Observational Study/Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	PRostAte Cancer vTe In SwEden: epidemiology and anticoagulation treatment of VTE **PRACTISE**
Report version and date	V1.0, 23 AUG 2021
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS29848
Active substance	B01A F DIRECT FACTOR Xa INHIBITORS (B01A F01 RIVAROXABAN, B01A F02 APIXABAN, B01A E07 DABIGATRAN ETEXILATE)
Medicinal product	Xarelto (Rivaroxaban), Eliquis (Apixaban), Dabigatran etexilate (Pradaxa)
Product reference	EU/1/08/472/001-041
Procedure number	EMEA/H/C/00944
Study Initiator and Funder	Bayer AG, Müllerstrasse 173, 13353 Berlin
Research question and objectives	This study aimed to identify the current landscape of VTE events and its treatment in patients with prostate cancer in Sweden. **Primary objective** Among <u>all men with prostate cancer</u>: • to describe socio-demographic and clinical characteristics at the date of an incident prostate cancer diagnosis. • to estimate the occurrence of cancer-related VTE.

	• to describe the cancer therapies used in men with prostate cancer during the initial time after diagnosis. Among men with prostate cancer and a first cancer-related VTE event: • to characterise the long-term anticoagulation treatment including choice of drug and duration of treatment. • to estimate the occurrence of recurrent VTE events by long-term anticoagulation treatment (LMWH, vitamin K antagonist [VKA] or DOAC) and its estimated duration (≤3 months, 3–6 months, ≥6 months). • to determine the time between a first cancer-related VTE event and a recurrent VTE event. • to estimate the incidence rate of post-VTE bleeding events leading to hospitalisation, and mortality, by anticoagulation treatment. **Secondary objective**: Among men without prostate cancer in the general population: • to describe their socio- demographic and clinical characteristics at the time of inclusion into the study. • to estimate the occurrence of VTE events.
Country(-ies) of study	Sweden
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Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen
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Confidentiality statement:

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1. Abstract

Acronym/Title	PRostAte Cancer vTe In SwEden: epidemiology and anticoagulation treatment of VTE **PRACTISE**
Report version and date **Authors**	V1.0, 23 AUG 2021 PPD Bayer AG PPD Bayer AB PPD
Keywords	Anticoagulants; Bleeding; Prostate Cancer; Venous Thromboembolism
Rationale and background	Venous thromboembolism is a leading cause of death in patients with cancer, being second only to death from the cancer itself. Prostate cancer is the most commonly diagnosed in middle aged and older men worldwide, and 5-year relative survival is high (~82% to 99%). The high number of men living with prostate cancer underscores the importance of understanding the magnitude of VTE in this population in order to prevent morbidity and mortality. Population-based data suggests that the risk of VTE is 2 to 3-fold higher in men with prostate cancer than among men of similar age without cancer. However, there are few reported estimates on this topic, and there is therefore a need to obtain comparable contemporary data to gain further knowledge in this field. Owing to the high prevalence of prostate cancer, VTE is commonly seen among affected men in clinical practice, hence the importance of prescribing effective agents for treatment and secondary prophylaxis. For the majority of patients with cancer-associated thrombosis, clinical guidelines recommend long-term anticoagulant therapy – usually with low-molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC) – to help prevent VTE recurrence. Some guidelines advocate at least 3 months of anticoagulant therapy, and others recommend 6 months or a minimum of 6 months, and there is currently no consensus regarding therapy beyond 6 months. Determining the optimal duration of anticoagulant therapy requires balancing the reduced risk of VTE recurrence against the increased risk of

	bleeding, which is also raised in patients with cancer. Whether prolonged anticoagulation beyond 6 months affords a favourable benefit–risk ratio is a question that remains unanswered.
Research question and objectives	This study aimed to identify the current landscape of VTE events and its treatment in patients with prostate cancer in Sweden. **Primary objective** Among <u>all men with prostate cancer</u>: • to describe socio-demographic and clinical characteristics at the date of an incident prostate cancer diagnosis. • to estimate the occurrence of cancer-related VTE. • to describe the cancer therapies used in men with prostate cancer during the initial time after diagnosis. Among <u>men with prostate cancer and a first cancer-related VTE event</u>: • to characterise the long-term anticoagulation treatment including choice of drug and duration of treatment. • to estimate the occurrence of recurrent VTE events by long-term anticoagulation treatment (LMWH, vitamin K antagonist [VKA] or DOAC) and its estimated duration (≤3 months, 3–6 months, ≥6 months). • to determine the time between a first cancer-related VTE event and a recurrent VTE event. • to estimate the incidence rate of post-VTE bleeding events leading to hospitalisation, and mortality, by anticoagulation treatment. **Secondary objective**: Among <u>men without prostate cancer in the general population</u>: • to describe their socio- demographic and clinical characteristics at the time of inclusion into the study. • to estimate the occurrence of VTE events.
Study design	Retrospective cohort study that used prospectively collected registry data from men with prostate cancer and men without prostate cancer in the general population of Sweden.

Setting	This study was set in the general male population of Sweden between 2007 and 2017.
Subjects and study size, including dropouts	**Prostate cancer cohort**: N=92,105 **Subcohort**: of the prostate cancer cohort: 1413 men with prostate cancer and VTE plus an outpatient anticoagulant prescription following prostate cancer diagnosis **Comparison cohort of men without prostate cancer**: N=466,241
Variables and data sources	**VTE:** Venous thromboembolism events occurring during the initial follow-up (index VTE events) were categorised as deep vein thrombosis (DVT; ICD-10 I801-802) or pulmonary embolism (PE; I26) or other (ICD-10 I809 or I82). **Anticoagulant treatment for VTE:** this was determined in the four weeks after the index (first) VTE date, and was categorised as either parenteral anticoagulant, VKA or DOAC. Anticoagulant duration was categorised as ≤3 months, >3 to 6 months, >6 to 9 months and >9 months irrespective of anticoagulant type. **Covariates:** age, education level and marital status, comorbidities including cardiovascular disease (CVD) and risk factors for CVD, medications including those for CVD and its risk factors, Charlson Comorbidity Index. **Outcomes following the index VTE:** recurrent VTE (categorised as DVT or PE, as described above), and major bleeding (intracranial, gastrointestinal, and urogenital)
Results	2955 men with prostate cancer and 9774 men in the comparison cohort experienced a first VTE during a median of 4.5 years' follow-up. DVT accounted for 52% of VTE cases in both cohorts. Median time from start of follow-up to VTE was 2.5 years (interquartile range [IQR], 0.9–4.7) in the prostate cancer cohort, and 2.9 years (IQR, 1.3–5.0) in the comparison cohort. Crude incidence rates of VTE per 1000 person-years (95% CI) were 6.54 (6.31–6.78) in the prostate cancer cohort (N=2955 events) and 4.27 (4.18–4.35) in the comparison cohort (N=9774 events). The incidence proportion ratio (95% CI) decreased from 2.53 (2.26–2.83) at 6 months to 1.59 (1.52–1.67) at 5 years' follow-

	up. Adjusted hazard ratios (HRs) (95% CI) were 1.48 (1.39–1.57) for DVT, and 1.47 (1.39–1.56) for PE after adjustment for patient characteristics. The outpatient anticoagulation prescribed was parenteral (64%), direct oral anticoagulant (31%), and vitamin K antagonist (20%). Median duration of anticoagulation was 7 months. Adjusted HRs (95% CI) for off-treatment recurrent PE were 0.32 (0.09–1.15) for >3–6 months' duration, 0.21 (0.06–0.69) for >6–9 months and 0.16 (0.05–0.55) for >9 months; corresponding HRs for DVT were 0.67 (0.27–1.66), 0.80 (0.31–2.07), and 1.19 (0.47–3.02). One-year incidence proportions of intracranial, gastrointestinal and urogenital bleeding were 0.9%, 1.7%, 3.0% during treatment, and 1.2%, 0.9%, 1.6% after treatment cessation.
Discussion	This study provides useful information on the benefits and risks of anticoagulation therapy beyond 6 months' duration for VTE in men with prostate cancer, on which there is currently no consensus. The results suggest the greatest potential for the reducing VTE recurrence occurs with >9 months treatment for PE and >3–6 months for DVT. Risks of major bleeding were low overall and did not differ substantially for events that occurred during anticoagulation and those that occurred after anticoagulation cessation (off-treatment events), particularly for intracranial bleeding. Physicians treating men with prostate cancer should be aware of the marked increase in VTE risk in these men, particularly in the first 6 months following cancer diagnosis, to help ensure timely VTE diagnosis. Further epidemiological studies are needed to confirm/refute our findings and help guide clinical decision making in routine practice. Other beneficial areas for further research in this field include the effects of specific anticoagulants on relevant clinical outcomes and gaining a better understanding of the prescribing choices.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen
Names and affiliations of principal investigators	PPD PPD

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2. List of abbreviations

ACE	Angiotensin converting enzyme
ATC	Anatomical Therapeutic Chemical (Classification System)
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
HR	Hazard ratio
IQR	Inter-quartile range
LMWH	Low-molecular weight heparin
ICD	International Classification of Diseases
MAH	Marketing Authorization Holder
N/A	Not Applicable
NOS	Not otherwise specified
NSAID	Non-steroidal anti-inflammatory drug
OS	Observational Study
PASS	Post-Authorization Safety Study
PCBaSe	Prostate Cancer dataBase Sweden
PE	Pulmonary embolism
PSA	Prostate-specific antigen
SD	Standard deviation
TNM	Tumour-node metastasis
TIA	Transient ischaemic attack
VKA	Vitamin K antagonist
VTE	Venous Thromboembolism

3. Investigators

Principle Investigator: PPD

Other Investigators: PPD

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Role:	OS Safety Lead
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Medical Expert
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Role:	OS Data Analyst/Statistician
Name:	PPD
Role:	OS Epidemiologist
Name:	PPD

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	30 May 2019	30 May 2019	–
End of data collection	30 Nov 2020	20 Nov 2020	–
Registration in the EU PAS register	27 May 2019	27 May 2019	–
Final report of study results	31 Aug 2021	23 Aug 2021	–

6. Rationale and background

Individuals with cancer have a higher risk of developing venous thromboembolism (VTE) than those without cancer, the magnitude of which varies by cancer type and disease stage.(1, 2) Venous thromboembolism is a leading cause of death in patients with cancer, being second only to death from the cancer itself.(1) In addition to being a leading cause of death in patients with cancer, VTE adversely affects patients' quality of life, bringing anxiety about the risk of recurrence, and potentially interrupting cancer treatment.(2-4)

Several factors contribute to an increased hypercoaguable state in patients with cancer, including treatment-related factors such as cancer therapy and surgery, and patient-related factors such as age, obesity, history of VTE and other comorbidities.(1-3) Prostate cancer is the most commonly diagnosed cancer in middle aged and older men worldwide,(5) and 5-year relative survival is high, with reported rates of 82% in Europe(6) and 99% in the United States.(7) The high number of men living with prostate cancer underscores the importance of understanding the magnitude of VTE in this population in order to prevent morbidity and mortality.

Although prostate cancer is associated with a low risk of VTE relative to other cancer types, population-based data suggests that the risk of VTE is 2 to 3-fold higher in men with prostate cancer than among men of similar age without cancer.(8-10) In our previous study published more than a decade ago, we compared observed rates of thromboembolic events that led to hospitalisation in men with prostate cancer with expected rates in the total Swedish male population for the period 1997 to 2007.(8) Other studies in this field,(9-11) including another previous study of ours that focused on surgical interventions,(11) have been conducted during comparable time periods. However, there are few other reported estimates on this topic, and there is therefore a need to obtain comparable contemporary data to gain further knowledge in this field.

Owing to the high prevalence of prostate cancer, VTE is commonly seen among affected men in clinical practice,(1) hence the importance of prescribing effective agents for treatment and secondary prophylaxis. Decisions about treating the VTE can be challenging, as risks of recurrent VTE and anticoagulant-associated bleeding are higher in patients with cancer. For the majority of patients with cancer-associated thrombosis, clinical guidelines recommend long-term anticoagulant therapy – usually with low-molecular weight heparin (LMWH) or a direct oral anticoagulant (DOAC) – to

help prevent VTE recurrence. Some guidelines advocate at least 3 months of anticoagulant therapy,(12) and others recommend 6 months(13) or a minimum of 6 months,(14, 15) and there is currently no consensus regarding therapy beyond 6 months. The pivotal clinical trials that shaped guideline development were limited to 3–6 months duration,(4) and observational data on the topic are limited. Determining the optimal duration of anticoagulant therapy requires balancing the reduced risk of VTE recurrence against the increased risk of bleeding, which is also raised in patients with cancer. Whether prolonged anticoagulation beyond 6 months affords a favourable benefit–risk ratio is a question that remains unanswered. Yet this is important because ageing populations with increasing life expectancy means that more men will be living with prostate cancer and at risk of VTE for many years.

