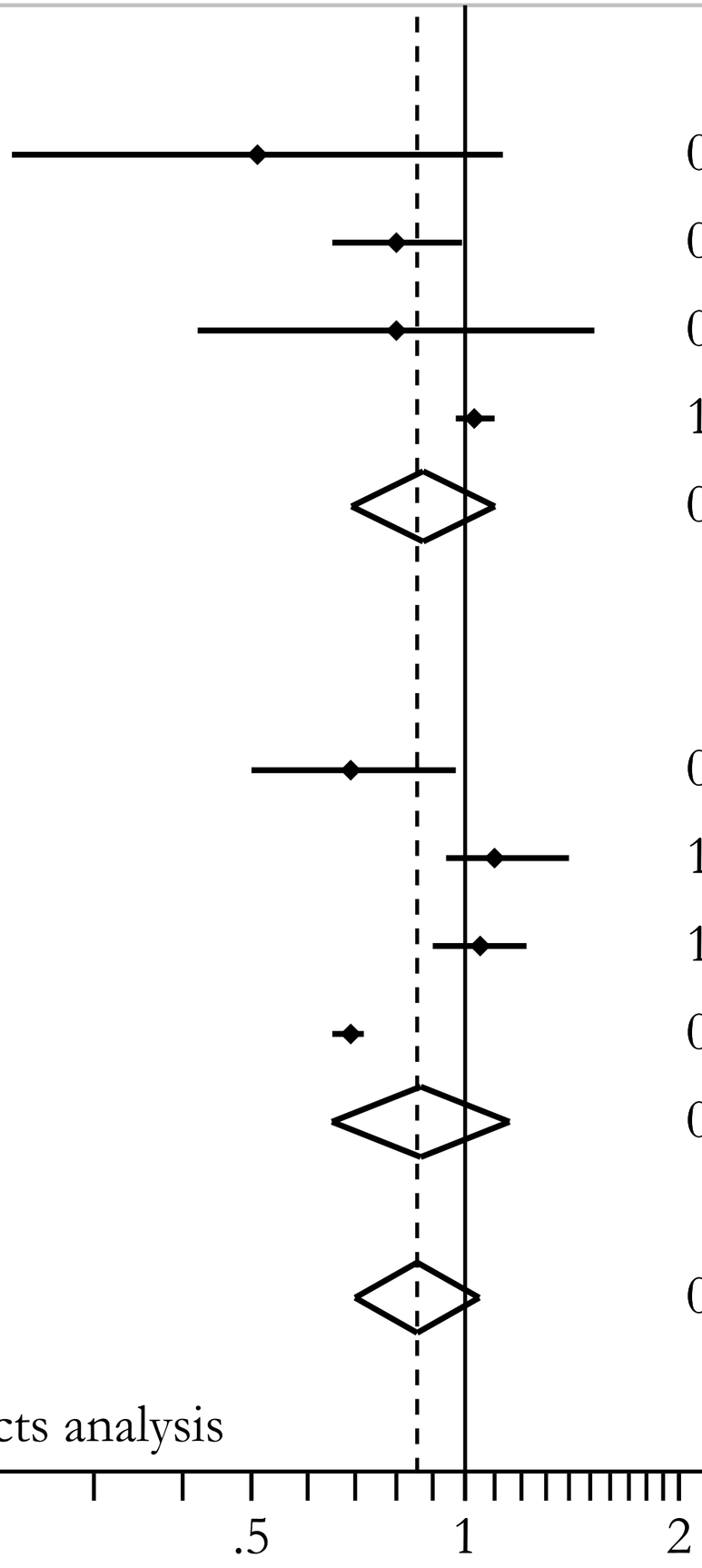


Table 1: Characteristics of prostate cancer cases and controls

Characteristic	Cases (n=38,832)	Controls (n=388,320)
Age		
Median (IQR, years)	69 (64–75)	69 (64–75)
<65 years	10,191 (26%)	101,910 (26%)
65–75 years	19,594 (50%)	195,940 (50%)
>75 years	9,047 (23%)	90,470 (23%)
Clinical stage (%)[1]		
Localized	23,868 (61%)	NA
Advanced	4,920 (13%)	NA
Unknown	10,044 (26%)	NA
Use of VKA (%)		
Non–use	35,912 (92%)	359,543 (93%)
Ever–use	2,920 (7.5%)	28,777 (7.4%)
Long–term use[2]	1,089 (2.8%)	10,803 (2.8%)
Modified Charlson Comorbidity Index[3] (%)		
0	26,166 (67%)	253,379 (65%)
1	7,323 (19%)	74,342 (19%)
2	2,995 (7.7%)	30,802 (7.9%)
≥3	2,348 (6.0%)	29,797 (7.7%)
Drug use (%)		
5α–reductase inhibitors	1,419 (3.7%)	12,498 (3.2%)
α–blockers	4,062 (10%)	32,081 (8.3%)
Statins	9,989 (26%)	102,701 (26%)
Acetylsalicylic acid	10,313 (27%)	106,521 (27%)
Non–aspirin NSAIDs	21,607 (56%)	205,167 (53%)
ACE inhibitors	9,308 (24%)	94,873 (24%)
ARBs	5,537 (14%)	51,941 (13%)
Medical history (%)		
Diabetes mellitus type 2	2,934 (7.6%)	37,941 (9.8%)
COPD	2,108 (5.4%)	22,190 (5.7%)
Ischemic heart disease or congestive heart failure	6,502 (17%)	68,389 (18%)
Conditions that might contraindicate VKA use	4,647 (12%)	51,493 (13%)
Highest achieved education, years (%)		
Short (7–10)	11,810 (30%)	130,485 (34%)
Medium (11–13)	16,709 (43%)	162,249 (42%)
Long (>13)	9,169 (24%)	78,304 (20%)
Unknown	1,144 (2.9%)	17,282 (4.5%)

