Observational Study Results Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Overall data disclosed, may differ from published or presented data and are a reflection of the limited information provided here. The results from a single study 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	Observational Studies in Cancer Associated Thrombosis for Rivaroxaban in SwEden (OSCAR-SE)
Report version and date **Author**	v 1.0, 12 April 2023 PPD Karolinska Institutet PPD Karolinska Institutet
IMPACT study number	21616
Keywords	Cancer associated thromboembolism, direct acting anticoagulants, low molecular weight heparin, major bleeding, recurrent venous thromboembolism, all-cause mortality
Rationale and background	Cancer is one of the leading causes of death globally and is known to increase the risk of Venous Thromboembolism (VTE) including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). Cancer Associated Thrombosis (CAT) is a major cause of morbidity and mortality in patients with cancer. During recent years treatment options for VTE in patients with cancer have expanded to include direct acting oral anticoagulants (DOACs) as an alternative treatment to Low Weight Molecular Heparins (LWMH) in patients with cancer after careful consideration of the risk of bleeding and possible interaction with cancer therapies. While their cancer is active, patients remain at increased risk of VTE. For reasons of convenience and route of administration, DOACs provide a less burdensome alternative to LMWH and are likely to improve adherence. However, there is a need to better understand how DOACs are used to treat VTE in patients with cancer, in particular in relation to cancer therapies, duration of use and risks of recurrent VTE events, major bleeding and death.
Research question and objectives	The research questions were to examine the occurrence of recurrent VTE, major bleeding and death; and associated treatments for VTE among subjects with cancer in Sweden. Patients with cancer with higher risk of bleeding were excluded. The objectives were: 1. To estimate the risk of recurrent VTE, major bleeding and all-cause mortality in individuals with cancer not associated with a high risk of bleeding (including upper gastrointestinal cancer, malignant immunoproliferative diseases and leukemia, see Appendix 1) in Sweden

	2. To describe the anticoagulation treatments for VTE including the choice of drug and duration of treatment 3. To estimate the risk of a recurrent VTE, major bleeding and all-cause mortality by type of anticoagulation treatment (LMWH, VKA or DOAC) as independent outcomes 4. To compare incidence rates of recurrent VTE, major bleeding and death in subjects treated with rivaroxaban versus LMWH; and DOACs versus LMWH
Study design	Cohort study
Setting	All residents in Sweden diagnosed with cancer from 2013 through 2019 were identified through the Swedish Cancer Register (SCR) and linked to other national health registers (National Patient Register [NPR], Prescribed Drug Register [PDR], Total Population Register [TPR], and Cause of Death Register [CDR]).
Subjects and study size, including dropouts	All patients diagnosed with cancer in Sweden from year 2013 to 2019 were identified. We observed 555,558 cases of cancer, of whom 12,685 had a first VTE. After applying inclusion and exclusion criteria, 8,058 individuals entered the study.
Variables and data sources	Type of cancer was identified through ICD10 codes C00-C97 (malignant neoplasms) including data on cancer stage and type at diagnosis. Baseline characteristics including demographic information as well as data on comorbidities through ICD10 codes (see Appendix 1) from hospitalizations and open care visits to specialists were collected. We obtained information on prescribed drugs through ATC codes (see Appendix 1) to capture dispensed prescriptions of DOACs, VKA and LMWH as well as other relevant medicines including cancer treatments, whenever available. ICD10 codes to identify the outcomes DVT, PE, VTE, major bleeding are presented in Appendix 1. The outcome all-cause mortality was identified from date of death registered in CDR. Data source was the Swedish health registries including the Swedish Cancer Register, the National Patient Register, the Prescribed Drug Register, and the Cause of Death Register.
Results	In total, 8,058 adult eligible individuals were recorded with cancer between 2013 and 2019 in SCR, and with CAT registered in NPR within 183 days of their cancer diagnosis. The comparative analyses included 5,737 individuals of whom 556 used DOACs and 5,181 used LMWH. Among the DOAC users, 283 used rivaroxaban.