As men with prostate cancer are very heterogeneous in their clinical characteristics, it would be extremely difficult to conduct a trial addressing all questions of interest. An observational study based on data from clinical practice is the most suitable way to provide a deeper understanding of the consequences of current anticoagulation approaches in the treatment of VTE in men with prostate cancer. This includes how the choice of a regimen influences risk of thrombotic and bleeding events. The generated evidence will support physicians in their treatment decisions.

7. Research question and objectives

This study aimed to identify the current landscape of VTE events and its treatment in patients with prostate cancer in Sweden.

7.1 Primary objective

Among all men with prostate cancer:

- to describe socio-demographic and clinical characteristics at the date of an incident prostate cancer diagnosis.
- to estimate the occurrence of cancer-related VTE.
- to describe the cancer therapies used in men with prostate cancer during the initial time after diagnosis.

Among men with prostate cancer and a first cancer-related VTE event:

- to characterise the long-term anticoagulation treatment including choice of drug and duration of treatment.
- to estimate the occurrence of recurrent VTE events by long-term anticoagulation treatment (LMWH, vitamin K antagonist [VKA] or DOAC) and its estimated duration (≤3 months, 3–6 months, ≥6 months).
- to determine the time between a first cancer-related VTE event and a recurrent VTE event.
- to estimate the incidence rate of post-VTE bleeding events leading to hospitalisation, and mortality, by anticoagulation treatment.

7.2 Secondary objective

Among men without prostate cancer in the general population:

- to describe their socio- demographic and clinical characteristics at the time of inclusion into the study.
- to estimate the occurrence of VTE events.

8. Amendments and updates

None.

9. Research methods

9.1 Study design

This was a retrospective cohort study that used prospectively collected registry data from men with prostate cancer and men without prostate cancer in the general population of Sweden. An overview of the study design is illustrated in **Figure 1**, and further details are provided in the following sections.

9.2 Setting

This study was set in the general male population of Sweden between 2007 and 2017.

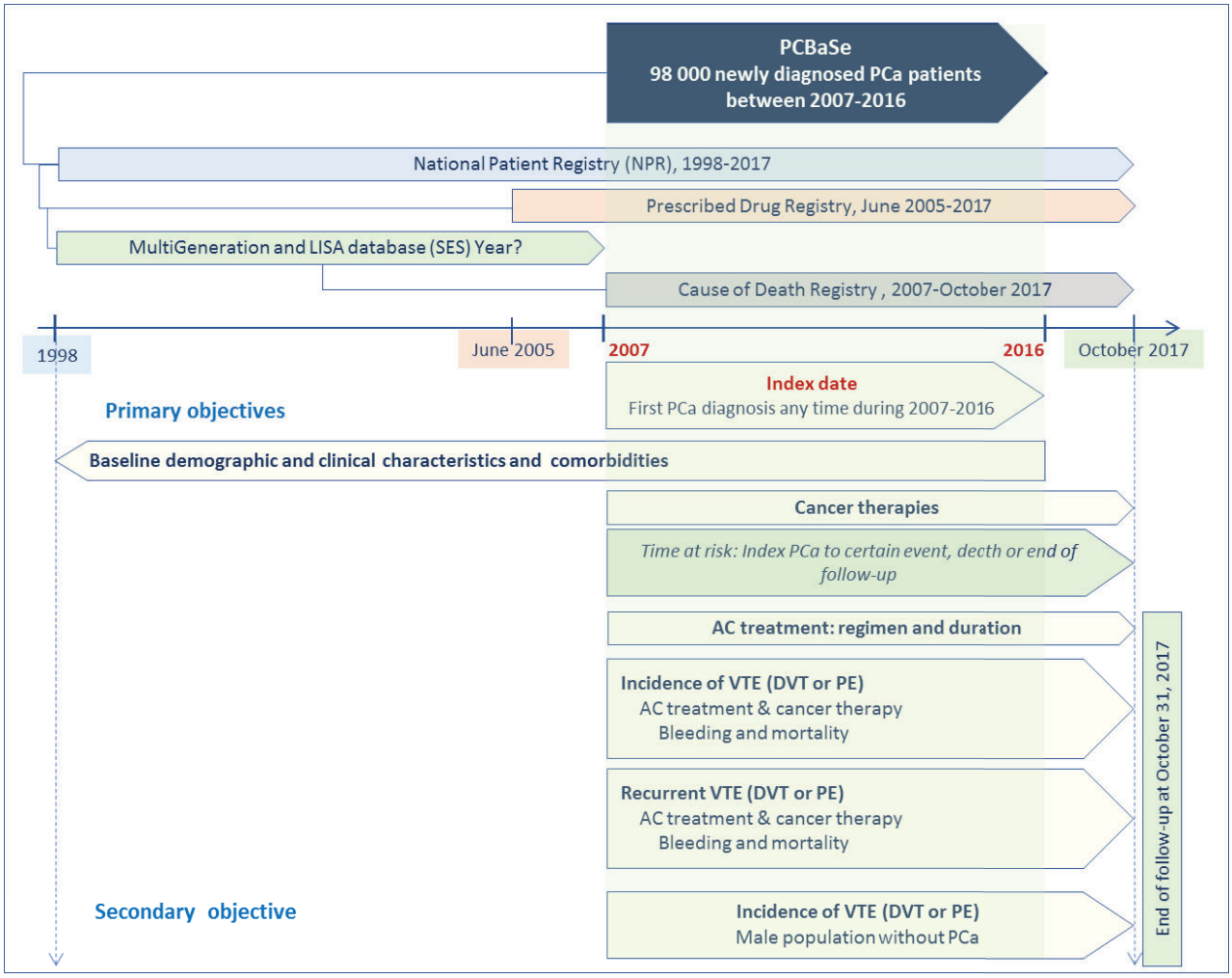


Figure 1. Overview of the study methodology in PCBaSe.

9.3 Subjects

Men with prostate cancer and comparison cohort of men without prostate cancer

All men in PCBaSe (see **Section 9.5** for details) with a first diagnosis of prostate cancer between 2007 and 2016 were included. Men with T stage 0 or X and those with a previous record of VTE (recorded as either primary or secondary diagnosis) were excluded. For each man with prostate cancer, their matched men from the general population were identified from PCBaSe (N=466,241; comparison cohort) (see **Section 9.5** for further details). The date of prostate cancer diagnosis was the index date for each case and for their respective matched men in the comparison cohort.

Follow-up

The two study cohorts were followed from the index date until the first inpatient/outpatient VTE (primary diagnosis; index VTE) recorded in the National Patient Registry, death or the end of the study period (December 2017), whichever came first. Men in the comparison cohort who were diagnosed with prostate cancer during follow-up were censored at the date of diagnosis (if this occurred earlier than other censoring variables)(16) and subsequently joined the prostate cancer cohort.

Subcohort of men with prostate cancer and VTE during follow-up (recurrent VTE and major bleeding analysis)

From within the cohort of men with prostate cancer and a first VTE during follow-up (index VTE), a subcohort of men with at least 1 year of observational follow-up, and with a prescription for an anticoagulant in the Prescribed Drug Registry any time after the index VTE were identified. Men with either a past record of VTE or atrial fibrillation and those with a prescription for oral anticoagulant treatment any time before the index VTE, or for parental anticoagulant treatment in the 2 weeks before the index VTE (see **Supplementary Table 1** for codes) were excluded. Only men whose index VTE was recorded between 2013 and 2017 were retained, to cover the period from which DOACs were approved in Sweden.

9.4 Variables

Venous thromboembolism events occurring during follow-up were categorised as deep vein thrombosis (DVT; ICD-10 I801-802) or pulmonary embolism (PE; I26) or other (ICD-10 I809 or I82)

Covariates

For all men, we obtained information on age, education level and marital status, comorbidities including cardiovascular disease (CVD) and risk factors for CVD, as a main or secondary diagnosis any time before the index date, medications including those for CVD and its risk factors (from the National Drug Prescription Register in the 120 days before the index date). We also calculated Charlson Comorbidity Index as a marker of general health. For men in the prostate cancer cohort,

we extracted data on tumour-node-metastasis (TNM) stage, prostate cancer risk category, and prostate-specific antigen (PSA) level at cancer diagnosis.

Anticoagulant treatment for VTE

The type of anticoagulant(s) dispensed during the four weeks after the index VTE date was categorised as either parenteral anticoagulant, VKA or DOAC; men could have been prescribed more than one type of anticoagulant during this period, either as a bridge between parenteral and oral agents or because they switched between drug class. The duration of an individual prescription was calculated based on all dispensed prescriptions any time after index VTE using information on pack size and the numbers of packs dispensed. Total anticoagulant exposure was determined by summing the lengths of individual consecutive prescriptions. A gap of more than 30% of supplied days was considered to represent the cessation of anticoagulant exposure. To check the validity of the computer algorithm used to determine treatment exposure, prescription start/end dates records for each patient were manually reviewed by one investigator (BF). Exposure duration was categorised as ≤3 months, >3 to 6 months, >6 to 9 months and >9 months irrespective of anticoagulant type.

Co-variates

We obtained information on sociodemographics (including educational and marital status), comorbidities and comedications before the index VTE. The Charlson comorbidity index was determined at the time of prostate cancer diagnosis.

Recurrent VTE

To identify cases of off-treatment recurrent VTE, men were followed from the date that their anticoagulation treatment ended until the earliest of the following: the first subsequent entry of a VTE diagnosis as the main diagnosis, death, the date of emigration, or the end of available follow-up (data lock point) in PCBaSe (31 December 2017). For this analysis, the study population was restricted to men whose treatment cessation occurred at least 1-year before the data-lock date to ensure adequate potential follow-up time to identify VTE events.

Major bleeding

We performed separate follow-ups to identify cases of major bleeding as the main cause of hospitalisation, one for each bleeding type (intracranial, gastrointestinal, urogenital or 'other bleeding' (see **Supplementary Table 2** for codes). Men were followed from the start of anticoagulation therapy until the earliest of the following: the first subsequent entry of the major bleeding, death, the date of emigration, or the end of follow-up. It was noted whether the bleeding event occurred on-treatment or off-treatment (after ending of the anticoagulant treatment).

9.5 Data sources and measurement

This study used data from the Prostate Cancer data Base Sweden (PCBaSe) 4.0. This is a research database comprising data from the National Prostate Cancer Register (NPCR) of Sweden and several other national healthcare registers.(17, 18) Notification of cancer has been mandatory in all Nordic counties for since 1958 and the NPCR has held information on 98% of incident cases of prostate cancer in the country since 1998. PCBaSe contains information on 180,000 men diagnosed with prostate cancer between 1998 and 2016.

In this study, we used data in PCBaSe from the NPCR and the following registers: the National Patient Register (hospital inpatient/outpatient diagnoses coded using International Classification of Diseases (ICD–10) codes, with a look-back period to 1998), the National Prescribed Drug Register (medication dispensed from Swedish pharmacies), the Cause of Death Register, the Swedish longitudinal integration database for health insurance and labour market Register (LISA) with sociodemographic data, and the Registries of Immigration and Emigration.

For each man with prostate cancer in PCBaSe, the database also includes a set of randomly selected men from the general population, matched 5:1 by year of birth and geographical region of residence, who were alive and free of prostate cancer at the end of the year of diagnosis for their matched case.(16)

9.6 Bias

All individuals meeting the inclusion criteria (see **Section 9.3**) were included in the study thereby minimizing selection bias.

9.7 Study size

All individuals meeting the study inclusion criteria were included in the study (see **Section 9.3**).

9.8 Data transformation

Data were extracted from PCBaSe by members of the PCBaSe team according to routine procedures by the database owners. Internal data analyst at Bayer had access to the anonymised data to carry out the analysis. Only outputs in the form of figures and tables, and no data on individual patients, were exported from the server.

9.9 Statistical methods

We calculated crude incidence proportions as the number of men with a first VTE during follow-up divided by the total number of men at the start of follow-up. We calculated incidence rates per 1000 person-years using the same numerator divided by the total person-years of follow-up. Incidence proportion ratios (IPRs) comparing incidence proportions in the prostate cancer and comparison cohorts were calculated along with 95% confidence intervals (CIs) based on the Binomial distribution. Crude incidence rate ratios (IRRs) were calculated with 95% CIs based on the Poisson

distribution. We used Cox proportional hazard regression to calculate hazard ratios (HRs) comparing the incidence rate of VTE between the prostate cancer and comparison cohorts, adjusted for confounders. Potential confounders were added sequentially retaining those that were deemed, on a subjective basis, to not materially change the HR. Variables included in the final model were age, atrial fibrillation, chronic heart failure, hypertension, diabetes, cancer, myocardial infarction and ischaemic stroke.

9.9.1 Main summary measures

Men with prostate cancer and men without prostate cancer

Characteristics of the men with prostate cancer and the men without prostate cancer at the start of follow-up were described using frequency counts and percentages for categorical variables, and with medians with interquartile range (IQR) for continuous variables.

Men with prostate cancer and a first VTE during follow-up prescribed anticoagulation

Characteristics of the 510 men with a first VTE and treated with anticoagulation during the recurrent VTE follow-up (including sociodemographics, clinical characteristics and duration of anticoagulant exposure) were also described using these summary measures.