[1]Defined using TNM codes, please see Appendix D for details
[2]Defined as three or more years of cumulative duration of use
[3]Cancer diagnoses was excluded from the Charlson Comorbidity Index
IQR: Interquartile range, VKA: Vitamin K antagonists, NSAID: Non–steroidal anti–inflammatory drugs, ACE: angiotensin–converting enzyme inhibitors, ARB: angiotensin II receptor blockers, COPD: Chronic obstructive pulmonary disease

Table 2: Odds ratios for prostate cancer associated with vitamin K antagonist (VKA) use compared with non-use

Exposure to VKA	Cases	Controls	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
Non–use	35,912	359,543	1.0 (ref.)	1.0 (ref.)
Ever–use	2,920	28,777	1.02 (0.98–1.06)	1.03 (0.99–1.07)
Long–term use[3]	1,089	10,803	1.01 (0.95–1.08)	1.03 (0.97–1.10)
Cumulative duration (years)				
<1	1,202	11,171	1.07 (1.01–1.14)	1.08 (1.02–1.15)
1–3	629	6,803	0.93 (0.86–1.01)	0.94 (0.86–1.02)
3–5	403	4,074	0.99 (0.89–1.10)	1.01 (0.91–1.12)
5–10	553	5,314	1.04 (0.95–1.14)	1.06 (0.97–1.16)
>10	133	1,415	0.94 (0.79–1.13)	0.98 (0.81–1.17)

[1]Adjusted for age, calendar time (by design)
[2]Adjusted for age, calendar time, and other covariates (see ´analytical variables´)
[3]Defined as three or more years of cumulative duration
OR: Odds ratio, CI: Confidence interval

Table 3: Odds ratios for prostate cancer associated with 3 or more years of vitamin K antagonist use compared with non-use specified by patient subgroups

Subgroup	Cases exposed/ unexposed	Controls exposed/ unexposed	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
Age				
<65 years	96/9,830	811/98,797	1.19 (0.96–1.48)	1.18 (0.95–1.47)
65–75 years	532/18,148	5,238/181,802	1.02 (0.93–1.12)	1.06 (0.97–1.16)
>75 years	461/7,934	4,754/78,944	0.97 (0.88–1.07)	0.98 (0.89–1.09)
Calendar period				
2005–2008	259/12,167	2,794/121,349	0.93 (0.81–1.05)	0.93 (0.82–1.06)
2009–2011	309/10,205	3,146/102,324	0.99 (0.88–1.12)	1.00 (0.89–1.13)
2012–2015	521/13,540	4,863/135,870	1.08 (0.98–1.18)	1.11 (1.01–1.22)
Clinical stage[3]				
Localized	573/22,267	5,931/222,269	0.97 (0.88–1.05)	1.00 (0.91–1.09)
Advanced	153/4,526	1,516/45,269	1.02 (0.86–1.21)	1.04 (0.87–1.24)
Unknown	363/9,119	3,356/92,005	1.09 (0.98–1.22)	1.09 (0.97–1.22)
Modified Charlson Comorbidity Index[4]				
0	392/24,990	3,484/243,206	1.08 (0.97–1.21)	1.05 (0.94–1.17)
1	314/6,522	3,061/66,318	0.99 (0.85–1.15)	1.00 (0.86–1.16)
2	181/2,538	1,860/26,154	1.14 (0.88–1.49)	1.25 (0.95–1.64)
≥3	202/1,862	2,398/23,865	1.12 (0.86–1.47)	1.13 (0.86–1.48)

[1]Adjusted for age, calendar time (by design)
[2]Adjusted for age, calendar time, and other covariates (see ´analytical variables´)
[3]Defined using TNM codes, please see Appendix D for details
[4]Cancer diagnoses was excluded from the Charlson Comorbidity Index
OR: Odds ratio, CI: Confidence interval, NSAID: Non–steroidal anti–inflammatory drugs

Use of vitamin K antagonists and risk of prostate cancer: Meta–analysis and nationwide case–control study

Kristensen et al.

