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Effectiveness and safety of oral anticoagulation treatment beyond 1 year after venous thromboembolism in patients at intermediate recurrence risk

Running title: Extended treatment for venous thromboembolism

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Abstract

Effectiveness and safety of long-term anticoagulation treatment is uncertain in venous thromboembolism (VTE) patients at intermediate risk of recurrence. We examined the association between treatment beyond one year and outcomes in a Danish nationwide register-based study. VTE patients at intermediate risk of recurrence, i.e. non-cancer patients with a first-time unprovoked VTE, who started oral anticoagulation treatment within 30 days and were alive 365 days after the index VTE were included and followed between 2007-2015. Exposure was extended (>365 days) or intermediate (91-365 days) treatment. Analyses were done using Cox regression on a propensity score weighted population. We included 18,609 patients with 7,232 (38.9%) receiving extended treatment. Mean duration of follow-up was 2.6 years. Compared with intermediate treatment, treatment beyond 365 days was associated with a lower weighted risk of recurrent VTE (hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.49-0.65) and all-cause mortality (HR 0.81, 95%CI 0.72-0.90) and an increased risk of major bleeding (HR 1.87, 95%CI 1.58-2.22). In conclusion, extended anticoagulation treatment (predominantly warfarin) beyond 1 year was in real-life settings associated with a lower risk of recurrent VTE and all-cause mortality among VTE patients with an intermediate risk of recurrence. However, an increased bleeding risk should be considered.

Abbreviations:
Venous Thromboembolism VTE
Deep venous thrombosis DVT
Pulmonary embolism PE
Oral anticoagulants OAC
Non-vitamin K antagonist oral anticoagulants NOAC
International Classification of Diseases, 10th revision ICD-10
Computed tomography CT, Confidence intervals (CI)

1. Introduction

Venous thromboembolism (VTE), i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE), is a frequent and serious medical condition associated with a substantial risk of adverse outcomes.[1-4] The proportion of patients who die within one year is approximately 20% for both DVT and PE.[3-4] Furthermore, VTE is associated with long-term complications including post-thrombotic syndrome and pulmonary hypertension.[5-6] Overall, VTE is among the three most common causes of cardiovascular death, only exceeded by acute coronary syndrome and stroke.[7]

VTE can effectively be treated with oral anticoagulant (OAC) therapy with vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (NOAC), which should be continued for at least 3 months in all patients with VTE.[7,8] Prolonging OAC therapy beyond this period depends on the estimated long-term risk of recurrent VTE if OAC therapy is discontinued, the risk of major bleeding resulting from extended OAC as well as patient preferences.[8,9] Guidelines recommend no treatment beyond six months, when the risk of recurrence is sufficiently low after a VTE provoked by temporary factors, e.g. immobilization or lower limb fracture.[8] In addition, there is consensus that extended or indefinite length anticoagulation therapy is warranted in patients at the highest risk of recurrence (i.e. patients with active metastatic cancer).[9] However, controversy remains regarding the appropriate duration of treatment for the large remaining group of patients with unprovoked VTE, who has an intermediate risk of recurrence as delineated in two recent papers from 2019, a systematic review and meta-analysis.[10,11] The risk of recurrence after cessation of OAC therapy is approximately 25% at five years among patents with incident unprovoked VTE, who have completed at least three months of treatment.[10] Hence, current guidelines suggest that all patients with unprovoked VTE and a non-high bleeding risk, should be considered for life-long therapy.[8-10] However, even though clinical trial data support the recommendation for

patients with VTE, data from real-life settings are sparse, and although the prevention of recurrence is certainly desirable, the risk of major bleeding, together with the burden of therapy and costs, still makes extended OAC therapy potentially controversial.[12]

The aim of this study was, therefore, to examine the association between extended OAC therapy beyond one year with clinical outcomes in patients with an intermediate risk of recurrent VTE.

2. Methods

Design and setting

We conducted a population-based follow-up study based on national Danish registers covering the entire population (≈5.7 million). The overall study design is illustrated in Figure 1. The Danish National Health Service provides universal tax-supported healthcare to all residents, providing unrestricted access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including anticoagulants.[13] The study was approved by the Danish Data Protection Agency (J.nr. KEA-2016-6). According to Danish law, ethical committee approval is not required for register-based studies.

Data sources

The study was based on individual-level record linkage of high-quality nationwide medical registers with information on hospitalization history, drug use and vital status. A complete list of the codes used for identification of the study population, exposure, outcomes and covariates are available in Supplementary Table 1.

The civil registration number unique to each Danish citizen, encoding sex and date of birth, enables unambiguous linkage between population-based registers.[14] The registry holds

electronic records of all changes in vital status and migration for the entire Danish

population, including changes in address, date of emigration, and date of death.

The Danish National Patient Registry covers all Danish hospitals and contains information on

all patients discharged from non-psychiatric hospitals since 1977 and on all emergency room

and outpatient specialty clinic visits since 1995.[15] Each hospital discharge or visit to an

outpatient clinic (but not to general practitioners) is recorded in the register with one primary

diagnosis (the main cause of admission) and one or more secondary diagnoses classified

according to the International Classification of Diseases, 10th revision (ICD-10) since 1994.

The Danish National Database of Reimbursed Prescriptions includes information on

reimbursed medications redeemed at all Danish community and outpatient pharmacies since

1 January 2004.[13] Each time a prescription is redeemed, the patient's civil registration

number, the redemption date, and the Anatomical Therapeutic Chemical Classification

System code, type, and quantity of the drug are recorded.