One-year incidence proportions of recurrent VTE and major bleeding were calculated. Incidence rates of recurrent VTE and major bleeding over the whole period of observation were also calculated. For off-treatment recurrent VTE, hazard ratios (HRs) with 95% CIs were calculated to evaluate the association with duration of anticoagulant exposure.

9.9.2 Main statistical methods

One-year incidence proportions of recurrent VTE and major bleeding were calculated by dividing the number of incident cases during the first year of follow-up by the number of men at the start of follow-up (patients were not censored at death or low-to follow-up), with 95% confidence intervals computed using the binominal distribution. For major bleeding, incidence proportion estimates were also stratified by type of bleeding.

Incidence rates of recurrent VTE and major bleeding over the whole period of observation were calculated as the number of VTE/major bleeding events divided by the total person-years of follow-up, with 95% CIs determined using the Poisson distribution.

Cox proportional hazards regression models was used to compute the HRs with 95% CIs for associations between duration of anticoagulant exposure and off-treatment recurrent VTE adjusted for confounders and using ≤3 months duration as the reference group. Age-adjusted HRs are presented in the results based on the finding that no additional variable made any notable change to the risk estimate when included into the model.

SAS version 9.4 was used for all analyses.

9.9.3 Missing values

Men with missing data on educational level and marital status were placed in a category 'missing' for the respective variable. Missing data was not applicable for other variables in the study.

9.9.4 Sensitivity analyses

None.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

The PCBaSe investigators participating in the study were required to archive documents and data sets, statistical programs, and study-relevant documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It was recommended that documents are stored for a retention period of at least 15 years, unless local regulations define otherwise.

10. Results

10.1 Participants

A total of 92,105 men with prostate cancer and 466,241 matched men without prostate cancer were identified after applying the exclusion criteria (**Figure 2**).

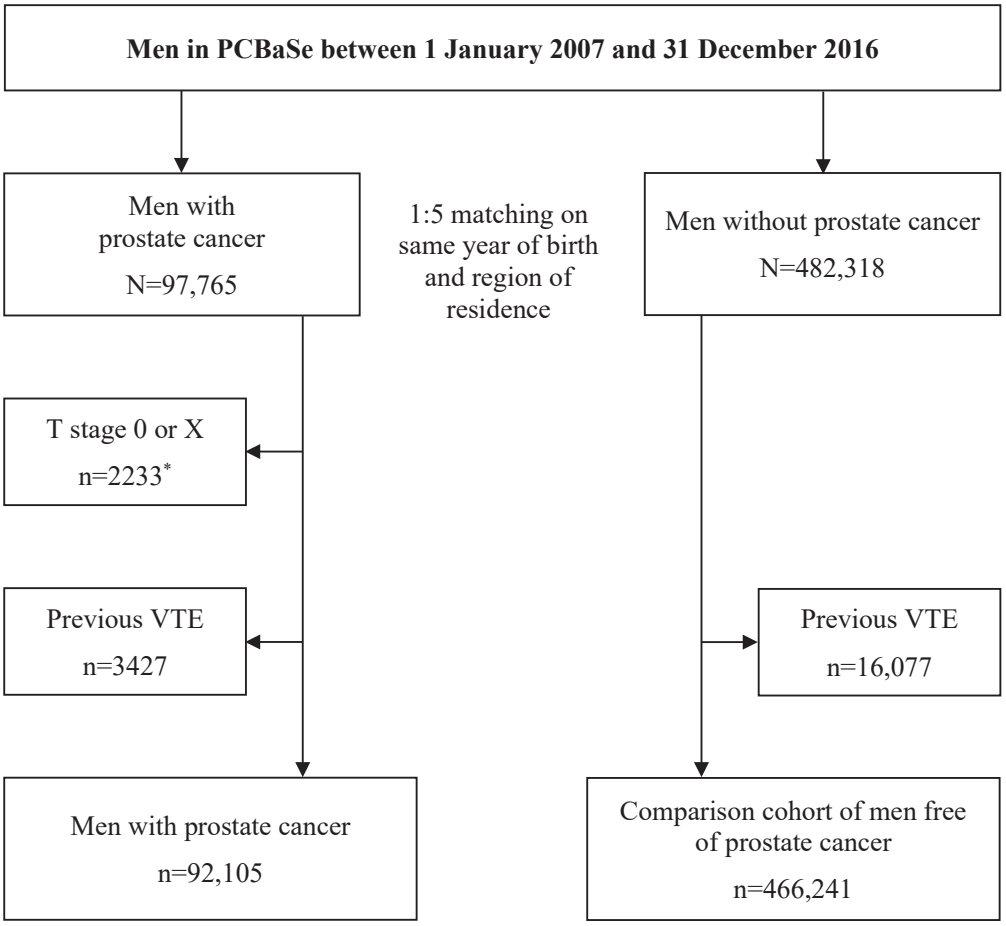


Figure 2. Flowchart depicting the identification of the two study cohorts: men with prostate cancer and men without prostate cancer.

In the analysis of anticoagulation use, among men with prostate cancer and first VTE during follow-up, a total of 1413 men were identified with a first VTE between 2013 and 2017 plus a prescription for an anticoagulation any time after the VTE (**Figure 3**) and their anticoagulation use was described. In the analysis of recurrent VTE and major bleeding, a total of 510 men had ≥365 days of follow-up after the end of first continuous episode of anticoagulant use and were included in these analyses (**Figure 3**).

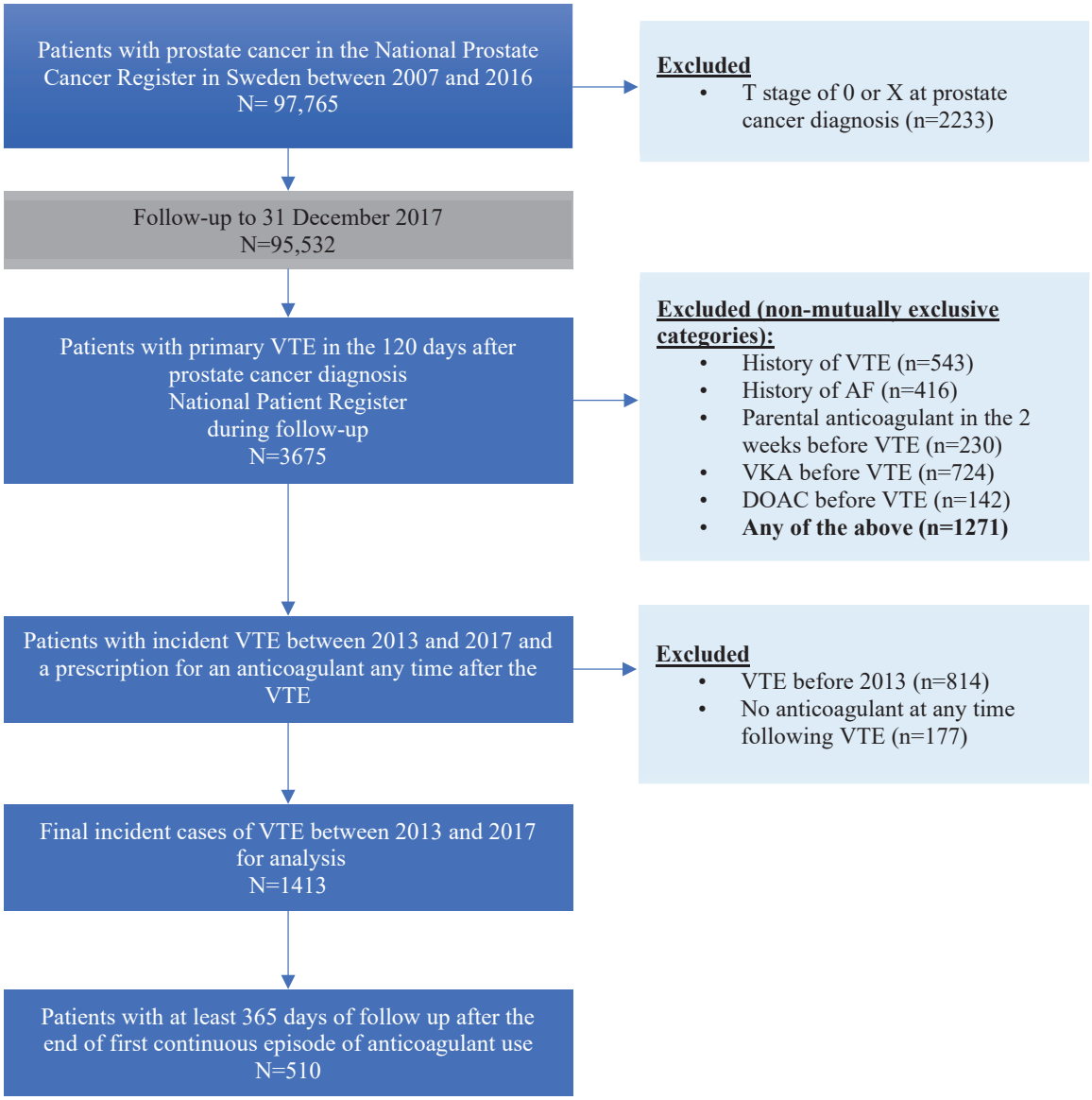


Figure 3. Identification of men with prostate cancer and VTE treated with anticoagulant therapy.
*ICD-10 codes I82, I801, I802, I803, I809 as main diagnosis.

10.2 Descriptive data

Descriptive data are part of the main results (see **Section 10.4**)

10.3 Outcome data

Outcome data are part of the main results (see **Section 10.4**)

10.4 Main results

10.4.1 Characteristics of men with prostate cancer and men without prostate cancer.

Apart from previous cancer, which was more common in the prostate cancer cohort than in the comparison cohort (13% vs. 7%), patient characteristics were broadly similar between the two cohorts (**Table 2**).

Over half of men (52%) in the prostate cancer cohort had T2 stage disease, 17% had metastases, and median PSA was 9 mg/l (IQR 5–20) at the time of the cancer diagnosis (**Supplementary Table 3**).

Table 2. Baseline characteristics of men with prostate cancer and randomly selected men free of prostate cancer from the general population matched on birth year and geographical region in PCBaSe 4.0.

	Men with prostate cancer N=92,105	**Men without prostate cancer N=466,241**
	n (%)	**n (%)**
Age (years), median (IQR)	PPD	
Educational level		
Low (<9 years)	30,977 (33.6)	166,338 (35.7)
Middle (9–12 years)	36,472 (39.6)	182,575 (39.2)
High (>12 years, university)	23,955 (26.0)	110,787 (23.8)
Missing	701 (0.8)	6541 (1.4)
Marital status		
Married	60,323 (65.5)	286,441 (61.4)
Unmarried	10,714 (11.6)	66,971 (14.4)
Divorced	13,859 (15)	76,631 (16.4)
Widower	7169 (7.8)	36,186 (7.8)
Missing	40 (0.04)	12 (0)
Charlson Comorbidity Index		
0	70,303 (76.3)	341,974 (73.3)
1	11,835 (12.8)	63,565 (13.6)
2	5485 (6)	31,184 (6.7)
3	2213 (2.4)	13,938 (3.0)
≥4	2269 (2.5)	15,580 (3.3)
Mean (SD)	0.5 (1.1)	0.5 (1.2)

	Men with prostate cancer N=92,105	Men without prostate cancer N=466,241
	n (%)	n (%)
Comorbidities[a]		
Hypertension	22,932 (24.9)	116,690 (25)
Valvular heart disease	2795 (3.0)	15,379 (3.3)
Coronary artery disease	13,163 (14.3)	74,009 (15.9)
Angina pectoris	9154 (9.9)	50,474 (10.8)
Myocardial infarction	7633 (8.3)	44,622 (9.6)
Peripheral arterial disease	2989 (3.2)	18,516 (4.0)
Atrial fibrillation	8628 (9.4)	47,540 (10.2)
Chronic heart failure	4642 (5.0)	30,040 (6.4)
Peripheral systemic embolism	261 (0.3)	1570 (0.3)
Haemorrhagic stroke	1077 (1.2)	6647 (1.4)
Ischaemic stroke	4298 (4.7)	26,604 (5.7)
Stroke NOS	1231 (1.3)	8425 (1.8)
TIA	2990 (3.2)	15,721 (3.4)
Diabetes mellitus	7897 (8.6)	51,139 (11)
Hyperlipidemia	574 (9.3)	46,220 (9.9)
Cancer	12,261 (13.3)	30,942 (6.6)
Obstructive sleep apnoea	1370 (1.5)	7396 (1.6)
COPD	2599 (2.8)	15,250 (3.3)
Bleedings		
Intracranial	1293 (1.4)	7900 (1.7)
Upper gastrointestinal	1904 (2.1)	9787 (2.1)
Lower gastrointestinal	626 (0.7)	3061 (0.7)
Urogenital	4251 (4.6)	15,829 (3.4)
Medications[b]		
Antiarrhythmics	463 (0.5)	2270 (0.5)
Statins	22,355 (24.3)	115,697 (24.8)
Cardiovascular drugs[c]	82,267 (89.3)	414,211 (88.8)
Antidiabetics	8364 (9.1)	53,108 (11.4)
NSAIDs	10,875 (11.8)	35,896 (7.7)
Antiplatelet drugs acetyl acid	19,870 (21.6)	105,195 (22.6)
Vitamin K antagonists	4516 (4.9)	24,725 (5.3)
DOACs	604 (0.7)	3320 (0.7)
Parenteral anticoagulant	2073 (2.3)	3346 (0.7)

