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Discontinuation of anticoagulants and occurrence of bleeding and thromboembolic events in vitamin K antagonist users with a life-limiting disease

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Abstract:
Background: Data on risks and benefits of long-term anticoagulants in patients with a life-limiting disease are limited. This cohort study aims to describe (dis)continuation of anticoagulants and incidences of bleeding and thromboembolic events in vitamin K antagonist (VKA) users with a life-limiting disease.
Methods: Data from five Dutch anticoagulation clinics were linked to data from Statistics Netherlands and the Netherlands Cancer registry. Prevalent VKA users diagnosed with a pre-specified life-limiting disease between 01/01/2013 and 31/12/2019 were included and followed until 31/12/2019. Hospitalization data were used to identify bleeding and thromboembolic events. Cumulative incidences of anticoagulant discontinuation were calculated, accounting for death as competing risk, and event rates were determined for both anticoagulant exposed and unexposed person-years (PYs).
Results: Among 18,145 VKA users (median age 81 years, 49% females, median survival time 2.03 years), the most common life-limiting diseases were heart disease (60.0%), hip fracture (18.1%), and cancer (13.5%). One year after diagnosis, the cumulative incidence of anticoagulant discontinuation was 14.0% (95%CI: 13.5-14.6). Over 80% of patients continued anticoagulant therapy until the last month before death, with median 14 days between discontinuation and death. Event rates per 100 PYs (95%CI) were comparable during anticoagulant use and after discontinuation for bleeding 2.6 (2.4-2.8) versus 2.1 (1.5-2.8); venous thromboembolism 0.2 (0.1-0.2) versus 0.4 (0.2-0.7); and arterial thromboembolism 3.1 (2.9-3.3) versus 3.3 (2.6-4.2).
Conclusion: Most VKA users with a life-limiting disease continued anticoagulant treatment during their last phase of life, with

similar rates of bleeding and thromboembolic events during use and after discontinuation.

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Discontinuation of anticoagulants and occurrence of bleeding and thromboembolic events in vitamin K antagonist users with a life-limiting disease

Running headline: VKA use in patients with life-limiting diseases

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Abstract

Background: Data on risks and benefits of long-term anticoagulants in patients with a life-limiting disease are limited. This cohort study aims to describe (dis)continuation of anticoagulants and incidences of bleeding and thromboembolic events in vitamin K antagonist (VKA) users with a life-limiting disease.

Methods: Data from five Dutch anticoagulation clinics were linked to data from Statistics Netherlands and the Netherlands Cancer registry. Prevalent VKA users diagnosed with a pre-specified life-limiting disease between 01/01/2013 and 31/12/2019 were included and followed until 31/12/2019. Bleeding and thromboembolic events were identified by hospitalization data. Cumulative incidences of anticoagulant discontinuation, accounting for death as competing risk, and event rates for both anticoagulant exposed and unexposed person-years (PYs) were determined.

Results: Among 18,145 VKA users (median age 81 years (IQR: 74-86), 49% females, median survival time 2.03 years (95%CI: 1.97-2.10)), the most common life-limiting diseases were heart disease (60.0%), hip fracture (18.1%), and cancer (13.5%). One year after diagnosis, the cumulative incidence of anticoagulant discontinuation was 14.0% (95%CI: 13.5-14.6). Over 80% of patients continued anticoagulant therapy until the last month before death, with median 14 days between discontinuation and death. Event rates per 100 PYs (95%CI) were comparable during anticoagulant use and after discontinuation for bleeding 2.6 (2.4-2.8) versus 2.1 (1.5-2.8); venous thromboembolism 0.2 (0.1-0.2) versus 0.4 (0.2-0.7); and arterial thromboembolism 3.1 (2.9-3.3) versus 3.3 (2.6-4.2).

Conclusion: Most VKA users with a life-limiting disease continued anticoagulant treatment during their last phase of life, with similar rates of bleeding and thromboembolic events during use and after discontinuation.

Keywords: Anticoagulants, Deprescriptions, Thromboembolism, Hemorrhage, Advance Care Planning

Summary Table

What is known about this topic?

- In patients with a life-limiting disease, use of long-term preventive medications, including anticoagulants, should be reconsidered and drugs should be deprescribed if potential harms outweigh benefits.

- The limited amount of data on the risks of anticoagulant associated bleeding and thromboembolism after discontinuing anticoagulants in these patients may create uncertainty for physicians and patients, complicating deprescribing decisions.

What does this paper add?

- This large-scale cohort study examined the current practice patterns of vitamin K antagonist (VKA) and overall anticoagulant treatment use in long-term VKA users with a life-limiting disease and showed that over 80% of patients continued anticoagulant therapy until shortly before death.
- While incidence rates of hospital admission for bleeding and thromboembolic events were comparable during anticoagulant use and after discontinuation, these findings should not be interpreted in a causal way.

Introduction

Anticoagulants are frequently prescribed for various indications. Direct oral anticoagulants (DOACs) are now the first choice for most common indications, such as venous thromboembolism (VTE) and prevention of thromboembolic complications in patients with non-valvular atrial fibrillation (AF)[1-3]. However, in certain patient groups, including patients with a mechanical heart valve[4-6], frail older patients with AF[7] or patients with antiphospholipid syndrome[3], vitamin K antagonists (VKAs) are still preferred over DOACs because of superior efficacy in preventing thromboembolic events and/or a safer bleeding risk profile[3].