SUPPLEMENTARY MATERIAL

APPENDIX A: Supplementary and sensitivity analyses

APPENDIX B: Systematic review

APPENDIX C: Danish nationwide registries

APPENDIX D: Definition of outcome and exposure variables

APPENDIX A: Supplementary and sensitivity analyses

Table a1: Odds ratios for prostate cancer associated with warfarin use compared with non-use

Exposure to warfarin	Cases	Controls	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
Non–use	35,912	359,543	1.0 (ref.)	1.0 (ref.)
Ever–use	2,718	26,714	1.02 (0.98–1.06)	1.03 (0.99–1.08)
Long–term use[3]	946	9,308	1.02 (0.95–1.09)	1.04 (0.97–1.11)
Cumulative duration (years)				
<1	1,151	10,729	1.07 (1.01–1.14)	1.08 (1.01–1.15)
1–3	621	6,677	0.93 (0.86–1.01)	0.94 (0.86–1.02)
3–5	387	3,957	0.98 (0.89–1.09)	1.00 (0.90–1.11)
5–10	475	4,497	1.06 (0.96–1.17)	1.08 (0.98–1.19)
>10	84	854	0.98 (0.78–1.23)	1.01 (0.81–1.27)

[1]Adjusted for age calendar time (by design)
[2]Adjusted for age, calendar time, and other covariates (see ´analytical variables´)
[3]Defined as three or more years of cumulative duration
OR: Odds ratio CI: Confidence interval

Table a2: Odds ratios for prostate cancer associated with phenprocoumon use compared with non-use

Exposure to phenprocoumon	Cases	Controls	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
Non–use	35,912	359,543	1.0 (ref.)	1.0 (ref.)
Ever–use	322	3,404	0.94 (0.84–1.06)	0.96 (0.86–1.08)
Long–term use[3]	150	1,624	0.92 (0.78–1.09)	0.94 (0.80–1.12)
Cumulative duration (years)				
<1	127	1,330	0.94 (0.78–1.13)	0.95 (0.79–1.14)
1–3	45	450	1.02 (0.75–1.39)	1.08 (0.79–1.47)
3–5	31	330	0.95 (0.66–1.38)	0.97 (0.67–1.41)
5–10	83	898	0.91 (0.73–1.15)	0.93 (0.74–1.17)
>10	36	396	0.91 (0.65–1.29)	0.96 (0.68–1.36)

[1]Adjusted for age, calendar time (by design)
[2]Adjusted for age, calendar time, and other covariates (see ´analytical variables´)
[3]Defined as three or more years of cumulative duration
OR: Odds ratio, CI: Confidence interval

Table a3: Odds ratios for prostate cancer associated with vitamin K antagonist use among patients with a diagnosis of atrial fibrillation or atrial flutter

Exposure to VKA	Cases	Controls	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
Non–use	35,912	359,543	1.0 (ref.)	1.0 (ref.)
Ever–use	1,642	16,130	1.02 (0.97–1.07)	1.03 (0.98–1.09)
Long–term use[3]	716	7,015	1.02 (0.94–1.10)	1.04 (0.96–1.12)
Cumulative duration (years)				
<1	479	4,508	1.06 (0.96–1.17)	1.07 (0.97–1.18)
1–3	447	4,607	0.98 (0.88–1.08)	0.98 (0.89–1.09)
3–5	273	2,841	0.96 (0.85–1.09)	0.97 (0.86–1.10)
5–10	374	3,428	1.09 (0.98–1.21)	1.11 (0.99–1.23)
>10	69	746	0.92 (0.72–1.18)	0.95 (0.74–1.22)

[1]Adjusted for age, calendar time (by design)
[2]Adjusted for age, calendar time, and other covariates (see ´analytical variables´)
[3]Defined as three or more years of cumulative duration
VKA: Vitamin K antagonists, OR: Odds ratio, CI: Confidence interval

Table a4: Odds ratios for prostate cancer associated with vitamin K antagonist use among patients with a diagnosis of deep venous thromboembolism or pulmonary embolism

Exposure to VKA	Cases	Controls	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
Non–use	35,912	359,543	1.0 (ref.)	1.0 (ref.)
Ever–use	652	6,211	1.05 (0.97–1.14)	1.06 (0.97–1.15)
Long–term use[3]	177	1,647	1.09 (0.93–1.28)	1.11 (0.95–1.30)
Cumulative duration (years)				
<1	370	3,411	1.09 (0.98–1.22)	1.09 (0.98–1.22)
1–3	105	1,153	0.91 (0.74–1.11)	0.90 (0.74–1.11)
3–5	66	537	1.26 (0.97–1.63)	1.28 (0.99–1.66)
5–10	84	795	1.07 (0.85–1.34)	1.09 (0.87–1.36)
>10	27	315	0.87 (0.59–1.30)	0.90 (0.61–1.34)

[1]Adjusted for age, calendar time (by design)
[2]Adjusted for age, calendar time, and other covariates (see ´analytical variables´)
[3]Defined as three or more years of cumulative duration
VKA: Vitamin K antagonists, OR: Odds ratio, CI: Confidence interval