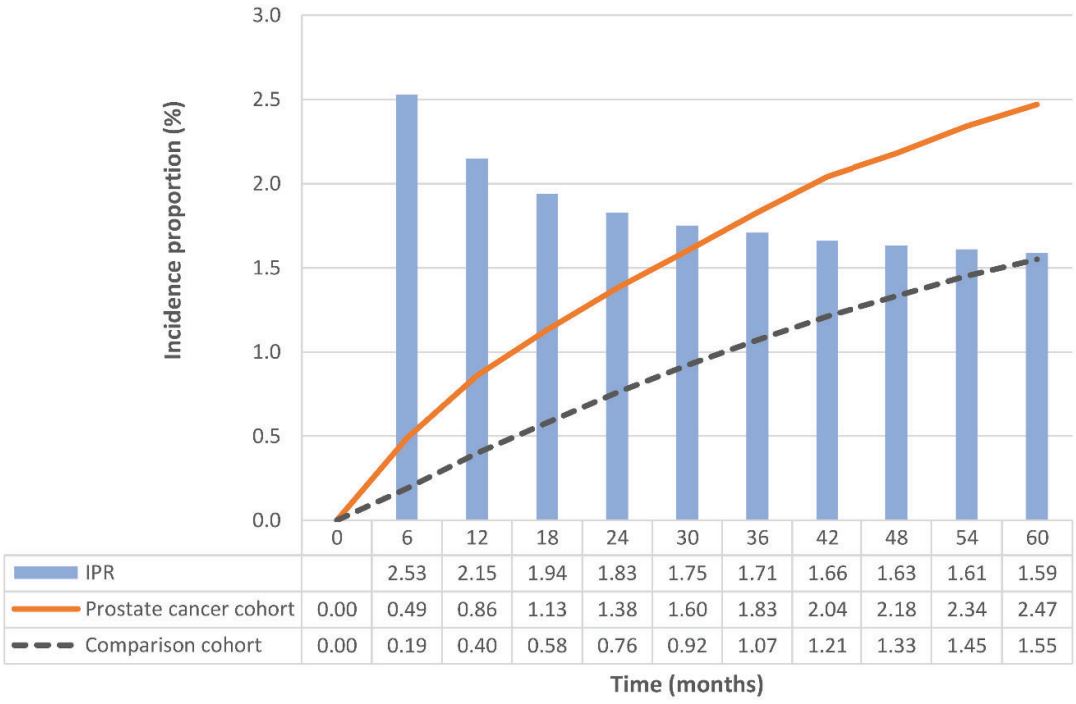
Data are n (%) unless otherwise stated.
[a]Comorbidities were identified through ICD-10 codes in National Patient Register as a main or secondary diagnosis any time before the index date.
[b]Medications were identified by ATC Classification codes in the Drug Prescription Register during the 120 days before the index date.
[c]Includes beta-blockers, calcium-channel blockers, ACE inhibitors, angiotensin II receptor blockers, and diuretics.

10.4.2 Incidence of VTE

A total of 2955 men with prostate cancer and 9774 men in the comparison cohort experienced a first VTE during a median of 4.5 years' follow-up (SD ±2.9 years); DVT accounted for 52% of VTE cases in both cohorts. Median time from the index date to VTE was 2.5 years (IQR, 0.9–4.7) in the prostate cancer cohort, and 2.9 years (IQR, 1.3–5.0) in the comparison cohort.

Incidence proportions

Incidence proportions over 60 months' follow-up increased in both cohorts over time, reflecting increased VTE incidence with age irrespective of cancer status (**Figure 4**; **Supplementary Table 4**). For example, incidence proportions in the prostate cancer and comparison cohorts, respectively, were 0.5% and 0.2% at 6 months, 1.4% and 0.8% at 2 years, and 2.5% and 1.6% at 5 years. Incidence proportion ratios decreased from 2.53 (95% CI: 2.26–2.83) at 6 months to 1.59 (95% CI: 1.52–1.67) at 5 years' follow-up (see **Supplementary Figure 1** and **Supplementary Figure 2**, and **Supplementary Table 5** **and** **Supplementary Table 6** for corresponding incidences for DVT and PE separately).



	0	6	12	18	24	30	36	42	48	54	60
IPR		2.53	2.15	1.94	1.83	1.75	1.71	1.66	1.63	1.61	1.59
Prostate cancer cohort	0.00	0.49	0.86	1.13	1.38	1.60	1.83	2.04	2.18	2.34	2.47
Comparison cohort	0.00	0.19	0.40	0.58	0.76	0.92	1.07	1.21	1.33	1.45	1.55

Figure 4. Incidence proportion (%) and incidence proportion ratio of first VTE in men with prostate cancer and men without prostate cancer.

Crude incidence rates per 1000 person-years

Crude incidence rates of VTE were 6.54 per 1000 person-years (95% CI: 6.31–6.78) in men with prostate cancer, and 4.27 per 1000 person-years (95% CI: 4.18–4.35) in the comparison cohort; the absolute risk difference was 2.27 per 1000 person-years (Table 3). The crude IRR (prostate cancer cohort vs. comparison cohort) was 1.53 (95% CI: 1.47–1.60), and the adjusted HR was 1.47 (95% CI: 1.41–1.53). Crude incidence rates increased with age, and crude IRRs decreased with age (Supplementary Table 7). Findings for DVT and PE separately were only very minimally different: adjusted HR for DVT was 1.47 (95% CI: 1.39–1.56), and adjusted HR for PE was 1.48 (95% CI: 1.39–1.57).

Table 3. Incidence rates of first VTE (overall and stratified by DVT and PE) per 1000 person-years (95% CI) in men with prostate cancer and men without prostate cancer, IRRs and HRs (95% CI) comparing rates in the two cohorts.

	Men with prostate cancer N=92,1015	Men without prostate cancer N=466,241
VTE		
Incidence rate per 1000 person-years (95% CI)	6.54 (6.31–6.78)	4.27 (4.18–4.35)
Crude IRR (95% CI)	1.53 (1.47–1.60)	1.0 (reference)
Adjusted HR[a] (95% CI)	1.47 (1.41–1.53)	1.0 (reference)
PE		
Incidence rate per 1000 person-years (95% CI)	3.12 (2.96–3.28)	2.02 (1.96–2.08)
Crude IRR (95% CI)	1.54 (1.45–1.64)	1.0 (reference)
Adjusted HR[a] (95% CI)	1.48 (1.39–1.57)	1.0 (reference)
DVT		
Incidence rate per 1000 person-years (95% CI)	3.38 (3.22–3.55)	2.22 (2.16–2.80)
Crude IRR (95% CI)	1.52 (1.44–1.61)	1.0 (reference)
Adjusted HR[a] (95% CI)	1.47 (1.39–1.56)	1.0 (reference)

[a]Adjusted for age, atrial fibrillation, chronic heart failure, hypertension, diabetes, cancer, myocardial infarction and ischaemic stroke.

10.4.3 Baseline characteristics of men with prostate cancer and first incident VTE during the recurrent VTE follow-up

A total of 1413 men with prostate cancer experienced a VTE and were dispensed anticoagulant therapy from a pharmacy: 50% (700/1413) had a PE, of which 68% were hospitalised, and 45% (640/1413) had a DVT, of which 12% were hospitalised (5%, 73/1413 had a non-specified VTE).

Clinical and sociodemographic characteristics are shown in Supplementary Table 8–Supplementary Table 10. Median age was PPD at VTE diagnosis. Median time from prostate cancer diagnosis to VTE diagnosis was 3 years (IQR 1–6). Approximately 20% of patients experienced their VTE within 1 year after prostate cancer diagnosis. Common comorbidities included hypertension (67%), cerebrovascular disease (10%), diabetes (14%) and hyperlipidaemia (12%), and just over 10% of patients had a history of urogenital bleeding.

Commonly used medications at baseline (any time before index VTE) included antihypertensives (67%), statins (35%) and antiplatelets (30%). No major differences were seen in the clinical profiles of men with DVT vs. those with PE.

10.4.4 Anticoagulation among men with prostate cancer and first incident VTE during follow-up during the recurrent VTE follow-up

The vast majority (96%) of men started their outpatient anticoagulant therapy within the four weeks after their VTE diagnosis. Men received their first prescription at a median of 2 days after their VTE (range 1–6 days). Almost two-thirds (64%) were prescribed parenteral anticoagulation, 31% a DOAC and 20% a VKA (**Figure 5**). The substantial decline between 2013 and 2017 in the use of parental anticoagulation (83% to 53%) and VKAs (45% to 4%) corresponded with a substantial increase in DOAC use (5% to 51%).

The prevalence of cardiovascular disease was slightly higher among men who received a VKA/DOAC than among those prescribed parenteral anticoagulation. A history of bleeding, in particularly urogenital bleeding, was more common among men who received parenteral anticoagulation.

The median duration of use was 7 months (IQR 3–13). Fifty seven per cent of men were prescribed >6 months' anticoagulation, and a quarter were prescribed >1 year of anticoagulation (**Supplementary Table 11**). In general, anticoagulation was longer for PE (median 8 months, IQR 5–15) than for DVT (median 6 months, IQR 3–9). Over two-thirds (67%) of men treated for PE received outpatient anticoagulation for more than >6 months, with over a third (35%) treated for >1 year (**Supplementary Table 11**).

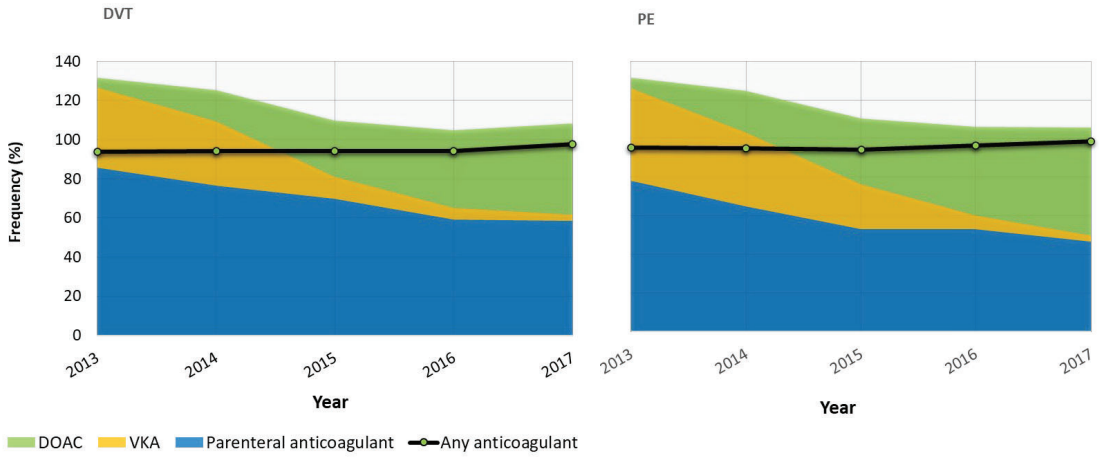


Figure 5. Type of anticoagulant(s) prescribed during the four weeks after the index VTE among the 1413 men with prostate cancer and VTE (2013–2017) stratified by type of VTE (DVT/PE).
Note: Men were eligible to have received more than one type of anticoagulant treatment during this four-week time period. In total, an outpatient prescription for an anticoagulant during the four weeks after the index VTE was issued to 95.5% of men, with 4.5% of me issued an anticoagulant prescription after four weeks.

10.4.5 Recurrent VTE and major bleeding among men with prostate cancer and first incident VTE

A total of 510 men were included in the analysis of recurrent VTE. Incidence rates of recurrent VTE over the whole of follow-up are shown in **Supplementary Table 12a**. The incidence rate of recurrent VTE per 100 person-years was 19.2 (95% CI: 11.2–30.8) in men with ≤3 months' therapy, 13.1 per 100 person-years (95% CI: 7.3–21.5) for >3–6 months, 14.7 per 100 person-years (95% CI: 8.9–22.6) for >6–9 months, and 15.0 per 100 person-years (95% CI: 8.9–23.7) for >9 months.

As shown in **Table 4**, compared with men with ≤3 months' anticoagulation for the index PE, adjusted HRs for recurrent VTE were 0.32 (95% CI: 0.09–1.12) for >3–6 months therapy, 0.26 (95% CI: 0.08–0.82) for >6–9 months, and 0.18 (95% CI: 0.15–0.60) for >9 months. Corresponding HRs relating to treatment of the index DVT were 0.67 (95% CI: 0.27–1.66) for >3–6 months, 0.80 (95% CI: 0.31–2.07) for >6–9 months, and 1.19 (95% CI: 0.47–3.02) for >9 months.