In patients with a life-limiting disease, the drawbacks of continuing long-term anticoagulants, including frequent international normalized ratio (INR) monitoring during VKA therapy or heparin injections[8] and an increased risk of clinically relevant bleeding[9], may outweigh its benefits. For these patients, Advance Care Planning (ACP), which involves

discussions about future care preferences between patients and their healthcare providers[10] and deprescribing drugs when potential harms outweigh benefits[11], is now standard care. Yet, uncertainty among prescribing physicians about the outcomes of continuing or discontinuing drugs remains a barrier to deprescribing[12]. In the context of anticoagulant treatment, there is a lack of data and consensus on whether or not to continue anticoagulants in patients towards their end of life[8,13-15]. Patients with advanced life-limiting diseases, such as cancer, chronic kidney disease or chronic obstructive pulmonary disease, face an increased risk of both bleeding and thromboembolic events, and this thromboembolic risk may increase if anticoagulant treatment is discontinued[16-22]. Furthermore, physicians might be reluctant to deprescribe anticoagulants because of the perceived thromboembolic risk associated with discontinuation[13].

Most previous studies on anticoagulant use during the last phases of life identified patients at the time of death and retrospectively analyzed their medical history backwards in time[14,23,24]. This approach can introduce selection bias if anticoagulant use influences survival and precludes the use of time-to-event analyses. Consequently, the use, risks and benefits of anticoagulants remain understudied in patients with life-limiting diseases[8]. Therefore, this large cohort study aims to (1) describe the use and discontinuation of VKAs and anticoagulant treatment overall, and (2) determine incidence rates of hospitalization for bleeding and thromboembolic events in VKA users with a life-limiting disease. This study is part of the "Towards Cancer Patient Empowerment for Optimal Use of Antithrombotic Therapy at the End of Life" (SERENITY) project[25].

Methods

Setting and data sources

Our cohort study used data from five large Dutch anticoagulation clinics, linked on an individual-level to data from Statistics Netherlands and the Netherlands Cancer Registry (NCR). Anticoagulation clinics monitor the VKA therapy of patients living in well-defined geographical areas in the Netherlands and provide detailed data on VKA treatment, including start and end dates of VKA therapy, treatment indications, and international normalized ratio (INR) measurements[26]. Data from these clinics were linked to data from Statistics Netherlands by sex, date of birth, postal code, and last known date to be alive. Statistics Netherlands provides nationwide data on personal characteristics[27], diagnoses made during hospital admissions in Dutch hospitals[28-31], cause of death[32], and date of death[33]. Diagnoses in the Dutch Hospital Data (DHD) registry are coded according to the International Classification of Diseases (ICD) (ICD-9 for diagnoses made from 2010 to 2012, and ICD-10 thereafter). Additionally, data on outpatient medication prescriptions covered by the Dutch statutory basic medical insurance were also obtained from Statistics Netherlands[34]. These data included the year of prescription and Anatomical Therapeutic Chemical (ATC) code. For anticoagulants specifically, more detailed prescription data were available, including dispending date and type of anticoagulant (i.e., VKA, DOAC or heparin group). However, data on medications received in hospitals and nursing homes were not available.

Data from the NCR were linked to Statistics Netherlands by sex, date of birth, and postal code. The NCR data are provided by the Netherlands Comprehensive Cancer Organization and comprises individual-level data on newly diagnosed cancer patients in the Netherlands[35]. This registry includes information on cancer diagnosis, tumor stage according to the TNM-classification[36], and whether a patient had received surgery, systemic chemotherapy and/or radiotherapy immediately after their index diagnosis. All data were anonymized, and each individual was assigned a unique identification code by Statistics Netherlands. A detailed description of the data sources is provided in *Supplemental Methods*.

Study population

The source population compromised VKA users who were treated at one of the participating anticoagulation clinics between 2013-2019. From this population, we included VKA users who were hospitalized with a pre-specified life-limiting disease or who received a severe cancer diagnosis. Life-limiting diseases were defined according to the definition of a severe medical condition by Kelley et al.: "*a diagnosis that carries an increased risk of mortality, hospitalization and emergency room visits*"[37]. To identify a cohort of patients with limited life expectancy, we restricted to diseases with median survival times of 2-4 years, which were predefined based on nationwide Dutch data. The following non-cancer diseases, derived from Statistics Netherlands data, were included: liver disease, dementia, heart disease, lung disease, diabetes mellitus with complications, and hip fracture (in patients >70 years of age) (*Table S1-2)*. Data on cancer diagnoses and severity were derived from the NCR. Similar to non-cancer diseases, we restricted to cancer types with a median survival time of 3 years or less at time of diagnosis. These included all stages of pancreatic, brain and hepatobiliary cancer and primary tumor unknown; stage III and IV cervical, bladder, ovarian, lung, esophageal and gastric cancer and neuro-endocrine tumors (NETs); and stage IV of endometrial, breast and colorectal cancer (*Table S3-4*). The index date was defined as the date of first hospitalization with a life-limiting disease or the date of the first severe cancer diagnosis during the study period, whichever came first. VKA users were defined as patients with two registered INR measurements in the six months preceding the index date, with at least one in the three months preceding the index date. Patients who did not meet this definition on their index date were not classified as a VKA user and therefore excluded. Patients were followed until the end of the study period (31st December 2019) or their date of death, whichever occurred first.

Baseline characteristics

Information on age, sex, immigration background, and standardized household income was collected at index date. Discharge codes from the DHD registry were used to collect information on comorbidities diagnosed within the 3 years before the index date (*Table S5*). We also collected data on outpatient prescriptions of steroids, antidepressants, antacids, antihypertensive, lipid lowering, anti-inflammatory, and antiplatelet drugs, and the presence of polypharmacy in the calendar year of the index date (*Table S6*). To account for changes within pharmacological subgroups, polypharmacy was defined as ≥5 registered prescriptions of different drug types at the therapeutic level (2nd) of the ATC classification[38] based on all dispensed outpatient drugs in the calendar year of the index date.