Table a5: Odds ratios for prostate cancer associated with vitamin K antagonist use applying a new–user design excluding all study subjects who redeemed a prescription for any vitamin K antagonist during 1995–1996

Exposure to VKA	Cases	Controls	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
Non–use	35,912	359,543	1.0 (ref.)	1.0 (ref.)
Ever–use	2,584	25,148	1.03 (0.99–1.08)	1.04 (1.00–1.09)
Long–term use[3]	852	8,329	1.03 (0.95–1.10)	1.04 (0.97–1.12)
Cumulative duration (years)				
<1	1,128	10,328	1.09 (1.02–1.16)	1.10 (1.03–1.17)
1–3	604	6,491	0.94 (0.86–1.02)	0.94 (0.87–1.03)
3–5	370	3,760	0.99 (0.89–1.10)	1.00 (0.90–1.12)
5–10	429	3,991	1.07 (0.97–1.19)	1.09 (0.98–1.21)
>10	53	578	0.91 (0.69–1.21)	0.94 (0.70–1.24)

[1]Adjusted for age, calendar time (by design)
[2]Adjusted for age, calendar time, and other covariates (see ´analytical variables´)
[3]Defined as three or more years of cumulative duration
VKA: Vitamin K antagonist, OR: Odds ratio, CI: Confidence interval

Table a6: Effects of varying lag–time on the association between three or more years of vitamin K antagonist use and risk of prostate cancer

Lag–time (months)	Crude OR[1] (95 % CI)	Adjusted OR[2] (95 % CI)
0	1.00 (0.94–1.05)	1.01 (0.95–1.07)
6	1.00 (0.95–1.06)	1.02 (0.96–1.08)
12	1.00 (0.94–1.06)	1.02 (0.96–1.08)
18	1.01 (0.95–1.08)	1.03 (0.97–1.10)
24[3]	1.01 (0.95–1.08)	1.03 (0.97–1.10)
30	1.02 (0.95–1.09)	1.04 (0.97–1.11)
36	1.02 (0.95–1.09)	1.04 (0.97–1.11)
42	1.02 (0.95–1.09)	1.04 (0.97–1.12)
48	1.02 (0.94–1.10)	1.04 (0.96–1.12)
54	1.00 (0.93–1.09)	1.03 (0.95–1.11)
60	1.00 (0.92–1.09)	1.02 (0.94–1.11)

[1]Adjusted for age calendar time (by design)
[2]Adjusted for age calendar time and other covariates (see ´analytical variables´)
[3]Corresponds to the lag–time use in the main analyses
OR: Odds ratio, CI: Confidence interval

APPENDIX B: Systematic review

The databases Pubmed, Embase and Cochrane Library were searched from inception until April 11, 2018. Eligible studies included human subjects, presented empirical data on vitamin K antagonist (VKA) use, and reported associations between VKA use and prostate cancer. We imposed no restrictions regarding language or publication date. Abstracts, conference proceedings, and unpublished work were not included. Besides original studies, reviews were eligible for full–text screening to identify additional references. Titles and abstracts were screened by two medical doctors (KBK and PHJ) independently. Disagreements were resolved by consensus. We searched references in all publications selected for full–text screening to detect relevant publications not identified by our search strategy. Data extraction was performed by KBK and PHJ independently and included name of first author, year of publication, study design, study setting, study size, number of included exposed and unexposed cases, eligibility criteria, exposure definition, statistical methods, and effect estimates including 95% confidence intervals.

For all studies included in the systematic review and the present study, we presented effect estimates in a forest plot. We presented studies reporting relative risks (odds ratios or relative risks) and studies reporting rate ratios (hazard ratios or rate ratios) separately. For studies reporting estimates for more than one exposure duration, we chose the estimate closest to our main exposure of three or more years of VKA. We assessed heterogeneity using the Chi^2 test and the I^2 statistic.

Full search strategy:

Embase:

1 (prostate* or prostatic*).mp.
2 exp prostate cancer/
3 exp coumarin derivative/
4 anticoagulant agent/ or exp anisindione/ or exp antivitamin k/ or exp coumarin anticoagulant/ or exp fluindione/ or exp phenindione/
5 (anti vitamin k or antivitamins K or menadione antagonist* or vitamin k antagonist* or coumadin* or 4–hydroxycoumarin* or acenocoumarol or dicoumarol or ethyl biscoumacetate or warfarin or phenprocoumon or VKA).mp.
6 1 or 2
7 3 or 4 or 5
8 6 and 7

PubMed:

1 (prostate* or prostatic*)
2 prostatic neoplasm[MeSH Terms]
3 anticoagulants[MeSH Terms]
4 4–hydroxycoumarins[MeSH Terms]
5 ("anti vitamin k" OR "antivitamins K" OR menadione antagonist* OR vitamin k antagonist* OR coumadin* OR 4–hydroxycoumarin* OR acenocoumarol OR dicoumarol OR ethyl biscoumacetate OR warfarin OR phenprocoumon OR VKA)
6 1 or 2
7 3 or 4 or 5
8 6 and 7