Table 4. HRs (95% CIs) for recurrent VTE after the cessation of anticoagulation for the index VTE by duration of use.

	DVT			PE			VTE*		
Duration of anticoagulant therapy	**Incident cases /person-yrs**	**Crude RR (95% CI)**	**Adjusted RR† (95% CI)**	**Incident cases /person-yrs**	**Crude RR (95% CI)**	**Adjusted RR† (95% CI)**	**Incident cases /person-yrs**	**Crude RR (95% CI)**	**Adjusted RR† (95% CI)**
≤3 months N=102	11 / 68	1.00	1.00	5 / 13	1.00	1.00	**17**† / 88	1.00	1.00
>3 to 6 months N=127	9 / 75	0.74 (0.31–1.79)	0.71 (0.29–1.74)	6 / 35	0.47 (0.14–1.55)	0.32 (0.09–1.12)	15 / 115	0.68 (0.34–1.37)	0.66 (0.33–1.33)
>6 to 9 months N=150	9 / 60	0.93 (0.39–2.24)	0.99 (0.41–2.43)	11 / 68	0.45 (0.16–1.29)	0.26 (0.08–0.82)	20 / 137	0.77 (0.40–1.46)	0.76 (0.40–1.45)
>9 months N=131	9 / 39	1.41 (0.58–3.40)	1.39 (0.56–3.44)	8 / 75	0.30 (0.10–0.90)	0.18 (0.05–0.60)	18† / 120	0.78 (0.40–1.52)	0.74 (0.38–1.44)

*Includes 73 men with VTE not specified as either DVT/PE, either ICD-10 I809 or I82)
†Adjusted for age, time from prostate cancer to VTE diagnosis, and the following comorbidities before the index VTE: cardiovascular disease, hypertension, diabetes, major bleeding, cerebrovascular disease, and use of statins or NSAIDS before the index VTE.
†One case was classified as neither DVT or PE, but as 'other VTE'.
Notes: Analysis included 510 men with VTE and at least 1 year of follow-up after the end of therapy). Anticoagulants included LMWH, VKAs and DOACs.

One-year incidence proportions of recurrent VTE were 17% for ≤3 months, 12% >3–6 months, 13% for >6–9 months, and 14% for >9 months (**Supplementary Table 13**). The incidence proportion of recurrent VTE was highest in men with ≤3 months anticoagulation at all timepoints during the year after treatment cessation. Incidence proportions at 60 days after anticoagulation cessation were 7% for men who received ≤3 months' duration, 4% for >3–6 months or >6–9 months' therapy, and 2% for >9 months' therapy (**Figure 6**); corresponding estimates at 180 days were 14%, 8%, 9%, and 7%, respectively, and at 360 days, they were 17%, 12%, 13%, and 14%, respectively.

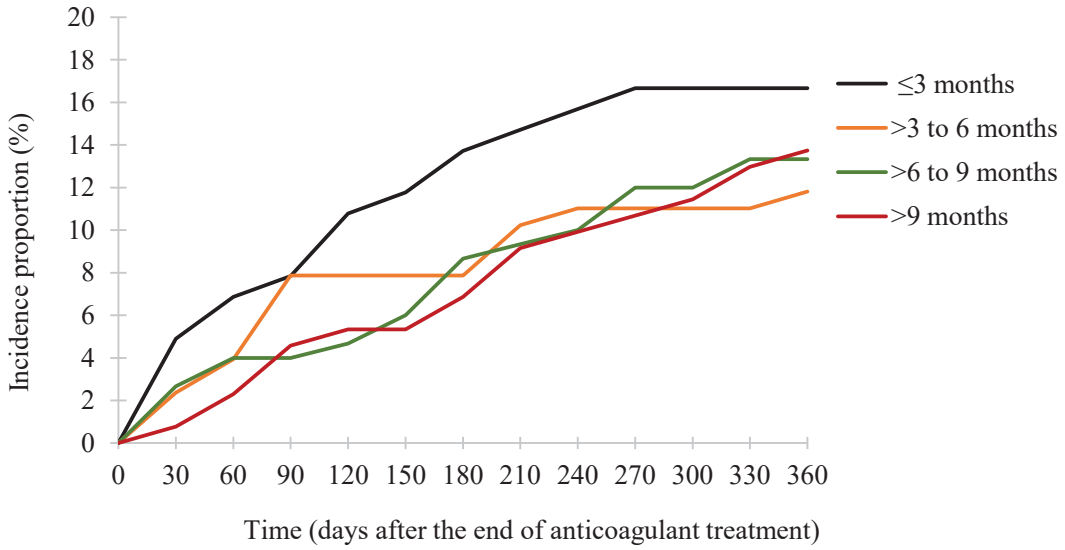


Figure 6. Incidence proportion (%) of recurrent VTE after the cessation of anticoagulant treatment by duration of therapy and time since cessation of therapy.
Note: Analysis included 510 men with VTE and at least 1 year of follow-up after the cessation of therapy.

Incidence rates of major bleeding rates were low; rates over the whole of follow-up are shown in **Supplementary Table 12b**. For one-year incidence proportions, on-treatment estimates were slightly higher or similar to the respective off-treatment estimates. For urogenital bleeding these were 3.0% (on-treatment) compared with 1.6% (off-treatment), 1.7% (on-treatment) and 0.9% (off-treatment) for gastrointestinal bleeding, and 0.9% (on-treatment) and 1.2% (off-treatment) for intracranial bleeding (**Figure 7; Supplementary Table 14**). The incidence proportion of most types of major bleeding increased most rapidly over the first 90 days and increased more steadily thereafter (**Figure 7**).

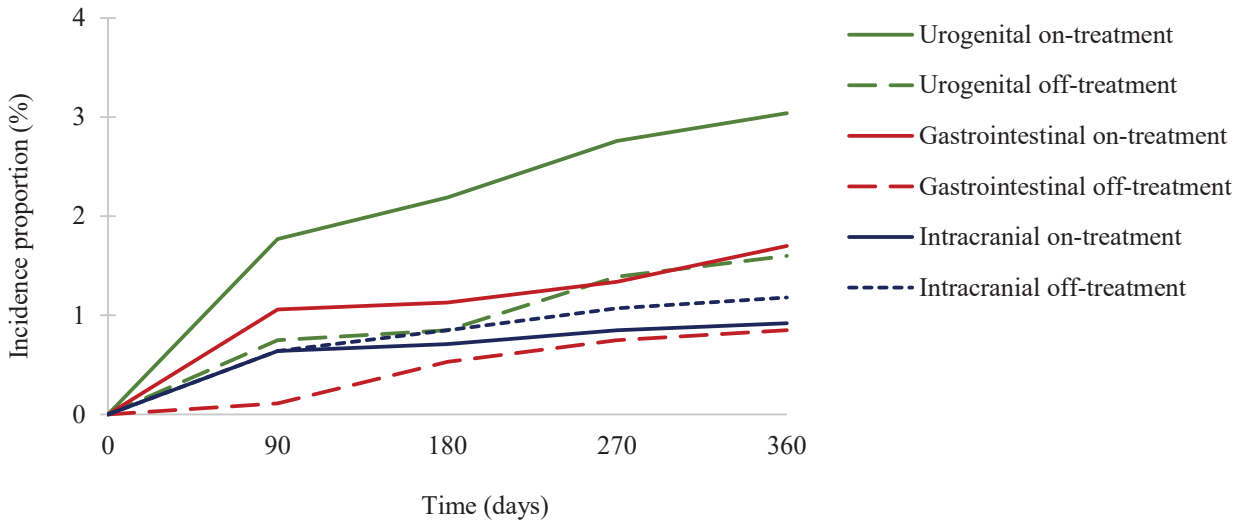


Figure 7. Incidence proportion (%) of on-treatment and off-treatment major bleeding of anticoagulant therapy.
Note: On-treatment analysis included all 1413 men with VTE, and off-treatment analysis include 936 patients.

10.5 Other analyses

None.

10.6 Safety data (Adverse events/adverse reactions)

N/A.

11. Discussion

11.1 Key results

Incidence of VTE in men with prostate cancer and men without prostate caner

In this nationwide study in Sweden, men with prostate cancer had a 50% increased risk of a first VTE in the 5 years following cancer diagnosis compared with men free of prostate cancer in the general population, after adjusting for age and other confounders. The risk was mostly increased in the first 6 months of prostate cancer diagnosis, decreasing steadily thereafter, and the average time to develop a first VTE was shorter in men with prostate cancer than in men free of prostate cancer of a similar age (3.1 vs. 3.4 years). Adjusted HRs differed only marginally from crude estimates indicating that this excess risk is likely to due to effects of the prostate cancer itself and/or residual confounding. Additionally, VTE incidence increased in both study cohorts over time, reflecting an increased incidence with age irrespective of cancer status.

These findings support those from previous studies on this topic, although the magnitude of increased risk among men with prostate cancer in our study was lower than other reports.(8-10) This could be explained by the longer follow-up in our study, and also the inclusion of both inpatient and outpatient VTE cases – the latter likely representing less serious events. In a previous study using PCBaSe, incidence rates of DVT and PE were 2-fold higher in men with prostate cancer (2.5 higher in those on endocrine therapy or who received curative treatment) compared with the expected rates from the general male Swedish population.(8) In a registry study from Denmark, Cronin-Fenton *et al*(10) reported a three-fold increased risk of hospitalised VTE among 4457 men with prostate cancer compared with matched general population controls after adjusting for confounders (median follow-up 1.23 and 3.5 years in the all cancer and general population cohorts, respectively).

The magnitude of increased VTE risk among men with prostate cancer seen in this study is lower than that seen for other cancer types as seen in previous studies, and likely attributable to the high proportion of men with localised disease and at low risk of cancer progression.(1, 9, 10) In a larger study from the UK using linked primary care, secondary care and National Statistic Cause of Death data, Walker *et al*(9) found a 2.6 (95% CI: 2.4–2.9) increased rate of VTE among 10,238 men with prostate cancer compared with a non-cancer comparison cohort, after adjusting for age and calendar year (median follow-up 2.0 years and 2.6 years in the all cancer cohort and comparison cohort, respectively). Their exclusion of patients with other cancers in their comparison cohort would have meant this group was probably healthier than our comparison cohort that did not exclude men with other cancers, and thus could also be a reason for their observed higher relative risk. Furthermore, the smaller relative increase in VTE risk seen in our study occurred over a longer follow-up duration (median 4.5 years) than the two aforementioned studies. As we observed a higher relative incidence

of VTE in the first 6 months from cancer diagnosis – as seen previously(8, 11) – it is logical that higher relative risks would be observed in shorter studies. The higher risk in the months after cancer prostate cancer may reflect the higher risks of VTE associated with surgical interventions such as radical prostatectomy.

Duration of anticoagulation un men with prostate cancer and a first VTE

In this study, the average duration of outpatient anticoagulant therapy for the treatment and secondary prophylaxis of VTE was 7 months; however, duration of treatment varied between patients. A fifth of men received anticoagulation for ≤3 months, while a quarter received ≥1 year duration of therapy. For cases of PE, anticoagulation was, on average, prescribed for a longer period.

Previous studies on this topic included patients across several cancer sites with different anticoagulation requirements and have evaluated VTE risks using different definitions. The average duration of anticoagulation among our study cohort (7 months) is similar to that seen among cancer patients in the international RIETE registry (6 months).(19) In US claims database studies, the average length of anticoagulation for VTE has been higher. Between 2007 and 2011, Kaatz *et al*[20] found that cancer patients were anticoagulated for VTE (mostly warfarin) for an average of 10 months, while for the period 2007–2014, Khorana *et al*[21] reported a median duration of 8 months for warfarin/rivaroxaban therapy among patients with cancer.

We observed a significant increase in DOAC use for VTE among men in our study (reaching 51% in 2017), with a corresponding decline in use of VKAs (4% in 2017) and of parenteral anticoagulants (53% in 2017), albeit the latter was still used by over half of men long-term. This rise in DOAC use is consistent with temporal trends in other cancer populations, and reflect the current guideline recommendations.[22]

Risk of recurrent VTE

A reduced risk of recurrent VTE was seen among patients prescribed >3–6 months therapy (vs ≤3 months therapy), with >9 months treatment appearing to offer the greatest benefit for PE, and >3–6 months offering affording the greatest benefit for DVT. A higher risk of recurrent VTE was seen in men treated with ≤3 months' anticoagulation vs longer durations, consistent with findings among cancer patients in the claims database study by Khorana et al 2019.(23)

Risk of major bleeding

Risks of major bleeding were low and did not appear to be substantially higher during the on-treatment period than after treatment cessation. This was especially apparent for intracranial bleeding, while for urogenital bleeding, the risk was somewhat increased during the on-treatment period.