	For recurrent VTE, the cumulative incidence proportions varied between 3.5% and 8.4%, the incidence rates varied between 54 events per 1000 person-years and 241 events per 1000 person-years. For major bleeding, the cumulative incidence proportions varied between 4.5% and 7.7%, the incidence rates varied between 24 events per 1000 person-years and 89 events per 1000 person-years, the cumulative incidence function varied between 0.8% and 6.7%. For all-cause mortality, the cumulative incidence proportions varied between 11.3% and 52.5%, the incidence rates varied between 263 events per 1000 person-years and 894 events per 1000 person-years, the cumulative incidence varied between 11.3% and 53.5%. The number of patients treated with DOACs has increased 10 times from 2013 and onwards, for LMWH the number of patients have been constant over time, approximately 750 per year. The number of patients treated with VKA has decreased from 52 patients in 2013 to 6 patients in 2019. The use of LMWH decreased from 88% at study start to 45% after 2 years. The use DOACs were mainly represented by apixaban and rivaroxaban. The use of apixaban increased from 4% at initiation to 20% after 2 years, correspondingly the use of rivaroxaban went from 5% at study start to 19% after 2 years. The duration of use of DOACs were mainly evenly distributed over the studied lengths. Rivaroxaban showed somewhat higher proportions for the longer durations, 57.9% of patients treated with rivaroxaban used it for more than 6 months, whereas 47.8% of those treated LMWH used it more than 6 months. VKAs were mostly used for a short time, less than 3 months (74%). In individuals under LMWH treatment, recurrent VTE cumulative incidence proportions varied between 3.8% and 8.7%; recurrent VTE incidence rates varied between 57 events per 1000 person-years and 228 events per 1000 person-years; and cumulative incidence functions for recurrent VTE varied between 4% and 11%. Under LMWH treatment, major bleeding cumulative incidence proportions varied between 0.9% and 4.9%; major bleeding incidence rates varied between 22 events per 1000 person-years and 95 events per 1000 person-years; and cumulative incidence functions for major bleeding varied between 0.9% and 6.8%. Under LMWH treatment, all-cause mortality cumulative incidence proportions varied between 12.2% and 56.4%; all-cause mortality incidence rates varied between 289 events per 1000 person-years and 980 events per 1000 person-years; and

	cumulative incidence functions for all-cause mortality varied between 12.2% and 57.4%. In individuals under DOAC treatment, recurrent VTE cumulative incidence proportions varied between 0.5% and 11.4%; recurrent VTE incidence rates varied between 11 events per 1000 person-years and 399 events per 1000 person-years; and cumulative incidence functions for recurrent VTE varied between 0.5% and 13%. Under DOAC treatment, major bleeding cumulative incidence proportions varied between 0.4% and 13%; major bleeding incidence rates varied between 12 events per 1000 person-years and 95 events per 1000 person-years; and cumulative incidence functions for major bleeding varied between 0.4% and 14.4%. Under DOAC treatment, all-cause mortality cumulative incidence proportions varied between 0.7% and 28%; all-cause mortality incidence rates varied between 27 events per 1000 person-years and 401 events per 1000 person-years; and cumulative incidence functions for all-cause mortality varied between 0.7% and 29.1%. In individuals under rivaroxaban treatment, recurrent VTE cumulative incidence proportions varied between 1.0% and 11.1%; recurrent VTE incidence rates varied between 11 events per 1000 person-years and 391 events per 1000 person-years; and cumulative incidence functions for recurrent VTE varied between 1% and 12%. Under rivaroxaban treatment, major bleeding cumulative incidence proportions varied between 0.5% and 10%; major bleeding incidence rates varied between 15 events per 1000 person-years and 57 events per 1000 person-years; and cumulative incidence functions for major bleeding varied between 0.5% and 11.1%. Under rivaroxaban treatment, all-cause mortality cumulative incidence proportions varied between 1.3% and 24%; all-cause mortality incidence rates varied between 26 events per 1000 person-years and 265 events per 1000 person-years; and cumulative incidence functions for all-cause mortality varied between 1.3% and 25.4%. Incidence rates of bleeding or recurrent VTE comparing DOACs and LMWH were similar, all hazards ratios were close to one. For the comparison of all-cause mortality between DOACs and LMWH all results were statistically significant favoring DOACs. A similar pattern was found comparing rivaroxaban with LMWH, all hazards ratios were close to one except for all-cause mortality favoring rivaroxaban.
Discussion	Results indicate that DOACs and rivaroxaban was associated with similar risks of major bleeding and recurrent VTE as

	LMWH. The all-cause mortality was lower in patients treated with DOACs and rivaroxaban as compared to LMWH, worth noting a likely effect of residual confounding why results for all-cause mortality should be interpreted with caution. We conclude that rivaroxaban may serve as alternative to LMWH in treating patients with cancer-associated thrombosis.
Marketing Authorization Holder(s)	Bayer AG, Müllerstrasse 173, 13353 Berlin

2. List of abbreviations

APX	Apixaban
ATC	Anatomical Therapeutic Chemical (Classification System)
CAT	Cancer Associated Thrombosis
CDR	Cause of Death Register
CI	Confidence Interval
CIF	Cumulative Incidence Function
CIP	Cumulative Incidence Proportion
DBG	Dabigatran
DEGURBA	Degree of Urbanization
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
EDX	Edoxaban
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
IR	Incidence Rate
ITT	Intention To Treat
LMWH	Low Molecular Weight Heparin
MAH	Marketing Authorization Holder
N/A	Not Applicable
NE	Not Estimable
NPR	National Patient Register
OAC	Oral Anticoagulant
OS	Observational Study
OT	On Treatment
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PDR	Prescribed Drug Register