Cochrane Clinical Library:

1 prostate* or prostatic*:ti,ab,kw
2 MeSH descriptor: [Prostatic Neoplasms]
3 MeSH descriptor: [Anticoagulants]
4 MeSH descriptor: [4–Hydroxycoumarins]
5 "anti vitamin k" or "antivitamins K" or menadione antagonist* or vitamin k antagonist* or coumadin* or 4–hydroxycoumarin* or acenocoumarol or dicoumarol or ethyl biscoumacetate or warfarin or phenprocoumon or VKA:ti,ab,kw
6 1 or 2
7 3 or 4 or 5
8 6 and 7

Figure b1: Flowchart of studies included in the systematic review

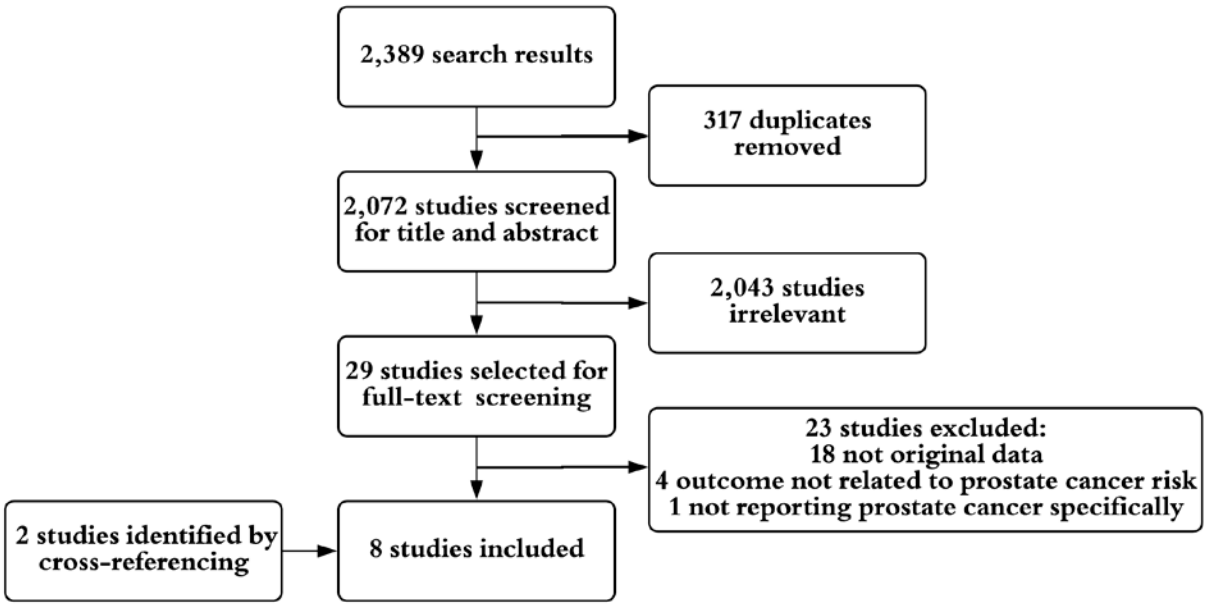


Figure b2: Forest plot of effect estimates with 95% confidence intervals for vitamin K antagonist use associated with prostate cancer stratified according to odds/risk ratios and hazard/incidence rate ratios excluding a study with high risk of bias