11.2 Limitations

- Although the use of several linked data sources enabled information on a wide range of potential confounders to be ascertained, including comorbidities, medications and socio-demographic factors, lack of information on height, weight, smoking status and alcohol intake.
- Some men in the comparison cohort may have developed another type of cancer during follow-up thereby increasing their risk of developing a VTE. This would have diluted the relative risk estimates observed.
- Confounding may have been present due to lack of information on factors that influence VTE risk, such as cancer stage/grade, cancer treatment (including surgery), age and comorbidity profile, (11, 24) and in the analysis of recurrent VTE, there may have been some confounding due to lack of information on VTE severity.
- Other factors that influence VTE risk, may also have influenced treatment decisions, with the duration of treatment dependent the individual's risk profile.
- Prostate cancer stage at the time of VTE diagnosis was unknown and we did not have sufficient information to analyse specific cancer treatments. There was no attempt to define the observed VTE events as 'cancer-associated VTE' due to the fact that this could not be ascertained with confidence. Instead, the aim was to describe the risk of VTE in the unselected total population of men living with prostate cancer. The prostate cancer cohort consisted of men in different disease risk categories, and in some the cancer may have been indolent for a long time making it difficult to attribute VTE events to the cancer itself.
- Validation of the VTE diagnoses were was not possible because the results of imaging procedures are not routinely recorded in the Patient Register. Additionally, anticoagulant duration may have been misclassified because information on adherence was unavailable, and this may have impacted the VTE recurrence/bleeding analyses.
- Some of the analyses may have been underpowered to detect significant differences between anticoagulant duration categories.

11.3 Interpretation

- The findings quantifying the increased risks of VTE in men with prostate cancer suggest that physicians should be particularly vigilant of these patients in the first 6 months following diagnosis.
- The descriptive analyses of anticoagulation duration indicate reflect the adoption of an individualised approach to treating VTE in this heterogenous population.
- Notwithstanding the necessity for personalized treatment approaches, a higher risk of recurrent VTE was seen in men treated with ≤3 months' anticoagulation vs longer durations, consistent with findings among cancer patients in the claims database study by Khorana et al 2019.(23)

- The small possible increase in recurrent DVT risk observed in men treated for >9 months is likely to be an artefact from an inherent increased in this subset of patients.

11.4 Generalisability

The good quality and national coverage of the linked data sources,(18) mean that the results have good internal validity and are generalisable to the male population of Sweden as a whole

12. Other information

It is important to note that data in the Swedish registers used did not enable us to determine whether a recurrent VTE event was 'cancer-associated', nor was this the aim of the study – our focus was on all men with prostate cancer who were diagnosed with a VTE at any time point following cancer diagnosis, irrespective of treatment. In men with prostate cancer, it is challenging to determine whether a VTE event is cancer-associated because this type of cancer can have slow progression, and patients may require different treatments depending on disease stage; thrombotic activity could therefore be triggered at different times in different patients. Furthermore, it is noteworthy that only about 20% of men in our study were diagnosed with a VTE within a year of cancer diagnosis.

In addition to the good generalizability of the study results, another major strength of our study is the focus on a single cancer type. the large sample size enabling the calculation of precise incidence estimates. Selection bias was minimized because the cohort included unselected men with prostate cancer of different stages/grades, across all ages and including those with comorbidities. Sweden has a tax-funded public healthcare system. Data completeness in the Swedish Prescribed Drug Register is virtually complete because Swedish pharmacies are required to participate by law. Therefore anticoagulant treatment patterns were captured in virtually all men with prostate cancer and VTE in the country, none of whom were lost to follow-up.

Although drugs issued in hospital are not captured in PCBaSe, the interest of this study was in long-term anticoagulation, where the minimum recommended duration is 3 months. Furthermore, the proportion of men hospitalised for their VTE was low (68% for PE and 12% for DVT). Both inpatient and outpatient VTE events were included, based on previous knowledge that a high proportion of VTE events in cancer patients occur in the ambulatory setting.(25) Other strengths are the focus on one specific cancer type and the near absence of any loss-to follow-up. Patients with VTE who were either hospitalised or managed on an outpatient basis were included, maximising the sensitivity of the VTE case definition.

13. Conclusion

This study provides useful information on the benefits and risks of anticoagulation therapy beyond 6 months' duration for VTE in men with prostate cancer, on which there is currently no consensus. The results suggest the greatest potential for the reducing VTE recurrence occurs with >9 months treatment for PE and >3–6 months for DVT. Risks of major bleeding were low overall and did not differ substantially for events that occurred during anticoagulation and those that occurred after anticoagulation cessation (off-treatment events), particularly for intracranial bleeding.

Physicians treating men with prostate cancer should be aware of the marked increase in VTE risk in these men, particularly in the first 6 months following cancer diagnosis, to help ensure timely VTE diagnosis.

Further epidemiological studies are needed to confirm/refute our findings and help guide clinical decision making in routine practice. Other beneficial areas for further research in this field include the effects of specific anticoagulants on relevant clinical outcomes and gaining a better understanding of the prescribing choices.

14. References

1. Iorga RA, Bratu OG, Marcu RD, Constantin T, Mischianu DLD, Socea B, et al. Venous thromboembolism in cancer patients: Still looking for answers (Review). Exp Ther Med. 2019 2019/12/01;18(6):5026–32.
2. Ay C, Beyer-Westendorf J, Pabinger I. Treatment of cancer-associated venous thromboembolism in the age of direct oral anticoagulants. Ann Oncol. 2019 Jun 1;30(6):897–907.
3. Lee AYY. When can we stop anticoagulation in patients with cancer-associated thrombosis? Blood. 2017 Dec 7;130(23):2484–90.
4. Wang TF, Li A, Garcia D. Managing thrombosis in cancer patients. Res Pract Thromb Haemost. 2018 Jul;2(3):429–38.
5. World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2020.
6. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014 Jan;15(1):23–34.
7. SEER Cancer Statistics Review, 1975-2013 [Internet]. National Cancer Institue, Bethesda, MD. 2016. Available from: https://seer.cancer.gov/csr/1975_2015/.
8. Van Hemelrijck M, Adolfsson J, Garmo H, Bill-Axelson A, Bratt O, Ingelsson E, et al. Risk of thromboembolic diseases in men with prostate cancer: results from the population-based PCBaSe Sweden. Lancet Oncol. 2010 May;11(5):450–8.
9. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. Eur J Cancer. 2013 Apr;49(6):1404–13.
10. Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006. Br J Cancer. 2010 Sep 28;103(7):947–53.
11. Van Hemelrijck M, Garmo H, Holmberg L, Bill-Axelson A, Carlsson S, Akre O, et al. Thromboembolic events following surgery for prostate cancer. Eur Urol. 2013 Feb;63(2):354–63.
12. National Comprehensive Cancer Network. Cancer-Associated Venous Thromboembolic Disease. 2020.
13. Mandalà M, Falanga A, Roila F. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2011 Sep;22 Suppl 6:vi85–92.
14. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. The Lancet Oncology. 2019;20(10):e566-e81.
15. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2020 Feb 10;38(5):496–520.
16. Van Hemelrijck M, Wigertz A, Sandin F, Garmo H, Hellström K, Fransson P, et al. Cohort Profile: the National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. Int J Epidemiol. 2013 Aug;42(4):956–67.

17. Hagel E, Garmo H, Bill-Axelson A, Bratt O, Johansson JE, Adolfsson J, et al. PCBaSe Sweden: a register-based resource for prostate cancer research. Scand J Urol Nephrol. 2009;43(5):342–9.
18. Van Hemelrijck M, Garmo H, Wigertz A, Nilsson P, Stattin P. Cohort Profile Update: The National Prostate Cancer Register of Sweden and Prostate Cancer data Base--a refined prostate cancer trajectory. Int J Epidemiol. 2016 Feb;45(1):73–82.
19. Farge D, Trujillo-Santos J, Debourdeau P, Bura-Riviere A, Rodriguez-Beltrán EM, Nieto JA, et al. Fatal Events in Cancer Patients Receiving Anticoagulant Therapy for Venous Thromboembolism. Medicine. 2015;94(32):e1235–e.
20. Kaatz S, Fu A-C, AbuDagga A, LaMori J, Bookhart BK, Damaraju CV, et al. Association between anticoagulant treatment duration and risk of venous thromboembolism recurrence and bleeding in clinical practice. Thrombosis Research. 2014 2014/10/01/;134(4):807–13.
21. Khorana AA, McCrae KR, Milentijevic D, Fortier J, Nelson WW, Laliberte F, et al. Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. Res Pract Thromb Haemost. 2017 Jul;1(1):14–22.
22. Angelini DE, Elson P, McCrae K, Khorana AA. Anticoagulant Prescription Patterns for Cancer Associated Thrombosis: New Insights into the Use of Direct Oral Anticoagulants. Blood. 2017;130(Supplement 1):4725-4725.
23. Khorana AA, McCrae KR, Milentijevic D, Fortier J, Nelson WW, Laliberte F, et al. Duration of anticoagulant therapy and VTE recurrence in patients with cancer. Support Care Cancer. 2019 Oct;27(10):3833–40.
24. Khorana AA, Cohen AT, Carrier M, Meyer G, Pabinger I, Kavan P, et al. Prevention of venous thromboembolism in ambulatory patients with cancer. ESMO Open. 2020;5(6):e000948.
25. Streiff MB. Association between cancer types, cancer treatments, and venous thromboembolism in medical oncology patients. Clin Adv Hematol Oncol. 2013 Jun;11(6):349–57.

Appendices

Annex 1: List of stand-alone documents

N/A

Annex 2 Additional information

Supplementary Table 1. ATC codes for anticoagulant drugs.

Class	Drug name	ATC classification code
Parenteral anticoagulants	Heparin	B01AB01
	Enoxaparin	B01AB05
	Dalteparin	B01AB04
	Nadroparin	B01AB06
	Tinzaparin	B01AB10
	Reviparin	B01AB08
	Parnaparin	B01AB07
	Bemiparin	B01AB12
	Fondaparinux	B01AX05
	Danaparoid	B01AB09
	Bivalirudin	B01AE06
	Argatroban	B01AE03
Vitamin K antagonists	Warfarin	B01AA03
	Phenprocoumon	B01AA04
	Acenocoumarol	B01AA07
	Dicoumarol	B01AA01
	Tioclomarol	B01AA11
	Ethyl biscoumacetate	B01AA08
	Fluindione	B01AA12
	Phenindione	B01AA02
	Chlorindione	B01AA09
	Diphenadione	B01AA10
Direct oral anticoagulants	Rivaroxaban (Xarelto)	B01AF01
	Dabigatran (Pradaxa)	B01AE07
	Apixaban (Eliquis)	B01AF02
	Edoxaban (Savaysa/Lixiana)	B01AF03

Supplementary Table 2. ICD-10 codes for major bleeding outcomes.

Condition	**ICD-10 or Swedish procedure codes**
Intracranial bleeding	I60-62, S064, S065, S066
Gastrointestinal bleeding	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922
Urogenital bleeding	N02, R319, N95
Other bleeding	H431, R04, R58, D629, procedure code DR029

Supplementary Table 3. Clinical characteristics of men with prostate cancer at cancer diagnosis (N=92,105).

	Prostate cancer cohort 92,105 n (%)	
	n	**%**
TNM stage		
T1	47,658	51.7
T2	27,389	29.7
T3	14,342	15.6
T4	2,612	2.8
Missing	104	0.1
N0	17,789	19.3
N1	2725	3.0
NX	71,445	77.6
Missing	146	0.2
M0	57,637	62.6
M1	7310	7.9
MX	26,990	29.3
Missing	168	0.2
Prostate cancer risk group		
Low	26,251	28.5
Intermediate	29,235	31.7
High	19,523	21.2
Regionally metastasized	5294	5.7
Distant metastases	10,615	11.5
Missing	1187	1.3
PSA at diagnosis (mg/l)		
<3	3331	3.6
3–10	49,178	53.4
11–50	26,284	28.5
≥51	11,822	12.8
Missing	1490	1.6
Mean (SD)	72.7	565.6
Median (Q1–Q3)	8.8	5.4–20.0

Supplementary Table 4. Five-year incidence proportion (95% CI) and incidence proportion ratio of first VTE among men with and without prostate cancer.

	Prostate cancer cohort N=92,1015		Comparison cohort N=466,241		
Time (months)	**First incident VTE cases, N**	**Incidence proportion (95% CI)**	**First incident VTE cases, N**	**Incidence proportion (95% CI)**	**IPR (95% CI)**
0	0		0		
6	453	0.49 (0.45–0.54)	908	0.19 (0.18–0.21)	2.53 (2.26–2.83)
12	790	0.86 (0.80–0.92)	1858	0.40 (0.38–0.42)	2.15 (1.98–2.34)
18	1 045	1.13 (1.07–1.21)	2721	0.58 (0.56–0.61)	1.94 (1.81–2.09)
24	1 275	1.38 (1.31–1.46)	3524	0.76 (0.73–0.78)	1.83 (1.72–1.95)
30	1 473	1.60 (1.52–1.68)	4270	0.92 (0.89–0.94)	1.75 (1.65–1.85)
36	1 688	1.83 (1.75–1.92)	4986	1.07 (1.04–1.10)	1.71 (1.62–1.81)
42	1 857	2.04 (1.95–2.13)	5651	1.21 (1.18–1.24)	1.66 (1.58–1.75)
48	2 009	2.18 (2.09–2.28)	6220	1.33 (1.30–1.37)	1.63 (1.56–1.72)
54	2 156	2.34 (2.24–2.44)	6774	1.45 (1.42–1.49)	1.61 (1.54–1.69)
60	2 277	2.47 (2.37–2.57)	7245	1.55 (1.52–1.59)	1.59 (1.52–1.67)

Supplementary Table 5. Five-year incidence proportion (95% CI) and incidence proportion ratio of **first DVT** among men with and without prostate cancer.