Study population

All patients ≥18 years with a first-time hospitalization for VTE at any Danish hospital from 1

January 2006 to 31 December 2014 who redeemed an OAC prescription within 30 days were

identified. Both in- and outpatient diagnoses (including both primary and secondary

diagnoses) were considered, whereas emergency room contacts were excluded due to a low

predictive value.[16] This algorithm has previously been validated, and the VTE diagnosis was

confirmed in 90% of the patients after review of medical records.[17] Patients diagnosed with

both DVT and PE during the same index admission were included in the PE group only.

Patients with provoked VTE (pregnancy, surgery, trauma or fracture occurring within 90 days

before diagnosis) were excluded [8,9]. In addition, VTE patients with cancer were excluded

due to their expected need for indefinite anticoagulation therapy. Patients treated exclusively with low-molecular weight heparin (LMWH) were also excluded as this treatment practice may reflect an unrecorded cancer diagnosis. Furthermore, patients not surviving the first 365 days after their index VTE episode were excluded. Finally, patients with treatment breaks in the first 365 days after VTE diagnosis were excluded (please see below for assessment of duration of OAC therapy) as were patients with a recurring VTE event within 365 days after the index VTE date. Thus, a total of 19,516 patients were included in the study (Figure 1).

Anticoagulation therapy

We obtained information on all filled prescriptions for OAC therapy and considered a patient as treated with a given NOAC from the day of filling a prescription and for the subsequent number of days corresponding to the number of tablets in a package for rivaroxaban (used once daily except for patients without renal failure using 15 mg tablets, where two tablets per day were assumed) or half the number of tablets in a package for dabigatran and apixaban (used twice daily). For vitamin K antagonists, almost exclusively warfarin, we assumed an average dose of one tablet per day. The patient's first non-LMWH prescription was used to categorize the treatment type. A 30-day grace period was added for all drugs to account for minor non-compliance and irregular prescription refills. Finally, any excess pill accumulation was limited to a maximum of 30 days.

We assessed the duration from the date of the index VTE episode and divided the study population into patients having received either intermediate (91-365 days) or extended (>365 days) therapy.

Clinical outcomes

The following outcomes were assessed:

Recurrence of VTE: Defined as a hospital-based diagnosis of DVT or PE with an ultrasound or CT scan. This algorithm has previously been validated and a positive predictive value of 79% was reported.[17]

Major bleeding: Defined as a hospital admission with a discharge diagnosis of intracranial, gastrointestinal, and other bleeding (including respiratory and urinary tract bleeding and anaemia caused by bleeding). Only unplanned admissions were included.

All-cause mortality: Death from any cause registered in the Danish Civil Registration System.

Patient characteristics

We obtained information on the following variables for each patient at the time of start of follow-up, i.e. one year after VTE diagnosis:

Sex, age, history of congenital or acquired thrombophilia, heart failure, autoimmune disorders, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, severe obesity, pulmonary hypertension, nephrotic syndrome, myocardial infarction, stroke, diabetes mellitus, atrial fibrillation, history of bleeding and respiratory failure. In addition, we computed the Charlson comorbidity index score one year after VTE diagnosis, which was adapted for use with hospital discharge register data.[18,19] We defined three levels of comorbidity: a score of 0 ("low"); a score of 1-2 ("moderate comorbidity"); and a score ≥ 3 ("high comorbidity"). Furthermore, we obtained information on filled prescriptions for antidiabetic drugs, anti-psychotics, postmenopausal hormone therapy, statins, and

antiplatelets (including low-dose aspirin, clopidogrel, dipyridamole, ticagrelor, and prasugrel). We used a 3-month time window preceding the date for start of follow-up, ie, 365 days after the index VTE event, for all drugs to identify ongoing treatment. The exception was antidiabetic drugs where we used the entire available prescription history and combined it with the patient's hospitalization history to identify patients with a history of diabetes (defined as a hospital discharge diagnosis or at least two redeemed prescriptions). Furthermore, we obtained information on the type of anticoagulation used when redeeming their first prescription after the index VTE, including Vitamin K antagonist, dabigatran, rivaroxaban, or apixaban.

Statistical analysis

Patients were followed from day 365 after admission for the index VTE episode until discontinuation of anticoagulation therapy, the occurrence of the clinical outcome of interest, death or end of the study period (31 December, 2015), whichever occurred first. In addition, patients with intermediate term treatment were censored if they resumed treatment during follow-up.

We first computed incidence rates of the clinical outcomes (overall and separately for DVT and PE). Weighted cumulative incidence curves were constructed for each of the outcomes. Death was considered as a competing risk for recurrent VTE and major bleeding. In addition, discontinuation of anticoagulation treatment in the extended treatment group and re-start of treatment in the intermediate treatment group were considered as competing risks. Cumulative incidences were calculated using the LIFETEST procedure in SAS using the eventcode option in the TIME statement to handle competing risks.

We used propensity score weighting using stabilized average treatment effect in the population weights to compare the clinical outcomes for patients receiving intermediate and extended OAC therapy.[20,21.]