Exposure to VKAs and other anticoagulants

Exposure to VKAs during follow-up was primarily derived from INR records and the start and end dates of VKA therapy, as registered by anticoagulation clinics. Continuous VKA exposure was defined as subsequent INR measurements ≤8 weeks apart, consistent with guidelines used by Dutch anticoagulation clinics[39]. To account for switching to non-VKA anticoagulants or transfers to non-participating anticoagulation clinics, we used data on dispensed prescriptions for VKAs, DOACs, and Low-Molecular-Weight Heparins (LMWHs) from 2012 to 2020 from Statistics Netherlands. This allowed us to examine VKA and anticoagulant exposure after the registered VKA end dates from the anticoagulation clinics. Both VKA and anticoagulant exposure were modelled by constructing treatment periods of person-time exposed according to dispensed prescriptions, considering only prescriptions after the VKA end dates recorded by anticoagulation clinics. Construction of treatment periods for the different anticoagulant types is illustrated in *Figure S1-2* and described in the

Supplemental Methods. Anticoagulant treatment periods could consist of VKA, DOAC or LMWH therapy.

Study outcomes

For the first objective, the study outcomes were discontinuation of VKAs and discontinuation of anticoagulant treatment overall. To address this, the last VKA and anticoagulant treatment periods for each patient were identified. Patients were considered to have discontinued VKAs and/or anticoagulants if the end date of their last treatment period occurred before their end of follow-up (date of death or 31st December 2019, whichever occurred first). In addition, we calculated the proportion of days covered (PDC) with anticoagulants for each patient, defined as the ratio of days treated with anticoagulants following the index date to the total number of follow-up days.

For the second objective, the study outcomes were hospital admissions for major and non-major clinically relevant bleeding, VTE, and arterial thromboembolism (ATE), including stroke and transient ischemic attacks (TIA), myocardial infarction, and other ATE. These outcomes were identified from the DHD registry and restricted to primary or main diagnoses during hospitalization (*Supplemental Methods & Table S7*). For each outcome, separately, patients were followed until first event of interest, death, or end of follow-up, whichever occurred first, regardless of anticoagulant treatment.

Statistical analyses

For descriptive analyses, continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were presented as numbers with percentages. Survival curves and median survival time were estimated by the Kaplan-Meier estimator, and median follow-up time was calculated by the reverse Kaplan-Meier[40]. For the first objective, the cumulative incidences of VKA and anticoagulant

discontinuation were calculated with death as a competing risk, based on the Fine & Gray method[41]. We also estimated crude incidence rates of VKA and anticoagulant discontinuation as events per 100 person-years (PYs) with corresponding 95% confidence intervals (95%CI). Additionally, for patients who died during follow-up, we described the use of anticoagulants during the last period of life. For this analysis, we categorized patients into subgroups according to their available follow-up time from index date to the date of death: at least 365 days, 180-364 days, and 90-179 days. Point estimates with corresponding 95%CI for the proportion of patients exposed to anticoagulants were calculated for different time points in the period before death, ranging from 1 week to 1 year before death.

Similarly, for the second objective, cumulative incidences of first bleeding and thromboembolic events, separately, were calculated with death as competing risk. In addition, incidence rates per 100 PYs of first bleeding and thromboembolic events were estimated stratified by anticoagulant exposure. Observation time was categorized as anticoagulant exposed and unexposed, and events were assigned to the relevant exposure stratum at the time of the event. All analyses were stratified by cancer versus non-cancer disease. Statistical analyses were performed in SPSS® Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and R 4.4.0[42]. R packages used are listed in the *Supplemental Methods*.

Sensitivity analyses

To examine the impact of our assumptions about treatment duration, we performed several sensitivity analyses when constructing treatment periods for both VKAs and anticoagulants based on dispensed prescriptions (*Supplemental Methods*). To examine possible time-related bias due to misclassification of anticoagulant exposure and/or outcome, the period exposed to

anticoagulants was extended by seven days when calculating incidence rates of bleeding and thromboembolic events stratified by anticoagulant exposure.

Ethics approval

The study received approval from the Science Committee of the department of Clinical Epidemiology at Leiden University Medical Center with a waiver for participant consent due to the use of pre-existing, de-identified data (#A0178).

Results

Baseline characteristics

Between 2013 and 2019, 18145 VKA users had a hospital admission for a life-limiting disease or received a severe cancer diagnosis (*Figure 1*). At index date, the median age of the cohort was 81 years (IQR 74-86), 49% was female, and 86% was native Dutch (*Table 1 & Table S8*). In addition, 45% had one or more comorbidities, and almost all patients (94.6%) fulfilled our definition of polypharmacy. The most common life-limiting diseases were heart disease (60.0%), hip fracture (18.1%), and cancer (13.5%). AF or other arrhythmias were the most common indication for VKA therapy (78.7%), with other indications including cardiomyopathy (5.8%), VTE (5.6%), and mechanical heart valves (5.3%). Among patients with cancer, the most common cancer type was lung (39.1%), followed by pancreatic (11.6%) and colorectal (10.8%) cancer (*Table 1 & Table S9)*.

Follow-up and all-cause mortality

The overall median follow-up time (IQR) was 3.59 years (1.95-5.22), with 3.41 years (2.06-5.07) in patients with cancer and 3.60 years (1.95-5.22) in patients with non-cancer diseases (*Table S10)*. During follow-up, 10,948 patients died, with an overall median survival time

(95%CI) of 2.03 years (1.97-2.10) (*Figure S3A*). Patients with cancer had shorter survival time than patients with non-cancer diseases (0.35 years (0.32-0.38) and 2.50 years (2.43-2.59), respectively) (*Figure S3B*).

According to INR records from the anticoagulation clinics, 5893 (32.5%) patients had at least one registered VKA end date during follow-up, and 382 (2.1%) patients interrupted their VKA treatment with a median duration of treatment interruption of 231 days (IQR 161-475). Despite having a VKA end date registered by the anticoagulation clinics, 10.9% of all VKA treatment periods (N=18560) indicated that patients continued to be exposed to anticoagulants after their VKA end date according to dispensing data from Statistics Netherlands. Specifically, 0.7% of patients (N=129) interrupted their VKA therapy according to INR records, whereas these patients continued to be exposed to anticoagulants according to dispensed prescriptions.