	Prostate cancer cohort N=92,1015		Comparison cohort N=466,241		
Time (months)	**First incident DVT cases, N**	**Incidence proportion (95% CI)**	**First incident DVT cases, N**	**Incidence proportion (95% CI)**	**IPR (95% CI)**
0	0		0		
6	240	0.26 (0.23–0.30)	487	0.10 (0.10–0.11)	2.49 (2.14–2.91)
12	422	0.46 (0.42–0.50)	986	0.21 (0.20–0.22)	2.17 (1.93–2.43)
18	558	0.61 (0.56–0.66)	1454	0.31 (0.30–0.33)	1.94 (1.76–2.14)
24	659	0.72 (0.66–0.77	1880	0.40 (0.39–0.42)	1.77 (1.62–1.94)
30	765	0.83 (0.77–0.89)	2273	0.49 (0.47–0.51)	1.70 (1.57–1.85)
36	855	0.93 (0.87–0.99)	2641	0.57 (0.55–0.59)	1.64 (1.52–1.77)
42	940	1.02 (0.96–1.09)	2997	0.64 (0.62–0.67)	1.59 (1.48–1.71)
48	1020	1.11 (1.04–1.18)	3297	0.71 (0.68–0.73)	1.57 (1.46–1.68)
54	1105	1.20 (1.13–1.27)	3589	0.77 (0.74–0.80)	1.56 (1.46–1.67)
60	1171	1.27 (1.20–1.35)	3835	0.82 (0.80–0.85)	1.55 (1.45–1.65)

Supplementary Table 6. Five-year incidence proportion (95% CI) and incidence proportion ratio of **first PE** among men with and without prostate cancer.

	Prostate cancer cohort N=92,1015		**Comparison cohort N=466,241**		
Time (months)	**First incident PE cases, N**	**Incidence proportion (95% CI)**	**First incident PE cases, N**	**Incidence proportion (95% CI)**	**IPR (95% CI)**
0	0		0		
6	193	0.21 (0.18–0.24)	388	0.08 (0.08–0.09)	2.52 (2.12–2.99)
12	343	0.37 (0.33–0.41)	803	0.17 (0.16–0.18)	2.16 (1.91–2.45)
18	455	0.49 (0.45–0.54)	1188	0.25 (0.24–0.27)	1.94 (1.74–2.16)
24	581	0.63 (0.58–0.68)	1554	0.33 (0.32–0.35)	1.89 (1.72–2.08)
30	670	0.73 (0.67–0.78)	1907	0.41 (0.39–0.43)	1.78 (1.63–1.94)
36	791	0.86 (0.80–0.92)	2248	0.48 (0.46–0.50)	1.78 (1.64–1.93)
42	877	0.95 (0.89–1.02)	2558	0.55 (0.53–0.57)	1.74 (1.61–1.87)
48	951	1.03 (0.97–1.10)	2837	0.61 (0.59–0.63)	1.70 (1.58–1.83)
54	1 023	1.11 (1.04–1.18)	3116	0.67 (0.65–0.69)	1.66 (1.55–1.78)
60	1 078	1.17 (1.10–1.24)	3344	0.72 (0.69–0.74)	1.63 (1.52–1.75)

Supplementary Table 7. Age-stratified incidence rates of first VTE per 1000 person-years (95% CI) in men with prostate cancer and men without prostate cancer, and IRR (95% CI) comparing rates in the two cohorts.

Age (years)	Prostate cancer cohort (N=92,1015)	Comparison cohort (N=466,241)
<60		
Incidence rate of VTE per 1000 person-years (95% CI)	4.56 (4.05–5.13)	2.38 (2.21–2.55)
Crude IRR (95% CI)	1.92 (1.67–2.20)	1.0 (reference)
60–64		
Incidence rate of VTE per 1000 person-years (95% CI)	5.20 (4.74–8.72)	3.36 (3.19–3.54)
Crude IRR (95% CI)	1.55 (1.39–1.72)	1.0 (reference)
65–69		
Incidence rate of VTE per 1000 person-years (95% CI)	6.32 (5.88–6.80)	4.02 (3.86–4.19)
Crude IRR (95% CI)	1.57 (1.44–1.71)	1.0 (reference)
70–74		
Incidence rate of VTE per 1000 person-years (95% CI)	7.24 (6.71–7.84)	4.66 (4.60–4.86)
Crude IRR (95% CI)	1.56 (1.42–1.70)	1.0 (reference)
75–79		
Incidence rate of VTE per 1000 person-years (95% CI)	7.92 (7.22–8.67)	5.53 (5.27–5.80)
Crude IRR (95% CI)	1.43 (1.29–1.59)	1.0 (reference)
80–84		
Incidence rate of VTE per 1000 person-years (95% CI)	8.40 (7.46–9.47)	6.11 (5.75–6.49
Crude IRR (95% CI)	1.37 (1.20–1.57)	1.0 (reference)
≥85		
Incidence rate of VTE per 1000 person-years (95% CI)	9.86 (8.45–11.49)	6.88 (6.35–7.45)
Crude IRR (95% CI)	1.44 (1.21–1.71)	1.0 (reference)

Note, follow-up for on-treatment events was from the index VTE until the bleeding event or the end of anticoagulant treatment (n=1413). Follow-up for off-treatment events was from the end of the anticoagulant treatment to the bleeding event or the end of follow-up (n=936)

Supplementary Table 8. Clinical and sociodemographic characteristics of the 1413 men with prostate cancer and VTE (2013–2017) at the time of prostate cancer diagnosis.

	DVT N=640	PE N=700	VTE* N=1413
Age at prostate cancer diagnosis (years), median (IQR)	PPD		
Prostate cancer risk group*			
Low-intermediate	354 (55.3)	380 (54.3)	777 (55.0)
High-locally metastatic	207 (32.3)	203 (29.0)	428 (30.3)
Distant metastases	70 (10.9)	110 (15.7)	192 (13.6)
Missing	9 (1.4)	7 (1.0)	16 (1.1)
TNM stage			
T1	299 (46.7)	348 (49.7)	684 (48.4)
T2	186 (29.1)	206 (29.4)	416 (29.4)
T3	126 (19.7)	124 (17.7)	260 (18.4)
T4	29 (4.5)	22 (3.1)	53 (3.8)
N0	122 (19.1)	151 21.6)	283 (20.0)
N1	35 (5.5)	35 (5.0)	75 (5.3)
NX	481 (75.2)	514 (73.4)	1053 (74.5)
M0	392 (61.3)	422 (60.3)	858 (60.7)
M1	45 (7.0)	84 (12.0)	139 (9.8)
MX	201 (31.4)	194 (27.7)	414 (29.3)
PSA at prostate cancer diagnosis (mg/l)			
<3	23 (3.6)	24 (3.4)	53 (3.8)
3–10	309 (48.3)	370 (52.9)	717 (50.7)
11–50	197 (30.8)	198 (28.3)	412 (29.2)
≥51	99 (15.5)	99 (14.1)	210 (14.9)
Missing	12 (1.9)	9 (1.3)	21 (1.5)
Time from prostate cancer diagnosis to VTE diagnosis (years)			
≤1	123 (19.2)	144 (20.6)	280 (19.8)
>1–2	81 (12.7)	96 (13.7)	187 (13.2)
>2–3	67 (10.5)	108 (15.4)	186 (13.2)
>3	369 (57.7)	352 (50.3)	760 (53.8)
Median (IQR)	3.9 (1.3–6.1)	3.0 (1.4–5.5)	3.3 (1.4–5.7)
Median age (IQR) at incident VTE diagnosis (years)	PPD		
Hospitalised for VTE	77 (12.0)	478 (68.3)	576 (40.8)
Educational level			
Low (<9 years)	213 (33.3)	254 (36.3)	487 (34.5)
Middle (9–12 years)	264 (41.3)	266 (38.0)	560 (39.6)
High (>12 years/university)	160 (25.0)	171 (24.4)	353 (25.0)
Missing	3 (0.5)	9 (1.3)	13 (0.9)
Marital status			
Married	413 (64.5)	472 (67.4)	933 (66.0)
Unmarried	75 (11.7)	79 (11.3)	165 (11.7)
Divorced	109 (17.0)	95 (13.6)	212 (15.0)
Widower	43 (6.7)	53 (7.6)	102 (8.2)

Data are n (%) unless otherwise stated.
*Includes 73 men with VTE not specified as either DVT/PE, either ICD-10 I809 or I82).

Supplementary Table 9. Charlson comorbidity index, and distribution of comorbidities, among the 1413 men with prostate cancer and VTE (2013–2017).

	DVT N=640	PE N=700	VTE* N=1413
Charlson comorbidity index (at prostate cancer diagnosis)			
0	527 (82.3)	551 (78.7)	1137 (80.5)
1	56 (8.8)	71 (10.1)	135 (9.6)
2	27 (4.2)	44 (6.3)	76 (5.4)
3	15 (2.3)	21 (3.0)	37 (2.6)
≥4	15 (2.3)	13 (1.9)	28 (2.0)
Valvular heart disease	14 (2.2)	19(2.7)	35 (2.5)
Cardiovascular disease	125 (19.5)	144 (20.6)	281 (19.9)
Chronic heart failure	42 (6.6)	48 (6.9)	92 (6.5)
Coronary artery disease	86 (13.4)	96 (13.7)	191 (13.5)
Unstable angina pectoris	25 (3.9)	27 (3.9)	52 (3.7)
Angina pectoris	62 (9.7)	68 (9.7)	134 (9.5)
Peripheral arterial disease	36 (5.6)	41 (5.9)	81 (5.7)
Myocardial infarction	60 (9.4)	68 (9.7)	134 (9.5)
Hypertension			
ICD-10	261 (40.8)	303 (43.3)	590 (41.8)
ICD-10 or ATC Classification code	420 (65.6)	482 (68.9)	952 (67.4)
Diabetes mellitus			
ICD-10	79 (12.3)	75 (10.7)	166 (11.7)
ICD-10 or ATC	98 (15.3)	88 (12.6)	200 (14.2)
Liver disease	8 (1.3)	6 (0.9)	14 (1.0)
Hyperlipidemia	74 (11.6)	88 (12.6)	169 (12.0)
Obstructive sleep apnea	16 (2.5)	15 (2.1)	31 (2.2)
COPD	38 (5.9)	51 (7.3)	93 (6.6)
Diabetic retinopathy	15 (2.3)	7 (1.0)	23 (1.6)
Acute renal failure	14 (2.2)	22 (3.1)	39 (2.8)
Peripheral systemic embolism	4 (0.6)	4 (0.1)	6 (0.4)
Limb ischemia	13 (2.0)	11 (1.6)	25 (1.8)
Limb ulcer	4 (0.6)	7 (1.0)	11 (0.8)
Cerebrovascular disease	65 (10.2)	73 (10.4)	143 (10.1)
Ischaemic stroke	42 (6.6)	45 (6.4)	89 (6.3)
Stroke NOS	16 (2.5)	10 (1.4)	26 (1.8)
TIA	18 (2.8)	20 (2.9)	40 (2.8)
Hemorrhagic stroke	11 (1.7)	19 (2.7)	31 (2.2)
Any major bleeding	110 (17.2)	118 (16.9)	238 (16.8)
Intracranial bleeding	15 (2.3)	25 (3.6)	41 (2.9)
Upper GI bleeding	30 (4.7)	31 (4.4)	61 (4.3)
Lower GI bleeding	5 (0.8)	6 (0.9)	13 (0.9)
Urogenital bleeding	69 (10.8)	72 (10.3)	150 (10.6)

Data are n (%).
*Includes 73 men with VTE not specified as either DVT/PE, either ICD-10 I809 or I82).
Note: comorbidities are any time before the index VTE.

Supplementary Table 10. Frequency distribution of prescribed drugs any time before the VTE among the 1413 men with prostate cancer and VTE (2013–2017).