Propensity scores were estimated using logistic regression including the following covariates: age (included as a restricted cubic spline), sex, calendar year, history of congenital or acquired thrombophilia, heart failure, autoimmune disorders, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, severe obesity, pulmonary hypertension, nephrotic syndrome, myocardial infarction, stroke, diabetes mellitus, atrial fibrillation, history of bleeding (before the index VTE event and between the index VTE and start of follow-up), respiratory failure, filled prescriptions for antidiabetic drugs, anti-psychotics, postmenopausal hormone therapy, statins, antiplatelets, Vitamin K antagonist, dabigatran, rivaroxaban, or apixaban. To assess the positivity assumption (that any patient must have a non-zero probability of getting either treatment) we looked at the estimated weights.[22,23] The mean weight was approximately 1 in all analyses and none of the individual weights were considered extreme (minimum weight of 0.34 and maximum weight of 7.01 across all analyses), which support the assumption of positivity.

Covariate balance after weighting was assessed by looking at the standardized differences for each covariate included in the propensity score (PS)-model (Supplementum Figure 1), and by looking at the empirical cumulative distribution function of continuous variables (data not shown).

We used inverse probability of treatment weighted Cox proportional hazard regression to obtain hazard ratios adjusted for confounding with 95% confidence intervals (CI) for the individual clinical outcomes. CIs were calculated using a robust sandwich estimator. Analyses were performed overall and stratified according to type of index event (DVT or

PE), age and sex. As a sensitivity analysis, we also examined the association between duration of OAC therapy and risk of bleeding, defined as any in- or outpatient contact with bleeding (i.e., not restricted to acute hospital contacts). Finally, sensitivity analyses were done where the grace period and excess pill accumulation were set to either 0 or 60 days for both. We specified a separate PS-model in each subgroup/sensitivity analysis. The proportional hazard assumption was assessed using log(-log(survivals)) vs. log(time) plots in the ps-weighted populations. The overall conclusion across all models was that the proportional hazards assumptions were justifiable.

The direct relation between the treatment benefit (measured by decrease in the risk of VTE) and treatment harm (measured by increase in the risk of major bleeding) of anticoagulation treatment can be expressed as the net clinical benefit as suggested by Singer et al.[24] Net clinical benefit incorporates both benefits and risks into single endpoint determination. We calculated the net clinical benefit for short-term duration of anticoagulation treatment as follows:

Net clinical benefit = (Adjusted risk difference for recurrent VTE intermediate duration – extended duration) – (Adjusted risk difference for intracranial bleeding extended duration – intermediate duration)

The net clinical benefit is interpreted as the balance between the preventive effects of extended and intermediate duration of anticoagulation treatment on the risk of VTE events versus the harmful effect of induced risk of major bleeding events. Positive net clinical benefit favours extended duration over intermediate duration of oral anticoagulation.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Among the 18,609 patients included in the study, a total of 7,232 (38.9%) received extended treatment, i.e. OAC therapy beyond 365 days after the index VTE. The remaining 11,377 (61.1%) received OAC therapy for 91-365 days after the index VTE episode. The mean duration of follow-up was 2.6 years for all examined outcomes, including recurrent VTE, major bleeding and death. The median durations of follow-up for recurrent VTE, major bleeding and death, respectively, were all 0.8 year in the extended treatment group and 2.4-2.6 years in the intermediate group. The most frequent reason for censoring follow-up time was discontinuation of treatment in the extended treatment group (N=4,127 patients, 57.1%) and clinical events in the intermediate group (N=7,403, 65.1%). As patients in the extended treatment duration group were censored with discontinuing oral aniticoagulant therapy, the follow-up time reflected time on treatment during follow-up. Similarly, patients in the intermediate treatment group were censored if they restarted anticoagulant therapy and the follow-up time here reflected time off-treatment. Patient characteristics are presented in Table 1. The difference in patient characteristics was small in general, although a higher proportion of patients aged ≥75 years and patients with comorbidity were noted in the group receiving extended therapy.

The standardized difference was small for all covariates in all weighted populations (for the main analysis, see Supplementary Figure 1). Furthermore, the empirical cumulative distribution function of age was close to identical in both treatment groups in all weighted populations (results not shown). Both indicate that the PS weights has successfully created pseudo populations where there is no measured confounding due to the variables included in the PS.

Weighted cumulative incidence curves are presented in Figures 2-4. The curves show a lower incidence of recurrent VTE and all-cause mortality among patients receiving extended

therapy. In contrast, patients receiving intermediate-term therapy appeared to have a lower incidence of major bleeding. These observations are further supported by Table 2, which presents unweighted and weighted incidence rates of the clinical outcomes and corresponding weighted HRs according to duration of OAC therapy. Extended treatment beyond 365 days was associated with a lower risk of recurrent VTE (HR 0.56, 95% CI 0.49-0.65) and all-cause mortality (HR 0.81, 95%CI 0.72-0.90), but also an increased risk of major bleeding (HR 1.87, 95%CI 1.58-2.22) as well as all assessed subtypes of bleeding in the weighted analysis.

Stratified and sensitivity analyses

The findings appeared to be independent of the type of index event (DVT or PE) (Table 3).

Extended treatment appeared to be associated with higher effectiveness among the elderly. However, the incidence rates of major bleeding (but not the HRs) also increased substantially with age (Supplementary Table 2). When stratifying analyses according to sex, we found extended treatment to be associated with a lower risk of recurrent VTE among both men and women, even though the association appeared potentially stronger among men (Supplementary Table 3). There were also indications that the bleeding risk associated with extended treatment appeared to be lower among men compared with women, but with overlapping CIs.