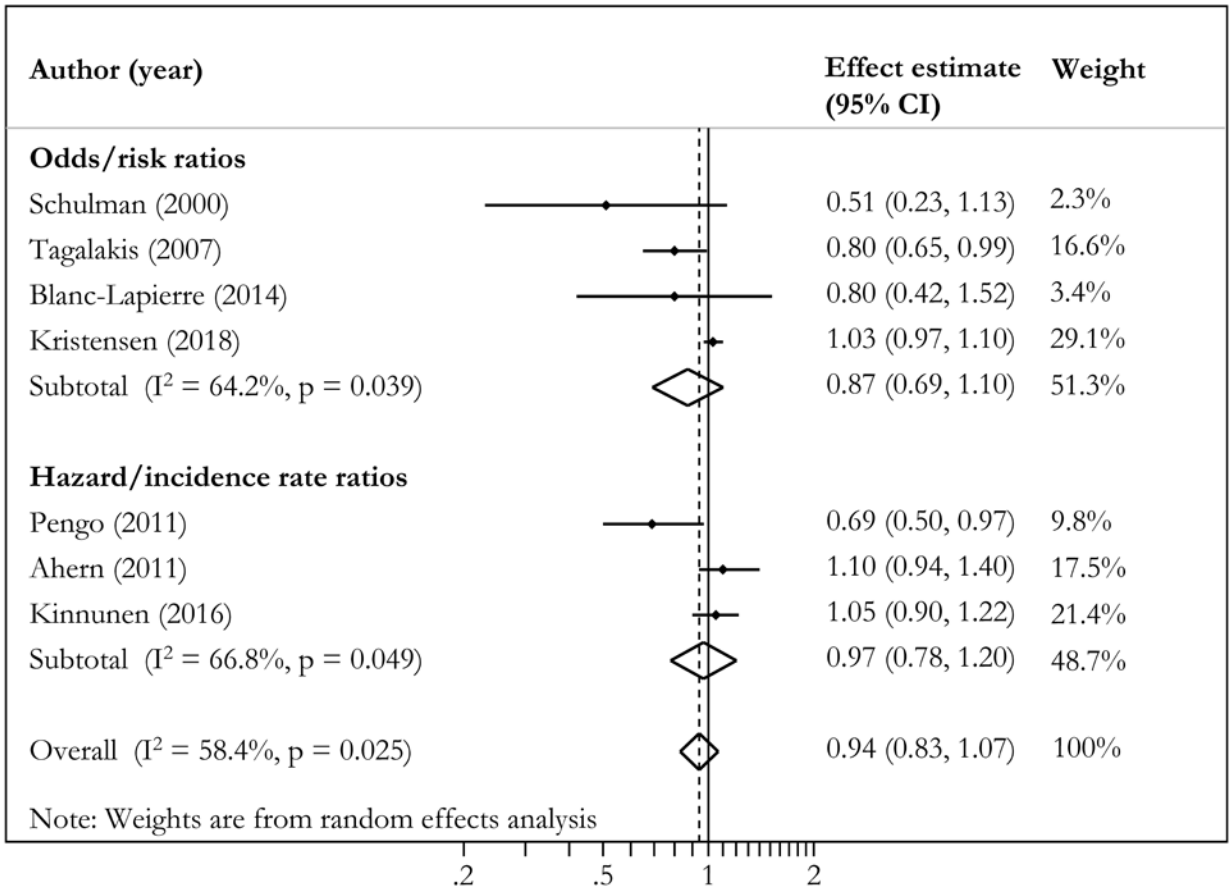


Table b1: Summary of included studies evaluating the risk of prostate cancer in patients treated with vitamin K antagonists

Author, year	Study design and setting	Number of cases (total/exposed)	Study population	Exposure	Statistical methods	Effect estimate (95 % CI)	Comments
Haaland et al, 2017[1]	Cohort, Norway, 2006–2012	25,917/1,699	Residents in Norway during the study period and born in 1924–1954.	Warfarin.	Maentel–Haenzel method.	IRR ≥6 months of use: 0.69 (0.65–0.72) adj.	2–year lag–time. Duration of VKA defined as the time between first and last prescription. Adjusted for sex and age.
Kinnunen et al, 2016[2]	Cohort, Finland, 1996–2012	6,537/1,210	Men enrolled in a RCT with s–PSA screening as intervention during 1996–1999. Age 55–67 years at enrollment. No history of prostate cancer.	Warfarin.	Cox proportional hazard regression.	HR current use: 1.18 (1.08–1.30) age 1.11 (1.01–1.22) adj. HR 2–5 years of use: 1.12 (0.96–1.31) age 1.05 (0.90–1.22) adj.	Lag–time only included as sensitivity analysis (data not provided). Adjusted for age, drug–use, and screening trial arm.
Blanc–Lapierre et al, 2014[3]	CC, Canada, 2005–2009	1,581/42	Age ≤75 years at diagnosis. Controls frequency matched by age.	Warfarin.	Unconditional logistic regression.	OR ever–use: 0.70 (0.47–1.05) crude 0.76 (0.50–1.16) adj. OR >3 years of use: 0.71 (0.38–1.33) crude 0.80 (0.42–1.52) adj.	1–year lag–time. Data collection retrospectively by means of patient interviews. Adjusted for age, ethnicity, education, family history of prostate cancer, prostate cancer screening frequency, body mass index, specific comorbid conditions, and drug–use.
Pottegård et al, 2013[4]	CC, Denmark, 2000–2009	22,163/463	No history of cancer except non–melanoma skin cancer. Controls risk–set matched by age and gender.	Warfarin and phenprocoumon.	Conditional logistic regression.	OR >3 years of use 0.85 (0.77–0.94) crude 0.86 (0.78–0.95) adj.	1–year lag–time. Adjusted for age and sex (by design), drug-use, specific comorbid conditions, and modified Charlson Comorbidity Index score.
Pengo et al., 2011[5]	Cohort, Italy, 1996–2007	1,029/36	Age 65–90 years, residents in Health Area 16, Veneto during 1996–2002. No history of cancer, superficial thrombophlebitis, or venous thromboembolism 2 years prior to enrolment.	Warfarin and acenocoumarol.	Cox proportional hazard regression.	HR ≥3 years of use: 0.66 (0.47–0.91) crude 0.69 (0.50–0.97) adj.	No lag–time. Exposure ascertainment only prior to enrolment, i.e. exposure during follow–up was not evaluated. Adjusted for age, sex, and time to event.
Ahern et al, 2011[6]	Cohort, Denmark, 1989–2006	1,229/120	Patients receiving a replacement heart valve in Denmark 1989–2006. No history of cancer. Unexposed subjects matched by age and sex.	Heart valve replacement used as instrumental variable for VKA therapy.	Poisson regression.	IRR heart valve replacement: 1.1 (0.94–1.4) crude IRR ever–use of VKA (validation subset): 1.3 (1.0–1.7) crude	1–year lag–time. Heart valve replacement used as instrumental variable. In a validation subset, ever-use of VKA was used as exposure in analyses adjusted for age and sex (by design).
Tagalakis et al, 2007[7]	CC, Canada, 1981–2002	11,502/455	Age ≥50 years, no history of cancer except skin cancer and in–situ carcinoma of the cervix.	Warfarin.	Conditional logistic regression.	OR ever–use: 0.94 (0.85–1.03) adj. OR 4–years of use: 0.80 (0.65–0.99) adj.	1–year lag–time. Adjusted for age, sex, time of diagnosis (by design) and drug use.
Schulman et al., 2000[8]	RCT, Sweden, 1988–1997	(Cases/controls) 6–week arm: 17/402 6–month arm: 9/426	Age ≥15 years with a first episode of DVT/PE. No history of cancer. Randomized to VKA treatment for either 6 weeks or 6 months and followed up with regards to incident cancers for a mean of 8.1 years.	Warfarin or dicoumarol.	RR calculated from summary statistics reported in the publication.*	RR 6–month arm vs. 6–week arm: 0.51 (0.23–1.13)	Secondary analysis of a RCT.