VKA and anticoagulation discontinuation

At 3 months after index date, the cumulative incidence (95%CI) of VKA discontinuation was 12.0% (11.5-12.5), which increased to 28.1% (27.4-28.8) at 3 years of follow-up (*Table 2*). Some patients switched to other types of anticoagulants, as illustrated by the lower cumulative incidence of overall anticoagulant treatment discontinuation, which ranged from 8.6% (8.2-9.0) at 3 months to 21.7% (21.1-22.4) at 3 years. The VKA and anticoagulant discontinuation rates per 100 PYs (95%CI) were 17.9 (17.4-18.4) and 12.9 (12.5-13.3), respectively. Throughout follow-up, the incidence of discontinuing both VKAs and overall anticoagulant treatment was higher in patients with cancer compared with non-cancer diseases (*Figure 2*), with an anticoagulant discontinuation rate per 100 PYs (95%CI) of 42.6 (39.7-45.7) in patients with cancer versus 11.0 (10.6-11.4) in patients with non-cancer diseases (*Table 2 & Table S11*). The overall mean PDC (SD) with anticoagulants was 91.8%

(22.2), with 88.0% of patients classified as adherent to anticoagulants defined by a PDC>80% (*Table S12*).

Anticoagulant use during the last phase of life

On their date of death, 69.2% of patients were still exposed to anticoagulants according to the constructed anticoagulant treatment periods. Among patients with a follow-up time of at least 365 days, the proportion exposed to anticoagulants (95%CI) decreased from 92.1% (91.2-92.8) at 1 year before death to 83.8% (82.7-84.9) at 1 month, and 76.8% (75.5-78.0) at 1 week before death (*Figure 3*). The median time gap between the constructed end of anticoagulant treatment and death among patients who discontinued anticoagulants before death (N=3372) was 14 days (IQR 4-63) (*Figure S5*).

Incidence of bleeding and thromboembolic events

Point estimates of the incidence rate per 100 PYs (95%CI) of hospital admission for major or clinically relevant bleeding were slightly higher during anticoagulant use than after discontinuation: 2.6 (2.4-2.8) versus 2.1 (1.5-2.8) (*Table 3*). Conversely for thromboembolic event-related hospital admissions, point estimates of the incidence rates were slightly lower during anticoagulant exposed than unexposed person-time, with rates of 0.2 (0.1-0.2) versus 0.4 (0.2-0.7) for VTE, and 3.1 (2.9-3.3) versus 3.3 (2.6-4.2) for the composite of ATE, respectively. Event rates were slightly higher in patients with cancer, but remained comparable regardless of anticoagulant use (*Table 4).* One year after index, the cumulative incidences (95%CI), irrespective of anticoagulant exposure, were 2.4% (2.1-2.6) for bleeding, 0.2% (0.1-0.3) for VTE, and 2.9% (2.6-3.1) for ATE (*Table 3*). Patients with cancer had a higher incidence of VTE, whereas patients with non-cancer diseases had a higher incidence of ATE (*Table 4 & Figure 4*).

Sensitivity analyses

Changing the construction of treatment periods based on anticoagulant prescriptions did not affect the observed rates of VKA or anticoagulant treatment discontinuation nor rates of bleeding or thromboembolic events stratified by anticoagulant exposure (*Table S13-15*). Event rates were also comparable to our main analysis after extending the anticoagulant exposed period by seven days (*Table S14*).

Discussion

Our large cohort study described the use and discontinuation of both VKAs and anticoagulant treatment overall and the incidence of bleeding and thromboembolic events in VKA users with a life-limiting disease. A key finding was the large proportion of prevalent VKA users who continued anticoagulant therapy during their last phase of life, with 69% remaining exposed to anticoagulants until death, and more than 80% continuing therapy until shortly before death. The observed VKA and anticoagulation discontinuation rates were relatively low at 17.9 for VKAs and 12.9 per 100 PYs for anticoagulants overall. Nevertheless, the incidence rates of hospital admission for bleeding and thromboembolic events were comparable during anticoagulant use and after discontinuation.

Discontinuation was more frequent in patients with cancer than in patients with non-cancer diseases, both for VKA and anticoagulant treatment overall. This difference may relate to the worse prognosis of cancer patients in our cohort, as illustrated by their median survival time of 0.35 years. Additionally, the bleeding risk associated with anticoagulant treatment may be higher in cancer than non-cancer patients[43], leading physicians or patients to consider discontinuation sooner. Furthermore, the life expectancy in patients with cancer may be more predictable than that of patients with other life-limiting diseases[44], although the introduction

of immunotherapy and targeted therapy may have changed this dynamic over the last decade[45]. More frequent discontinuation of VKAs in cancer patients may also reflect clinical guidelines recommending LMWH or DOACs for treatment of cancer-associated thrombosis[46].

Our observation that a substantial proportion of VKA users continued anticoagulant therapy aligns with previous studies on anticoagulant use in patients with a life-limiting disease[15,24,47,48]. A chart review conducted in the Netherlands also demonstrated that anticoagulants were frequently continued until the last week(s) before death. Discontinuation of anticoagulation primarily occurred in response to a bleeding event, difficulty swallowing pills, or upon patient's request[14]. Several complex, interacting factors may hinder deprescribing of anticoagulants during the last phase of life. One factor is prescribing inertia, defined as "*the failure to act despite awareness that prescribing is potentially inappropriate*"[12,49]. Prescribing inertia may arise from physicians', patients', or other stakeholders' fear of unknown or negative consequences of deprescribing[12]. Furthermore, the belief that the decision to continue or cease medication is the responsibility of another party (e.g. another prescriber, healthcare professional, or the patient) can also contribute to prescribing inertia[11,12]. Other barriers to deprescribing are the lack of awareness among prescribers and lack of evidence regarding the appropriateness of continuing anticoagulant use[12] and external factors, such as time constraints during patient encounters and guidelines that focus on prescribing rather than deprescribing[11,12].