We found higher incidence rates but virtually unchanged HRs in a sensitivity analysis, where major bleeding was defined as any in- or out-patient hospital contact with a bleeding diagnosis. The IRs of bleeding were approximately 50% higher in these analyses (data not shown). Moreover, the overall patterns remained when applying alternative grace period and excess pill accumulation, although some variation in the HRs was observed (Supplementary Table 4).

The overall net clinical benefit was 1.7, i.e., in favour of extended duration over intermediate duration of oral anticoagulation. The net clinical benefit was positive for both index DVT (2.2) and index PE (8.8).

4. Discussion

In this nationwide cohort study, extended OAC therapy, predominantly in the form of warfarin, beyond one year in patients with an estimated intermediate risk of recurrent VTE was associated with reduced risk recurrent VTE and all-cause mortality. However, extended therapy was also associated with a significantly increased risk of major bleeding.

 Our findings provide additional support for the hypothesis that extended OAC therapy should be considered for VTE patients with a non-high bleeding risk.[10-12] Hence, extended therapy beyond the standard length of 3-12 months also appears to be associated with a substantially lower risk of recurrent VTE in real-life settings. The challenge is obviously the higher bleeding risk, which from a clinical point of view is the vicious twin of the desired protection from recurrent VTE risk of OAC therapy. The risk of bleeding is a major concern for two principal reasons: Firstly, the absolute risk of bleeding is high. Secondly, the case-fatality risk associated with bleeding during OAC therapy has been reported to exceed 10%.[25] However, it is reassuring that extended therapy in our study, in line with a previous Danish study, was associated with a lower all-cause mortality indicating that the overall balance between the antithrombotic and bleeding inducing effect of OAC therapy was favourable.[26] We found indications of age- and sex-related differences in the effectiveness and safety of extended therapy in our study. However, more efforts are clearly needed in order to clarify, how best to identify the patients most likely to benefit from extended OAC therapy. Promising clinical prediction scores including the Vienna Prediction Model, the DASH score

as well as the 'MEN continue and HERDOO2' rule, have been suggested and studies are warranted to evaluate the impact of a more widespread clinical use of such tools.[27-30]

Study strengths and limitations

The strengths of our study include the access to nationwide registries covering the entire population, which reduces the risk of selection bias and provides high quality data with complete follow-up, including a validated algorithm for identifying recurrent VTE episodes based on hospital register data.[17] In addition, information on a broad range of patient characteristics allowed us to construct a detailed prognostic profile for each patient, which could be accounted for when comparing clinical outcomes among patients receiving different duration of OAC therapy.

The most important limitation is the observational study design with the inherent risk of unaccounted or residual confounding. In particular, detailed information such as laboratory values and patient preferences that may form the basis for clinical decisions on whether to extend or stop OAC therapy was not available. Furthermore, estimating the duration of prescription is a well-known challenge within pharmacoepidemiology, in particular for warfarin where the dose may vary between patients and over time for the same patient. To assess how much this uncertainty may have influenced our study findings, we performed additional sensitivity analyses using a grace period and maximum excess pill accumulation of both 0 and 60 days. The results showed little variation compared with the primary analysis using a grace period and maximum excess pill accumulation of 30 days, indicating that the uncertainty had no substantial impact on the study findings and supporting the robustness of the overall study conclusion. However, despite the use of an algorithm with >90% positive predictive value to identify index VTE events and 79% for recurrent VTE events, we cannot exclude the risk of misclassification in the administrative data. Still, it is unlikely that such

misclassification would differ between the extended and intermediate treatment groups.
Finally, the study covered a time period where the majority of patients were still using
Vitamin K antagonists rather than NOACs, and it was therefore not possible to make separate
analyses on type of OAC to determine any potential differences in effectiveness and safety.
However, it could be argued that the findings may still provide useful guidance for clinicians
and patients in the NOAC era. Hence, since real-life studies have confirmed the clinical value
of NOAC in shorter term VTE care, the positive findings on extended warfarin-based
treatment in our study indicate that extended NOAC-based treatment is also likely to be
effective and perhaps even with a better safety profile. This, of course, remains to be
supported by future studies.

In conclusion, extended anticoagulant treatment beyond 1 year was associated with a lower
risk of recurrent VTE and all-cause mortality among intermediate risk VTE patients. Still, the
associated increased risk of major bleeding should be taken into account.

Author contributions

S.P. Johnsen designed and conceptualized the study, obtained the official approvals,
interpreted the data and drafted the manuscript. T.B. Rasmussen handled data management
and statistical analysis, interpreted the data and revised the manuscript for intellectual
contents. AM Falstie-Jensen had a major role in the acquisition of data, interpreted the data
and revised the manuscript for intellectual contents. L. Harboe, L. Dybro, M.L. Hansen, A.
Brandes, EL Grove and AM Münster designed and conceptualized the study, interpreted the
data and revised the manuscript for intellectual contents.

Conflicts of interest

Funding sources

Data availability statement

Data cannot be shared publicly because of Danish legislation. Data can be accessed through the Danish Health Data Authority and Statistics Denmark for researchers at authorized institutions. Information on data access is available online (http://sundhedsdatastyrelsen.dk/da/forskerservice). Access to data requires approval from the Danish Data Protection Agency (https://www.datatilsynet.dk/english/legislation). The authors did not have special access privileges to these data.

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Table 1. Patient characteristics according to duration of treatment for venous thromboembolism.