*Effect estimate not stated explicitly for prostate cancer. We calculated relative risks with exact binomial 95% confidence intervals using cumulative incidence proportions given in the paper.
Adj: adjusted effect estimates, CC: Case–control study, RCT: Randomized controlled trial, PSA: Prostate specific antigen, VKA: Vitamin K antagonists, HR: Hazard ratio, OR: Odds ratio, IRR: Incidence rate ratio, RR: Risk ratio, DVT: Deep venous thrombosis, PE: Pulmonary embolism,

References:

1 Haaland GS, Falk RS, Straume O, Lorens JB. Association of Warfarin Use With Lower Overall Cancer Incidence Among Patients Older Than 50 Years. *JAMA Intern Med* 2017; **177**: 1774–80.

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3 Blanc–Lapierre A, Weiss D, Parent M–É. Use of oral anticoagulants and risk of prostate cancer: a population–based case–control study in Montreal, Canada. *Cancer Causes Control* 2014; **25**: 1159–66.

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5 Pengo V, Noventa F, Denas G, *et al*. Long–term use of vitamin K antagonists and incidence of cancer: a population–based study. *Blood* 2011; **117**: 1707–9.

6 Ahern TP, Pedersen L, Sværke C, Rothman KJ, Sørensen HT, Lash TL. The Association Between Vitamin K Antagonist Therapy and Site–specific Cancer Incidence Estimated by Using Heart Valve Replacement as an Instrumental Variable. *Am J Epidemiol* 2011; **174**: 1382–90.

7 Tagalakis V, Tamim H, Blostein M, Collet J–P, Hanley JA, Kahn SR. Use of warfarin and risk of urogenital cancer: a population–based, nested case–control study. *Lancet Oncol* 2007; **8**: 395–402.

8 Schulman S, Lindmarker P. Incidence of Cancer after Prophylaxis with Warfarin against Recurrent Venous Thromboembolism. *N Engl J Med* 2000; **342**: 1953–8.

APPENDIX C: Danish nationwide registries

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and provides accurate and almost complete records of cancer cases in Denmark.[1] Cancer diagnoses are coded according to the International Classification of Diseases Tenth Revision (ICD–10), and the ICD for Oncology, Third Revision (ICD–O–3) for Topography and Morphology.

The Danish National Prescription Registry contains data on all prescription drugs redeemed by Danish residents since 1995.[2] Data include the type of drug, date of filling, and quantity. The dosing information and the indication for prescribing are not available, and no information is available on drugs used at the hospital level. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the World Health Organization, and the quantity dispensed for each prescription is described by the number and strength of the pharmaceutical entities (e.g., tablets), as well as defined daily doses (DDD).

The Danish National Patient Registry contains nationwide data on all non–psychiatric hospital admissions since 1977 and on ambulatory hospital contacts and psychiatric admissions since 1995.[3] Discharge/contact diagnoses have been coded according to ICD–8 from 1977 to 1993 and ICD–10 since 1994.

Statistics Denmark is a governmental institution that collects and processes information for a variety of statistical and scientific purposes, such as education and income.[4,5] The Population Education Registry contains information on nearly all adult Danish residents and provides the highest completed level of education, e.g., defined as the longest duration of schooling.[4]

The Danish Civil Registration System contains data on addresses, migration, and deaths. This system allowed us to extract population controls and to keep track of all subjects during the study period.[6]

References:

1 Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health* 2011; **39**: 42–5.