Previous studies also observed comparable rates of hospital admissions and emergency department visits for thromboembolic and bleeding events during anticoagulant exposure and after discontinuation[50]. In patients with AF and active cancer, bleeding rates per 100 PYs (95%CI) were 7.2 (5.7–8.9) during anticoagulant treatment and 6.7 (2.1–16) after discontinuation and rates of thromboembolic complications were 5.4 (4.1–6.9) and 6.8 (2.2–

16), respectively[51]. Among older (>65 years of age) recipients of home palliative care, incidence rates per 100 PYs (95%CI) were 12.7 (11.8-13.7) and 10.4 (8.7-12.3) for bleeding and 4.9 (4.3-5.5) and 5.2 (4.1-6.6) for thrombotic events during anticoagulant treatment versus after discontinuation, respectively[15]. In our study, the comparable event rates could be partly attributed to confounding by indication (i.e., the decision to continue or discontinue anticoagulants is likely influenced by the estimated risk of both bleeding and thromboembolism of the individual patient) and restricting to first events only. Therefore, these findings should not be interpreted in a causal way.

The magnitude of the event rates per 100 PYs in our cohort of VKA users with a life-limiting disease were comparable to those reported among the general population of VKA users in the Netherlands from 2013 to 2019, ranging between 1.3 to 3.0 for major bleeding and 0.75 to 0.85 for the composite of thromboembolic events[52]. As these events were based on interviews regularly performed during visits at the anticoagulation clinic and information provided by hospitals rather than hospital admissions only, event rates in patients with a life-limiting disease are likely higher than in the general population of VKA users. Furthermore, we observed higher event rates than those reported among newly diagnosed non-valvular AF patients treated with VKAs between 2010 and 2015: 1.27 major bleeding (95%CI 1.07-1.52) and 1.13 stroke and systemic embolism (95%CI 1.07-1.52) per 100 PYs[53]. Another study performed in a cohort of VKA users treated between 2009 and 2012 at an anticoagulation clinic in Groningen, the Netherlands, reported event rates stratified by age-groups among patients aged 70 years or older[54]. Importantly, events were identified by computerized records from the clinic itself, complemented by information from general practitioners. The reported rates of clinically relevant non-major and major bleeding per 100 PYs were 14.8 in patients aged 70 to 79 years, 16.7 in patients aged 80 to 89 years, and 18.1 in patients 90 years or older[54]. For the composite of thrombotic events these were 0.8, 1.5, and 1.8, respectively[54].

The differences in event rates compared to our cohort may be attributed to the underlying risks of bleeding and thromboembolism in the population studied and differences in recording and identification of outcome events.

Strengths of our study include the large cohort of patients with limited life expectancy and different life-limiting diseases. In addition, we included both phenprocoumon and acenocoumarol users. Contrary to most other countries where warfarin is the most frequent VKA type, phenprocoumon and acenocoumarol are primarily used in the Netherlands[55].

Despite these strengths, several limitations of our study should be considered. First, misclassification and measurement error are inherent to the use of routinely-collected healthcare data, especially for patients in the last phase of life who may not always be referred to a hospital. Moreover, we only had access to hospital admission data and lacked information on diagnoses made in outpatient settings, such as in nursing homes, hospices, and by general practitioners. Hence, our estimates likely underestimate the true event rate in this patient population. However, it should be noted that the DHD registry includes information on emergency room visits over four hours.

Second, we cannot entirely rule out the possibility of misclassification in the assessment of VKA, anticoagulant exposure, and treatment discontinuation. Although we limited misclassification by directly obtaining data on VKA treatment from anticoagulation clinics, not all Dutch anticoagulation clinics participated, and we lacked data on VKA treatment during hospital stay and in nursing homes. Additionally, anticoagulation clinics do not provide longitudinal data on anticoagulant exposure after switching to non-VKA anticoagulant therapies, such as DOACs or LMWHs. To further minimize misclassification, we used data on outpatient anticoagulant prescriptions to construct anticoagulant treatment periods over time after the registered VKA end date from the anticoagulation clinics. However, the prescription database lacked detail on quantity and dosage for collected

prescriptions, requiring us to make assumptions about treatment duration. Furthermore, we were unable to distinguish therapeutic from prophylactic LMWH prescriptions. Reassuringly, our sensitivity analyses assessing these assumptions had little impact on our results.

Finally, we lacked information on whether patients received palliative care. An approach to study patients in their last phase of life would be to start follow-up when patients start receiving palliative care or are declared terminally ill[48]. Nevertheless, the validity and suitability of this method also depends on a homogenous definition of a palliative care patient[56] and the remaining follow-up time after being identified as such. Instead, we used a proxy by selecting patients with pre-specified life-limiting diseases and cancer types with a median survival of 3 years or less. This approach avoided selecting patients based on a future event (i.e., death), thereby decreasing the likelihood of selection bias in our study. However, presumably not all patients in our cohort truly had a life-limiting disease, at least not in its final stages.

Conclusion

In conclusion, the majority of VKA users with life-limiting diseases continued anticoagulant therapy during their last phase of life. Among those who discontinued anticoagulant therapy, discontinuation typically occurred only shortly before death, and incidence rates of hospital admission for bleeding and thromboembolic events were similar during anticoagulant use and after discontinuation. Our findings indicate that actively deprescribing anticoagulants is uncommon. Further research is warranted to examine the risks and benefits of continuing versus discontinuing anticoagulants in patients with life-limiting diseases. Moreover, healthcare providers need evidence-based tools to support the process of shared decision-making about the use of anticoagulants during the last phase of life with patients and their

caregivers. The SERENITY consortium is working towards developing and evaluating a shared decision-making support tool for this decision[25].