	Extended treatment (+365 days)		Intermediate treatment (91-365 days)		All patients	
	N	%	N	%	N	%
Number of patients	7,232	100.0	11,377	100.0	18,609	100
Men (%)	3,823	52.9	5,787	50.9	9,610	51.6
Pulmonary embolism	3893	53.8	4,029	35.4	7,922	42.6
Age groups (years):						
18-49	1,482	20.5	2,815	24.7	4,297	23.1
≥50-74	3,619	50.0	5,569	48.9	9,188	49.4
≥75	2,131	29.5	2,993	26.3	5124	27.5
Modified Charlson Comorbidity Index:						
0	4,164	57.6	7,466	65.6	11,630	62.5
1-2	2,366	32.7	3,094	27.2	5,460	29.3
3+	702	9.7	817	7.2	1,519	8.2
Congenital or acquired thrombophilia	327	4.5	373	3.3	700	3.8
Heart failure	502	6.9	424	3.7	926	5.0
Autoimmune disorders	435	6.0	573	5.0	1,008	5.4
Severe obesity	372	5.1	556	4.9	928	5.0
Pulmonary hypertension	96	1.3	54	0.5	150	0.8
Nephrotic syndrome	11	0.2	5	0.0	16	0.1
Diabetes mellitus	600	8.3	767	6.7	1,367	7.3
Ischemic stroke	302	4.2	337	3.0	639	3.4
Acute myocardial infarction	205	2.8	269	2.4	474	2.5
Atrial fibrillation	937	13.0	465	4.1	1,402	7.5
Bleeding history	536	7.4	820	7.2	1,356	7.3

	Extended treatment (+365 days)		Intermediate treatment (91-365 days)		All patients	
	N	*%*	*N*	*%*	*N*	*%*
Respiratory failure	225	3.1	290	2.5	515	2.8
Venous thromboembolism treatment:						
Apixaban	26	0.4	43	0.4	69	0.4
Dabigatran	37	0.5	13	0.1	50	0.3
Rivaroxaban	439	6.1	1,137	10.0	1,576	8.5
Vitamin K antagonist	6,730	93.1	10,184	89.5	16,914	90.9
Other medication:						
Antidiabetic drugs	455	6.3	530	4.7	985	5.3
Antipsychotics	297	4.1	412	3.6	709	3.9
Postmenopausal hormone therapy	238	3.3	393	3.5	631	3.4
Statins	1,418	19.6	1,694	14.9	3,112	16.7
Anti-platelets	773	10.7	1,810	15.9	2,583	13.9

Table 2. Incidence rates (IR) and inverse probability of treatment weighted hazard ratios (HR) of clinical outcomes among patients with venous thromboembolism (VTE) according to duration of anticoagulation treatment. Follow-up started after 365 days.

Clinical outcome	Unweighted IR pr 1000 PY	Weighted IR pr 1000 PY	Weighted HR
Recurrent VTE - Extended (+365 Days)	19.5	20.6	0.56 (0.49-0.65)
Recurrent VTE - Intermediate (91-365 Days)	31.8	32.2	Reference
Major Bleeding - Extended (+365 Days)	21.5	20.6	1.87 (1.58-2.22)
Major Bleeding - Intermediate (91-365 Days)	10.1	10.7	Reference
Intracranial Bleeding – Extended (+365 Days)	3.8	3.4	1.45 (0.99-2.12)
Intracranial Bleeding - Intermediate (91-365 Days)	2.2	2.3	Reference
Gastrointestinal Bleeding – Extended (+365 Days)	10.3	9.8	1.75 (1.37-2.22)
Gastrointestinal Bleeding - Intermediate (91-365 Days)	5.1	5.4	Reference
Other Bleeding – Extended (+365 Days)	8.7	8.6	2.35 (1.79-3.07)
Other Bleeding - Intermediate (91-365 Days)	3.5	3.6	Reference
All-cause Mortality - Extended (+365 Days)	37.6	34.1	0.81 (0.72-0.90)
All-cause Mortality - Intermediate (91-365 Days)	38.2	41.2	Reference

PY: Person years

Table 3. Incidence rates (IR) per 1000 person years and inverse probability of treatment weighted hazard ratios (HR) of clinical outcomes among patients with index deep venous thrombosis (DVT) and pulmonary embolism (PE) according to duration of oral anticoagulation therapy. Follow-up started after 365 days.