	DVT N=640		PE N=700		VTE* N=1413	
	n	**%**	**n**	**%**	**n**	**%**
Antiarrhythmics	2	0.3	1	0.1	3	0.2
Statins	222	34.7	254	36.3	500	35.4
Antihypertensive drugs	415	64.8	480	68.6	945	66.9
Beta-blockers	225	35.2	254	36.3	501	35.5
Calcium-channel blockers	208	32.5	249	35.6	476	33.7
ACE inhibitors	237	37.0	266	38.0	537	38.0
Angiotensin II receptor blockers	149	23.3	185	26.4	353	25.0
Diuretics	212	33.1	252	36.0	484	34.3
Antidiabetics	78	12.2	77	11.0	169	12.0
NSAID	454	70.9	509	72.7	1019	72.1
Antiplatelet drugs acetyl acid	181	28.3	224	32.0	421	29.8
Parenteral anticoagulant	219	34.2	211	30.1	444	31.4

*Includes 73 men with VTE not specified as either DVT/PE, either ICD-10 I809 or I82).

Supplementary Table 11. Duration of anticoagulation by type of VTE.

Duration of anticoagulation (days)	**DVT (N=640)**	**PE (N=700)**	**VTE* N=1413)**
≤3 months	178 (27.8)	100 (14.3)	298 (21.1)
>3 to 6 months	168 (26.3)	128 (18.3)	311 (22.0)
>6 to 9 months	132 (20.6)	151 (21.6)	297 (21.0)
>9 months	162 (25.3)	321 (45.9)	507 (35.9)
Median (IQR)	168 (85–278)	246 (157–462)	205 (103–376)

Data are n (%)
*Includes 73 men with VTE not specified as either DVT/PE, either ICD-10 I809 or I82).

Supplementary Table 12a. Incidence rates of recurrent VTE per 100 person-years after the cessation of anticoagulant therapy by duration of therapy.

Duration of anticoagulant therapy (months)	**Men with a recurrent VTE (n)**	**Person-time at risk (months)**	**Incidence per 100 person-years (95% CI)**
≤3	17	88	19.2 (11.2–30.8)
>3 to 6	15	115	13.1 (7.3–21.5)
>6 to 9	20	137	14.7 (8.9–22.6)
>9	18	120	15.0 (8.9–23.7)

*Off-treatment=any time after the end of anticoagulant treatment.

Supplementary Table 12b. Incidence rates of 'on-treatment' and 'off-treatment' major bleeding events per 100 person-years.

	Men with a major bleeding event (n)	**Person-time at risk**	**Incidence per 100 person-years (95% CI)**
During anticoagulant treatment ('on-treatment', n=1413)			
Intracranial	16	1234	1.30 (0.79–2.12)
Gastrointestinal	33	1225	2.69 (1.92–3.79)
Urogenital	49	1210	4.05 (3.06–5.36)
Any time after the end of anticoagulant therapy ('off-treatment, n=936)			
Intracranial	12	1367	0.88 (0.45–1.53)
Gastrointestinal	15	1366	1.10 (0.61–1.81)
Urogenital	25	1361	1.84 (1.19–2.71)

*Off-treatment=any time after the end of anticoagulant treatment.

Supplementary Table 13. Incidence proportion (%) of recurrent VTE after the cessation of anticoagulant therapy according to the duration of anticoagulant therapy for the index VTE.

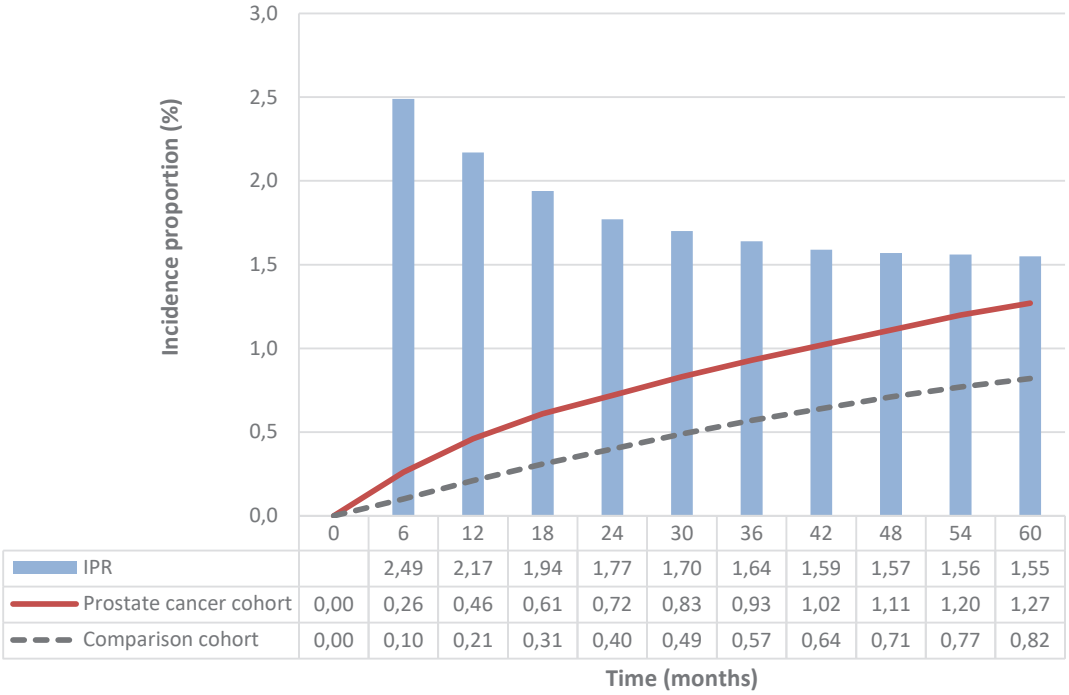
	Duration of anticoagulant therapy (days)							
Days after end of anticoagulant therapy	**≤3 months N=102**		**>3 to 6 months N=127**		**>6 to 9 months N=150**		**>9 months N=131**	
	n	**Incidence proportion (95% CI), %**	**n**	**Incidence proportion (95% CI), %**	**n**	**Incidence proportion (95% CI), %**	**n**	**Incidence proportion (95% CI), %**
90	8	7.8 (3.4–14.9)	10	7.9 (3.8–14.0)	6	4.0 (1.5–8.5)	6	4.6 (1.7–9.7)
180	14	13.7 (7.7–22.0)	10	7.9 (3.8–14.0)	13	8.7 (4.7–14.4)	9	6.9 (3.2–12.6)
270	17	16.7 (10.0–25.3)	14	11.0 (6.2–17.8)	18	12.0 (7.3–18.3)	13	9.9 (5.4–16.4)
360	17	16.7 (10.0–25.3)	15	11.8 (6.8–18.7)	20	13.3 (8.3–19.8)	18	13.7 (8.4–20.8)

*510 men with VTE and at least one year of follow-up after the end of therapy.

Supplementary Table 14. Incidence proportion (%) of on-treatment and off-treatment major bleeding.*

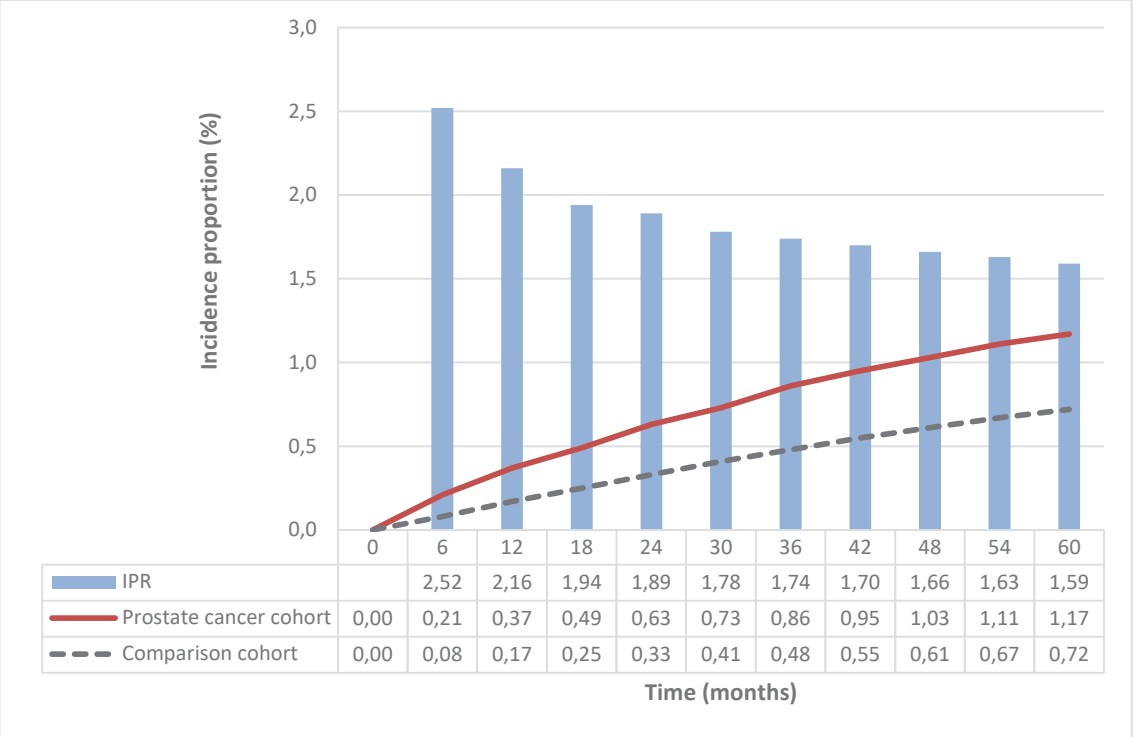
	1-year incidence proportion (95% CI)											
	Intracranial bleeding				Gastrointestinal bleeding				Urogenital bleeding			
	On-treatment n (%)		Off-treatment n (%)		On-treatment n (%)		Off-treatment n (%)		On-treatment n (%)		Off-treatment n (%)	
Time at risk (days)												
90	9	0.6 (0.3–1.2)	6	0.6 (0.2–1.4)	15	1.1 (0.6–1.7)	1	0.1 (0.0–0.6)	25	1.8 (1.1–2.6)	7	0.7 (03-1.5)
180	10	0.7 (0.3–1.3)	8	0.9 (0.4–1.7)	16	1.1 (0.6–1.8)	5	0.5 (0.2–1.2)	31	2.2 (1.5–3.1)	8	0.9 (0.4-1.7)
270	12	0.8 (0.4–1.5)	10	1.1 (0.5–2.0)	19	1.3 (0.8–2.1)	7	0.7 (0.3–1.5)	39	2.8 (2.0–3.8)	13	1.4 (0.7-2.4)
360	13	0.9 (0.5–1.6)	11	1.2 (0.6–2.1)	24	1.7 (1.1–2.5)	8	0.9 (0.4–1.7)	43	3.0 (2.2–4.1)	15	1.6 (0.9-2.6)

Note, follow-up for on-treatment events was from the index VTE until the bleeding event or the end of anticoagulant treatment (n=1413). Follow-up for off-treatment events was from the end of the anticoagulant treatment to the bleeding event or the end of follow-up (n=936)



	0	6	12	18	24	30	36	42	48	54	60
IPR		2,49	2,17	1,94	1,77	1,70	1,64	1,59	1,57	1,56	1,55
Prostate cancer cohort	0,00	0,26	0,46	0,61	0,72	0,83	0,93	1,02	1,11	1,20	1,27
Comparison cohort	0,00	0,10	0,21	0,31	0,40	0,49	0,57	0,64	0,71	0,77	0,82

Supplementary Figure 1. Five-year incidence proportion of first DVT in the prostate cancer cohort and the comparison cohort.



	0	6	12	18	24	30	36	42	48	54	60
IPR		2,52	2,16	1,94	1,89	1,78	1,74	1,70	1,66	1,63	1,59
Prostate cancer cohort	0,00	0,21	0,37	0,49	0,63	0,73	0,86	0,95	1,03	1,11	1,17
Comparison cohort	0,00	0,08	0,17	0,25	0,33	0,41	0,48	0,55	0,61	0,67	0,72

Supplementary Figure 2. Five-year incidence proportion of **first PE** among men with and without prostate cancer.

Annex 3 Signature Pages

Signature Page – Principal Investigator

Title	PRostAte Cancer vTe In SwEden: epidemiology and anticoagulation treatment of VTE **PRACTISE**
Report version and date	V1.0, 23 AUG 2021
IMPACT study number	20653
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS29848
Medicinal product	Xarelto (Rivaroxaban), Eliquis (Apixaban), Dabigatran etexilate (Pradaxa)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 9/23/2021, PPD _____

Signature Page – Exernal senior researcher/statistician

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Signature Page – OS Conduct Responsible and OS Epidemiologist

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Signature Page – MAH contact person (Regulatory Affairs)

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Print Name: PPD

Date, Signature: 9/29/2021, PPD

Signature Page – OS Safety Lead

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Print Name: PPD

Date, Signature: 9/22/2021, PPD

Signature Page – OS Medical Expert

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Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD on behalf of PPD (due to PPD leave)

Date, Signature: 9/22/2021 _____, PPD _____

Signature Page – OS Medical Expert

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Study Initiator and Funder	Bayer AG

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Print Name: PPD

Date, Signature: 10/5/2021 _____, PPD _____

Signature Page – OS Epidemiologist

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Print Name: PPD

Date, Signature: 9/22/2021 _____, PPD _____