Conflict-of-interest Disclosure

C. Visser received a travel award from the International Society on Thrombosis and Haemostasis (ISTH) for attending the ISTH congress 2024. I. Mahé reports grants from BMS-Pfizer Alliance, paid to her institution, and personal fees from BMS-Pfizer Alliance and Astra-Zeneca, outside the submitted work. S. Szmit has received honoraria for lectures from Bayer, BMS and Pfizer. S.I.R. Noble has received a payment for a lecture at Leo Pharma. F.A. Klok has received research support from Bayer, BMS, BSCI, AstraZeneca, MSD, Leo Pharma, Actelion, Farm-X, The Netherlands Organisation for Health Research and Development, The Dutch Thrombosis Foundation, The Dutch Heart Foundation and the Horizon Europe Program. All support was paid to the Leiden University Medical Center. Q. Chen was supported by the Chinese Government Scholarship (No. 201906380148) for his PhD study at the Leiden University Medical Center between September 2019 and September 2023 and received travel awards from the International Society on Thrombosis and Haemostasis (ISTH) for attending the ISTH congress between 2022-2024. The payments were made to himself. M.J.H.A. Kruip has received speaker fees from Roche paid to her institution. All authors declare that no known competing financial interests or personal relationships could have appeared to influence the work reported in this paper.

Author contributions

EKK, CV, ECTG, JG, QC, MJHAK and SCC designed the study. EKK and CV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EKK and CV performed all data analyses. EKK drafted the

initial version of the manuscript. CV, ECTG, JG, JEAP, MS, AGO, CD, DA, GG, SJA, KJL, AA, SJCML, MCN, IM, SPM, SS, ME, SIRN, FAK, QC, SCC and MJHAK contributed to the interpretation of the data and critically revised the manuscript. All authors approved the final version of the manuscript.

Data availability Statement

This study used non-public microdata from Statistics Netherlands and the Netherlands Cancer Registry from by the Netherlands Comprehensive Cancer Organization. These data cannot be shared directly by the authors. Under certain conditions, these data are accessible for statistical and scientific research. For additional information: microdata@cbs.nl and/or gegevensaanvraag@iknl.nl.

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Views and opinions expressed are however those of the authors only and do not necessarily reflect those of the European Union or The European Health and Digital Executive Agency. Neither the European Union nor the granting authority.

Ethics Approval Statement

The study received approval from the Science Committee of the department of Clinical Epidemiology at Leiden University Medical Center with a waiver for participant consent due to the use of pre-existing, de-identified data (#A0178). This study was performed on behalf of the SERENITY consortium[25].

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Figure 1. Flowchart of cohort selection

This figure presents the flowchart for the selection of the study cohort. A life limiting disease was defined according to the definition of a severe medical condition by Kelly et al. as “a diagnosis that carries an increased risk of mortality, hospitalization and emergency room

visits”[37]. Abbreviations: INR = international normalized ratio; VKA = vitamin K antagonist. Created in BioRender. Kruip, M. (2024) https://BioRender.com/e31d202

Figure 2. Cumulative incidences of VKA and anticoagulant treatment discontinuation stratified by cancer versus non-cancer diseases

This figure illustrates the cumulative incidences of vitamin K antagonist (A) and anticoagulant (B) treatment discontinuation, stratified by whether patients had a cancer or non-cancer life-limiting disease, and accounting for the competing risk of death. The number of events at 5 years is masked according to privacy policy of Statistics Netherlands. Abbreviations: AC = anticoagulation; VKA = vitamin K antagonist.

Figure 3. Percentage of patients exposed to anticoagulants before death

This figure displays the percentage of patients exposed to anticoagulants, along with corresponding 95% confidence intervals, at different time points before death. The analysis was stratified according to the amount of follow-up time between index date and date of death, and was restricted to patients who died during follow-up.

Figure 4. Cumulative incidences of bleeding and thromboembolic events stratified by cancer versus non-cancer diseases

This figure shows the cumulative incidences of first bleeding and thromboembolic events accounting for the competing risk of death. Venous thromboembolism included pulmonary embolism, deep vein thrombosis, cerebral sinus thrombosis, portal vein thrombosis and other types of venous thromboembolism. Arterial thromboembolism included ischemic stroke, transient ischemic attack, myocardial infarction, and other types of arterial thromboembolism.

Table 1. Baseline characteristics

	Total	**Cancer**	**Non-cancer**
	(N=18145)	(N=2457)	(N=15688)