| Clinical outcome	DVT			PE		
	Crude IR	Weighted IR	Weighted HR	Crude IR	Weighted IR	Weighted HR
Recurrent VTE - Extended (+365 Days)	15.8	16.4	0.54 (0.43-0.67)	22.6	23.6	0.51 (0.42-0.61)
Recurrent VTE - Intermediate (91-365 Days)	27.4	27.6	Reference	42.1	43.0	Reference
Major Bleeding - Extended (+365 Days)	18.0	18.0	1.86 (1.53-2.26)	24.4	24.2	1.75 (1.37-2.22)
Major Bleeding - Intermediate (91-365 Days)	8.9	9.0	Reference	13.1	13.6	Reference
Intracranial Bleeding – Extended (+365 Days)	2.2	2.2	0.98 (0.52-1.86)	5.2	4.8	1.96 (1.11-3.44)
Intracranial Bleeding - Intermediate (91-365 Days)	2.1	2.2	Reference	2.4	2.4	Reference
Gastrointestinal Bleeding – Extended (+365 Days)	9.4	9.2	1.93 (1.37-2.72)	11.0	10.7	1.55 (1.09-2.20)
Gastrointestinal Bleeding - Intermediate (91-365 Days)	4.6	4.6	Reference	6.3	6.9	Reference
Other Bleeding – Extended (+365 Days)	7.7	7.7	2.76 (1.84-4.12)	9.5	9.8	1.79 (1.24-2.57)
Other Bleeding - Intermediate (91-365 Days)	2.7	2.7	Reference	5.4	5.4	Reference
All-cause Mortality - Extended (+365 Days)	27.9	27.4	0.79 (0.66-0.94)	45.5	43.1	0.80 (0.69-0.92)
All-cause Mortality - Intermediate (91-365 Days)	33.7	34.1	Reference	48.9	53.2	Reference
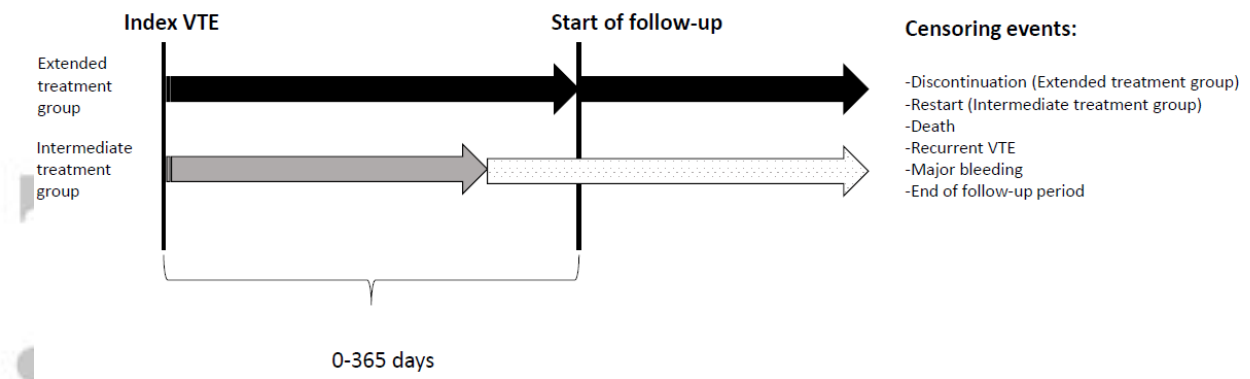
Figure 1. Study design
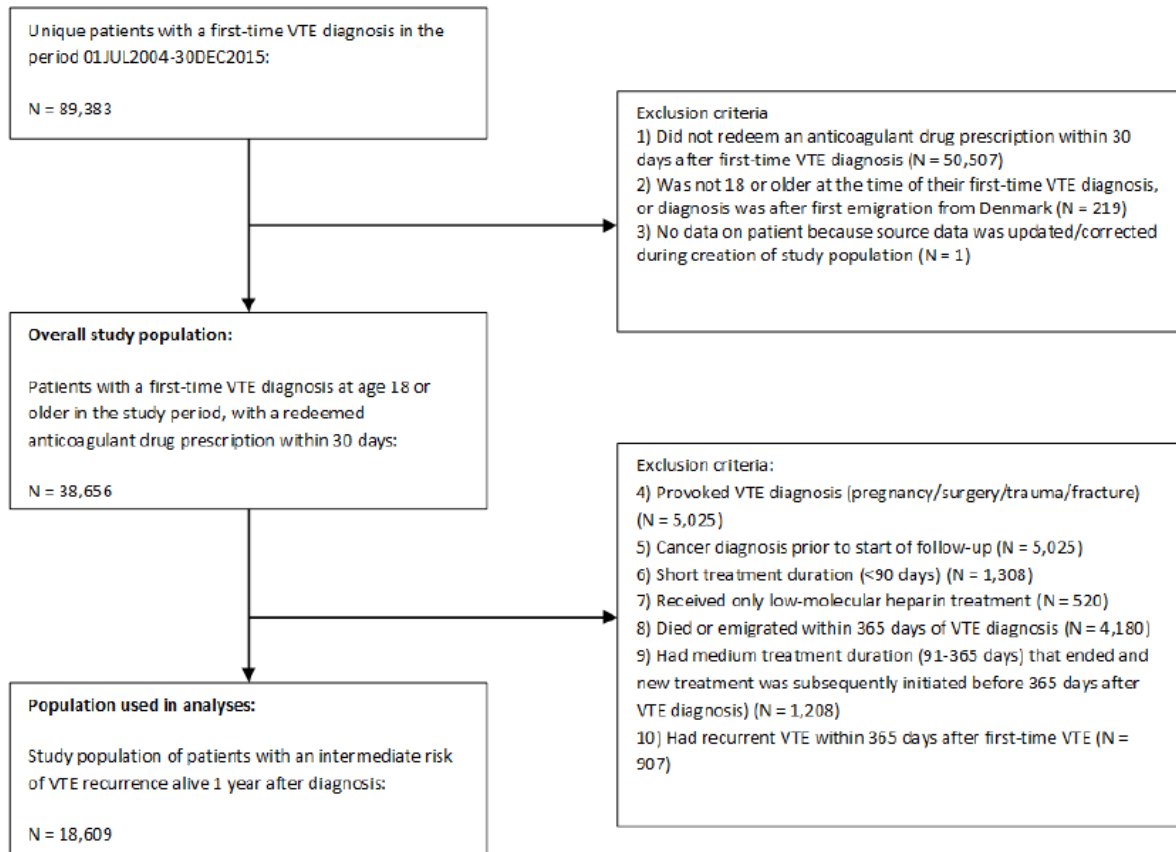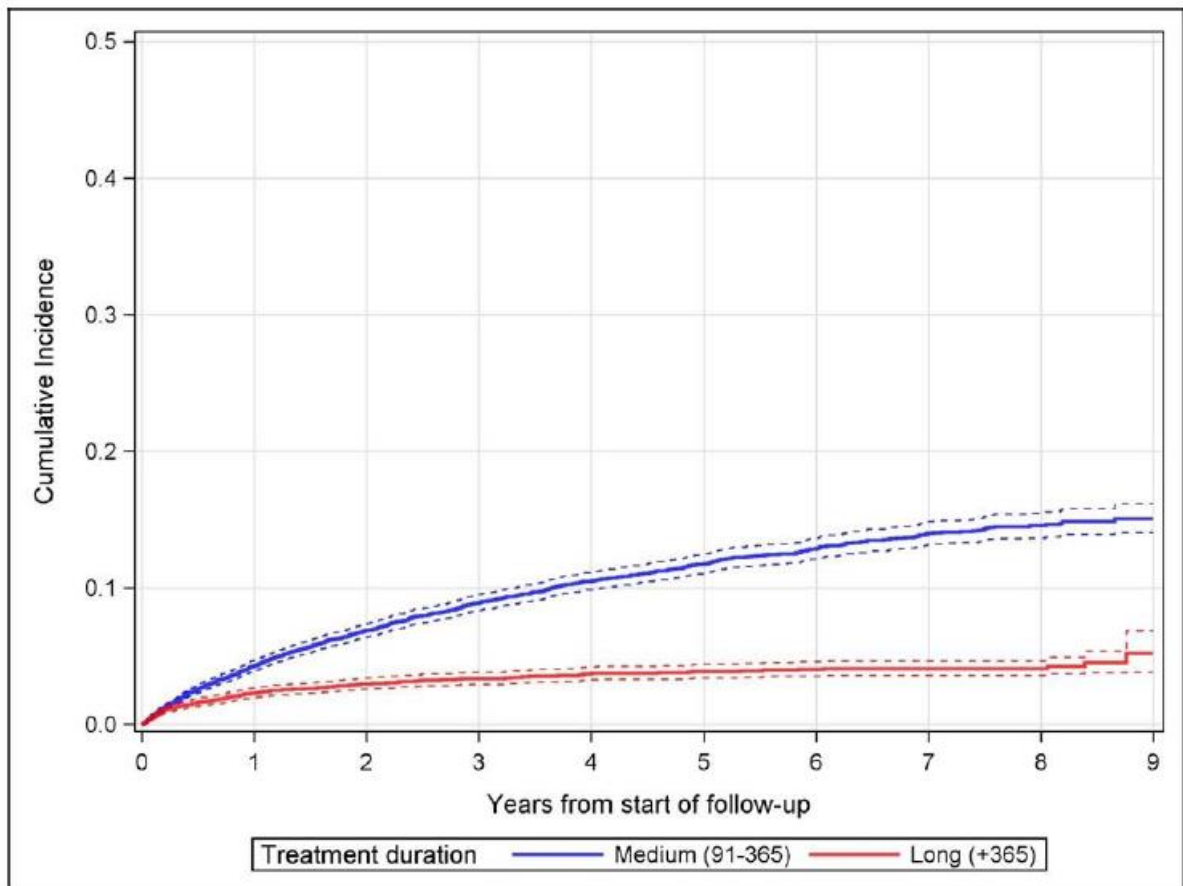
Figure 2. Study population flowchart

