Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

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.
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