Demographics			
Female sex, No. (%)	8841 (48.7)	893 (36.3)	7948 (50.7)
Age at index date, median [Q1, Q3], years	81.0 [74.0, 86.0]	77.0 [70.0, 82.0]	81.0 [74.0, 87.0]
Immigration background[a], No. (%)			
Dutch background	15649 (86.2)	2199 (89.5)	13450 (85.7)
First-generation migration background	1781 (9.8)	159 (6.5)	1622 (10.3)
Second-generation migration background	715 (3.9)	99 (4.0)	616 (3.9)
Year of diagnosis, No. (%)			
2013	2264 (12.5)	276 (11.2)	1988 (12.7)
2014	2596 (14.3)	362 (14.7)	2234 (14.2)
2015	2739 (15.1)	366 (14.9)	2373 (15.1)
2016	2738 (15.1)	362 (14.7)	2376 (15.1)
2017	2977 (16.4)	408 (16.6)	2569 (16.4)
2018	2536 (14.0)	345 (14.0)	2191 (14.0)
2019	2295 (12.6)	338 (13.8)	1957 (12.5)
Type of life-limiting disease[b], No. (%)			
Cancer	2457 (13.5)	2457 (100)	0 (0)
ILD	107 (0.6)	0 (0)	107 (0.7)
Liver disease	164 (0.9)	0 (0)	164 (1.0)
COPD	547 (3.0)	0 (0)	547 (3.5)
Dementia	387 (2.1)	0 (0)	387 (2.5)
Diabetes mellitus (complicated)	327 (1.8)	0 (0)	327 (2.1)
Hip fracture	3277 (18.1)	0 (0)	3277 (20.9)
Heart disease	10879 (60.0)	0 (0)	10879 (69.3)
Type of cancer, No. (%)			
Esophagus	165 (0.9)	165 (6.7)	NA
Stomach	104 (0.6)	104 (4.2)	NA
Colorectal	265 (1.5)	265 (10.8)	NA
Hepatobiliary	170 (0.9)	170 (6.9)	NA
Pancreas	284 (1.6)	284 (11.6)	NA
Bronchus and lung	960 (5.3)	960 (39.1)	NA
Breast	49 (0.3)	49 (2.0)	NA
Ovary	53 (0.3)	53 (2.2)	NA
Other female genital organs	28 (0.2)	28 (1.1)	NA
Bladder	115 (0.6)	115 (4.7)	NA
Brain	66 (0.4)	66 (2.7)	NA
Other[c]	16 (0.1)	16 (0.7)	NA
Unknown primary or multiple tumors	182 (1.0)	182 (7.4)	NA
TNM Stage[d], No. (%)			
I	70 (0.4)	70 (2.8)	NA
II	64 (0.4)	64 (2.6)	NA
III	572 (3.1)	572 (23.3)	NA
IV	1382 (7.6)	1382 (56.2)	NA
Unknown	31 (0.2)	31 (1.3)	NA
Not applicable	338 (1.9)	338 (13.8)	NA
Registered indications for VKA			

therapy[e], No. (%)			
Mechanical heart valve	960 (5.3)	101 (4.1)	859 (5.5)
Biological valve and other heart surgery	381 (2.1)	33 (1.3)	348 (2.2)
Atrial fibrillation and other arrhythmias	14282 (78.7)	1757 (71.5)	12525 (79.8)
Decompensation cordis and valvular disease	371 (2.0)	22 (0.9)	349 (2.2)
Cardiomyopathy	1054 (5.8)	81 (3.3)	973 (6.2)
Cerebral vascular disease	296 (1.6)	31 (1.3)	265 (1.7)
Arterial embolism	181 (1.0)	32 (1.3)	149 (0.9)
Peripheral arterial disease	156 (0.9)	24 (1.0)	132 (0.8)
Coronary syndrome and interventions	439 (2.4)	60 (2.4)	379 (2.4)
Vascular surgery	400 (2.2)	93 (3.8)	307 (2.0)
VTE	1024 (5.6)	304 (12.4)	720 (4.6)
Other	187 (1.0)	30 (1.2)	157 (1.0)
INR target range, No. (%)			
2.0-3.0	2606 (14.4)	325 (13.2)	2281 (14.5)
2.5-3.5	11929 (65.7)	1578 (64.2)	10351 (66.0)
3.0-4.0	2136 (11.8)	250 (10.2)	1886 (12.0)
Other	117 (0.6)	17 (0.7)	100 (0.6)
Unknown	1357 (7.5)	287 (11.7)	1070 (6.8)
Type of VKA, No. (%)			
Acenocoumarol	13871 (76.4)	1769 (72.0)	12102 (77.1)
Phenprocoumon	4269 (23.5)	688 (28.0)	3581 (22.8)
≥1 comorbidity present at index date[f], No. (%)	8195 (45.2)	956 (38.9)	7239 (46.1)
Medication use at index date[g], No. (%)			
Antiplatelet drugs	2853 (15.7)	261 (10.6)	2592 (16.5)
Antihypertensives	16964 (93.5)	2178 (88.6)	14786 (94.3)
Anti-inflammatory (non-steroidal)	1748 (9.6)	388 (15.8)	1360 (8.7)
Anti-depressants	2405 (13.3)	312 (12.7)	2093 (13.3)
Lipid-lowering	9828 (54.2)	1345 (54.7)	8483 (54.1)
Steroids	5244 (28.9)	1077 (43.8)	4167 (26.6)
Antacids	11572 (63.8)	1531 (62.3)	10041 (64.0)
Polypharmacy[h]	17168 (94.6)	2353 (95.8)	14815 (94.4)
Polypharmacy[i] (excluding antithrombotic agents)	16802 (92.6)	2305 (93.8)	14497 (92.4)
Unknown	467 (2.6)	27 (1.1)	440 (2.8)

COPD: Chronic Obstructive Pulmonary Disease; ILD: Interstitial Lung Disease; INR: International Normalized Ratio; IQR: Interquartile range; TNM: tumor, nodes and metastases; VKA; Vitamin K antagonist; VTE: Venous Thromboembolic Event.

[a]Immigration data were collected from Statistics Netherlands. Dutch background is defined as having both parents born in the Netherlands. First-generation migration background is defined as being born abroad with at least one parent who was born abroad; second-generation migration background is defined as being born in the Netherlands with at least one parent who was born abroad.