Figure 3. Recurrent venous thromboembolism. Weighted cumulative incidence curves according to duration of anticoagulation therapy (+365 days vs. 90-365 days). Follow-up started 365 days after the index venous thromboembolism.
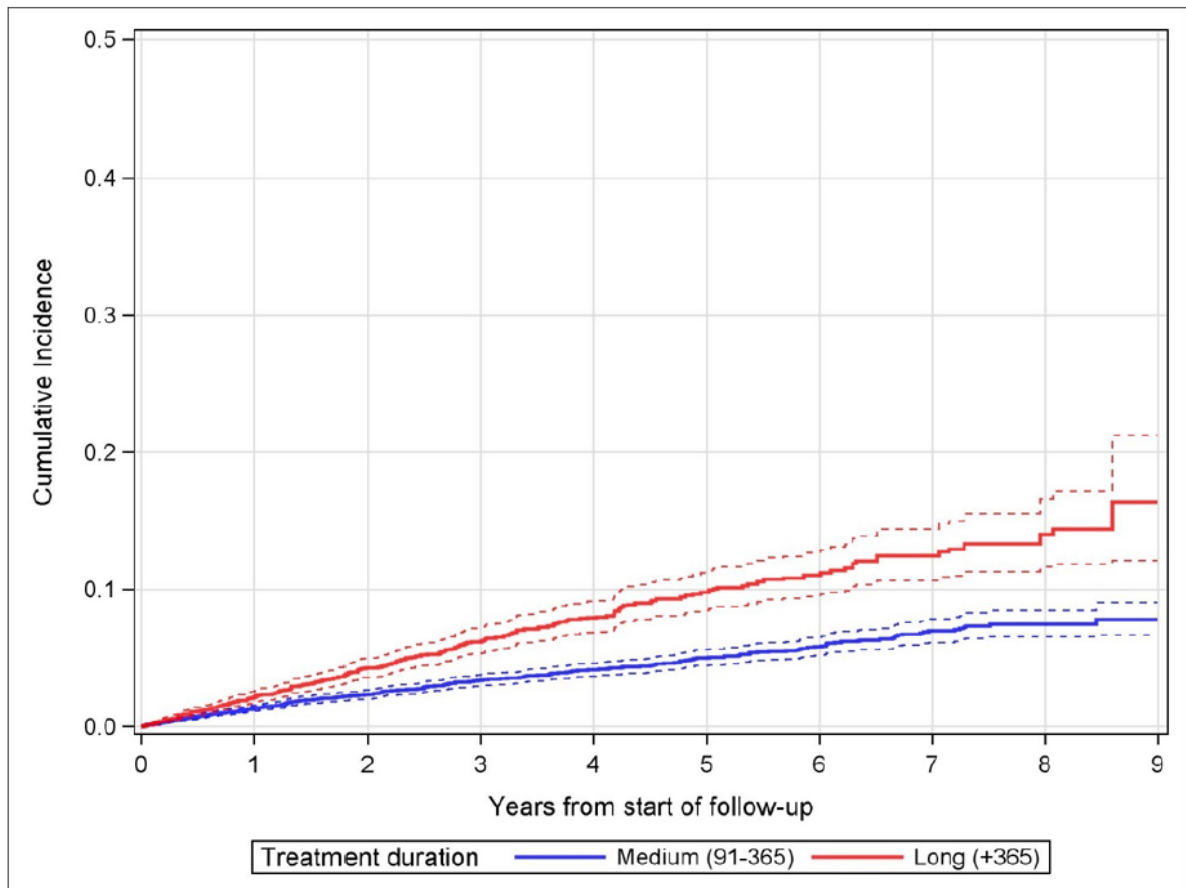
Figure 4. Major bleeding. Weighted cumulative incidence curves according to duration of anticoagulation therapy (+365 days vs. 90-365 days). Follow-up started 365 days after the index venous thromboembolism.
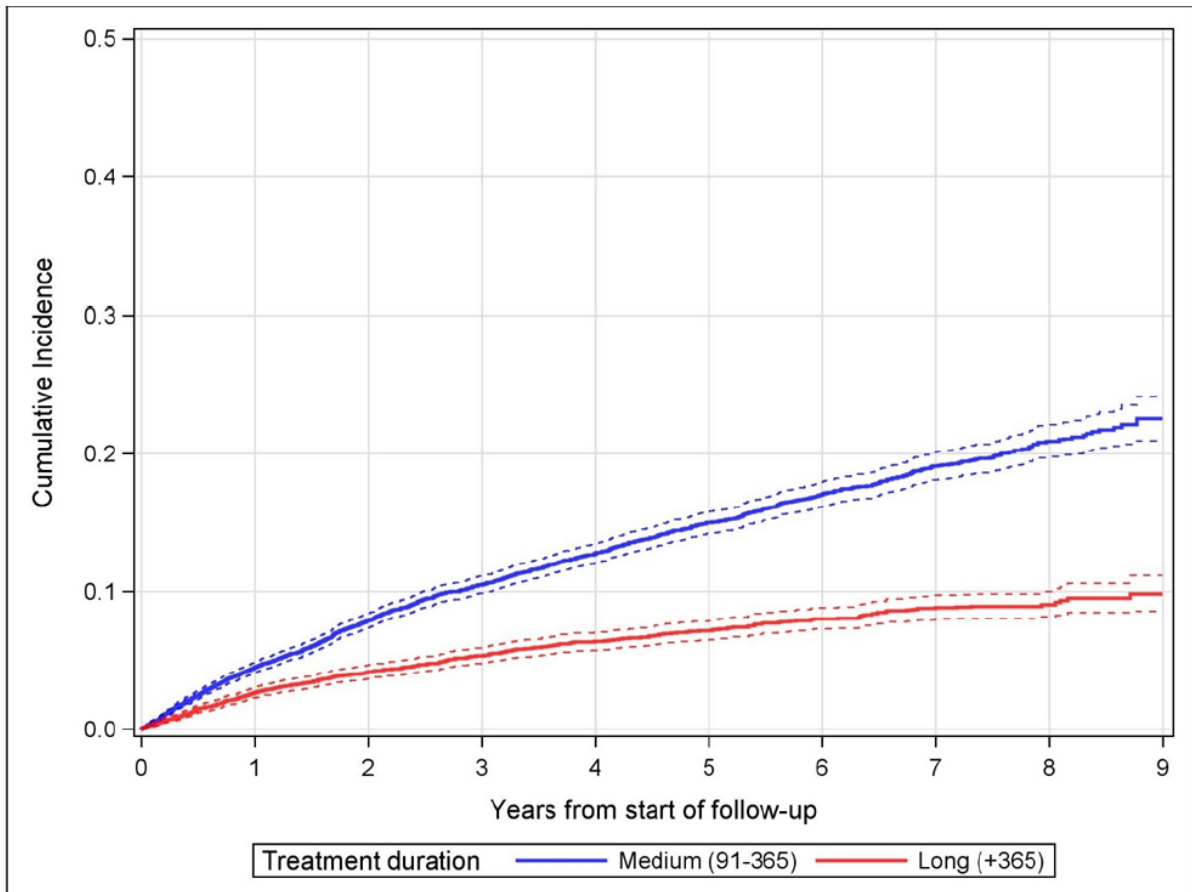
Figure 5. All-cause mortality. Weighted cumulative incidence curves according to duration of anticoagulation therapy (+365 days vs. 90-365 days). Follow-up started 365 days after the index venous thromboembolism.