2 Pottegård A, Schmidt SAJ, Wallach–Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol* 2017; 46: 798–798f.

3 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**: 30–3.

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5 Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health* 2011; **39**: 103–5.

6 Thygesen LC, Daasnes C, Thaulow I, Brønnum–Hansen H. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. *Scand J Public Health* 2011; **39**: 12–6.

APPENDIX D: Definition of outcome and exposure variables

Cancer definitions		
Prostate cancer	*ICD–10*	C61.9
Adenocarcinoma	*ICD–O–3*	8140/3
Clinical stage	*TNM classification*	Localized: T1–4,x; N0; M0 T1–2; N0; Mx T1–2; Nx; M0,x Advanced: T1–4,x; N1; M0 T1–4,x; N0; M1 T1–4,x; N1; M1 T1–4,x; Nx; M1 Unknown: T3–4,x; Nx; M0,x T3–4,x; N0, Mx T1–4,x; N1; Mx
Other cancers (exclusion criteria)	*ICD–10*	C00–97 (except C44)
Use of vitamin K antagonists		
Vitamin K antagonists	*ATC*	B01AA
Warfarin	*ATC*	B01AA03
Phenprocoumon	*ATC*	B01AA04
Drug use, covariate (≥2 filled prescriptions prior to index date)		
5α–reductase inhibitors	*ATC*	G04CB, D11AX10
α–blockers	*ATC*	G04CA
Statins	*ATC*	C10AA, C10BA02
Acetylsalicylic acid	*ATC*	B01AC06, B01AC30, N02BA01, N02BA51
Non–aspirin non–steroidal anti–inflammatory drugs	*ATC*	M01A, excluding M01AX
Angiotensin–converting enzyme inhibitors	*ATC*	C09A, C09B
Angiotensin II receptor blockers	*ATC*	C09C, C09D
Comorbidity, specific diagnoses (based on history of primary or secondary discharge/ambulatory diagnoses and/or two or more redeemed prescriptions)		
Diabetes mellitus type II	*ICD–8*	250.00, 250.08, 250.09
	ICD–10	E11
	ATC	A10B
Chronic obstructive pulmonary disease	*ICD–8*	490.00, 491.00, 491.01, 491.03, 491.04, 491.08, 491.09, 492
	ICD–10	J42–J44
	ATC	R03BB
Ischemic heart disease	*ICD–8*	410–414
	ICD–10	I20–I25
Congestive heart failure	*ICD–8*	427.09, 427.10, 427.11, 427.19, 428.99, 782.49
	ICD–10	I11.0, I13.0, I13.2, I42, I43, I50, I51.7
Heavy alcohol consumption	*ICD–8*	291, 303, 425.5, 537.5, 571.0, 571.1, 571.2, 571.3, 577.10
	ICD–10	E244, E529A, G31.2, G62.1, G72.1, I42.6, F10, K29.2, K70, K86.0, T519, Z502, Z714, Z72.1
	ATC	N07BB
Gastrointestinal bleeding	*ICD–8*	456.01, 530.91, 530.98, 535.01, 531.90, 531.92, 531.95, 532.90, 533.90, 534.90,

		569.15, 784.59, 785.79
	ICD–10	I85.0, K22.6, K25, K26, K27, K28, K29.0, K625, K92.0, K92.1, K92.2
Moderate to severe liver disease	*ICD–8*	070.00, 070.02, 070.04, 070.06, 070.08, 273.39, 456.0, 570, 571, 573
	ICD–10	B15.0, B16.0, B16.2, B19.0, D68.4C, K70, K71, K72, K73, K74, K75.2, K75.3, K75.8, K75.9, K76.6–9, I85, I98.2
Moderate to severe kidney disease	*ICD–8*	250.02, 403, 404, 582, 593.19, 593.20
	ICD–10	E10.2, E11.2, E12.2, E13.2, E14.2, I12–13 (÷I12.9), N01, N03, N08.3, N08.5, N11.8C, N14, N15.0, N16, N18 (÷N181), N19, N26, P96.0, Q60.1, Q60.2, Z99.2
Intracranial hemorrhages	*ICD–8*	430, 431
	ICD–10	I60–62, I690–692, S064–066
Presumed indication for VKA treatment		
Atrial fibrillation/flutter	*ICD–8*	427.93, 427.94
	ICD–10	I48
Venous thromboembolism (deep venous thrombosis or pulmonary embolism)	*ICD–8*	450.99, 451.00, 451.08, 451.09, 451.90, 451.92, 451.99
	ICD–10	I26, I801–803, I808, I809
Socioeconomic status (education)		
Educational level	*Duration of education*	
Basic		10 years
Short/medium		11–13 years
Long		>13 years

ICD–8: International Classification of Diseases Eight Revision, ICD–10: International Classification of Diseases Tenth Revision (ICD–10), ICD–O–3: International Classification of Diseases for Oncology, Third Revision for Topography and Morphology, ATC: Anatomical Therapeutic Chemical Classification System