[b]A life-limiting disease was defined according to the definition of a severe medical condition by Kelley et al. as "a diagnosis that carries an increased risk of mortality, hospitalization and

emergency room visits"[37]. These diseases were identified by ICD-10 codes of diagnoses registered as either main or primary diagnosis of the hospital admission or registered cancer diagnosis by the Netherlands Cancer Registry. Patients were classified according to the first type of life-limiting disease that occurred during the study period.
[c]Other cancer types included (neuro-endocrine) tumors located in the small intestine, peritoneum, or retroperitoneum.
[d]TNM stage was based on the 7th edition[57] of the tumor-node-metastasis cancer staging system for index dates between 2013 and 2016 and the 8th edition[36] of the tumor-node-metastasis cancer staging system for index dates between 2017 and 2019.
[e]All treatment indications for vitamin K antagonist treatment that have been registered until the date of data export and were identified from the Dutch anticoagulation clinics. One or more indications can be present.
[f]Comorbidities were identified by examining data on hospitalizations within 3 years before the index date using ICD-10 codes and ICD-9 codes restricting to main or primary diagnosis of hospital admission. One or more comorbidities can be present. The following comorbidities were identified: autoimmune disease or immune deficiency, thyroid disease, COPD, asthma or other chronic lung disease, major and clinically relevant bleeding, venous thromboembolism, arterial thromboembolism, stroke, myocardial infarction, anemia, coagulopathy, heart failure, valvular heart disease, atrial fibrillation, atherosclerosis, peripheral arterial disease, diabetes mellitus, hypertension, kidney, and liver disease.
[g]Medication use at index date was identified by examining outpatient medication prescriptions covered by the Basic Dutch Health Insurance based on ATC codes in the calendar year of the index date.
[h]Polypharmacy was defined as ≥5 different drug types in the calendar year of the index date, at the therapeutic (2nd) level of the ATC classification.
[i]Polypharmacy was defined as ≥5 different drug types in the calendar year of the index date, at the therapeutic (2nd) level of the ATC classification, excluding the therapeutic class antithrombotic agents (B01).

Table 2. Cumulative incidence and incidence rate of VKA and anticoagulant treatment discontinuation

	VKA discontinuation				Anticoagulation discontinuation			
	IR / 100 PY (95% CI)	**6-month Cumulative incidence % (95%CI)**	**1-year Cumulative incidence % (95%CI)**	**3-year Cumulative incidence % (95%CI)**	**IR / 100 PY (95% CI)**	**6-month Cumulative incidence % (95%CI)**	**1-year Cumulative incidence % (95%CI)**	**3-year Cumulative incidence % (95%CI)**
Total	17.9 (17.4-18.4)	15.0 (14.5-15.5)	18.7 (18.1-19.3)	28.1 (27.4-28.8)	12.9 (12.5-13.3)	10.9 (10.4-11.3)	14.0 (13.5-14.6)	21.7 (21.1-22.4)
Type of life-limiting disease								

Cancer	63.1 (59.3-67.0)	33.7 (31.9-35.6)	38.7 (36.7-40.6)	43.7 (41.7-45.8)	42.6 (39.7-45.7)	23.8 (22.1-25.5)	28.7 (26.9-30.5)	33.7 (31.7-35.6)
Non-cancer	15.2 (14.8-15.7)	12.1 (11.6-12.6)	15.6 (15.0-16.2)	25.6 (24.9-26.4)	11.0 (10.6-11.4)	8.9 (8.4-9.3)	11.8 (11.2-12.3)	19.8 (19.2-20.5)
Sex								
Females	18.0 (17.3-18.7)	14.9 (14.2-15.7)	19.0 (18.2-19.8)	29.0 (28.0-30.0)	13.3 (12.7-13.9)	11.1 (10.5-11.8)	14.5 (13.7-15.2)	22.9 (21.9-23.8)
Males	17.8 (17.2-18.5)	15.1 (14.3-15.8)	18.5 (17.7-19.3)	27.2 (26.3-28.2)	12.5 (12.0-13.1)	10.7 (10.0-11.3)	13.6 (12.9-14.4)	20.6 (19.7-21.5)

Cumulative incidences were computed taking the competing risk of death into account. Crude incidence rates (IR) were estimated as events per 100 person-years (PY). Abbreviations: CI = confidence interval; IR = incidence rate; PY = person-years; VKA = vitamin K antagonist.

Table 3. Cumulative incidences and incidence rates of first bleeding and thromboembolic events

	Events, N	**IR/100 PY AC exposed (95%CI)**	**IR/100 PY unexposed (95%CI)**	**6-month Cumulative incidence % (95%CI)**
Major and clinically relevant bleeding	824	2.6 (2.4-2.8)	2.1 (1.5-2.8)	1.5 (1.3-1.7)
Venous thromboembolism	62	0.2 (0.1-0.2)	0.4 (0.2-0.7)	0.1 (0.1-0.2)
Arterial thromboembolism	983	3.1 (2.9-3.3)	3.3 (2.6-4.2)	1.8 (1.6-2.0)
Myocardial infarction	365	1.1 (1.0-1.3)	0.9 (0.5-1.4)	0.7 (0.6-0.9)
Stroke	520	1.6 (1.4-1.7)	2.0 (1.5-2.7)	0.9 (0.8-1.0)
Other	144	0.4 (0.4-0.5)	0.5 (0.2-0.9)	0.2 (0.2-0.3)

Cumulative incidences were computed taking the competing risk of death into account. Crude incidence rates (IR) of first bleeding and thromboembolic events were estimated as events per 100 person-years (PY), stratified by anticoagulant exposure. Abbreviations: AC = anticoagulation; CI = confidence interval; IR = incidence rate; PY = person-years.

Table 4. Cumulative incidences and incidence rates of first bleeding and thromboembolic events stratified by cancer versus non-cancer diseases

	Cancer						
	IR/100 PY AC exposed (95%CI)	**IR/100 PY unexposed (95%CI)**	**6-month Cumulative incidence % (95%CI)**	**1-year Cumulative incidence % (95%CI)**	**3-year Cumulative incidence % (95%CI)**	**IR/100 PY AC exposed (95%CI)**	**IR/100 PY unexposed (95%C**
Major and clinically relevant bleeding	4.5 (3.6-5.7)	4.5 (2.1-8.6)	2.0 (1.5-2.7)	2.6 (2.0-3.3)	3.5 (2.8-4.3)	2.5 (2.3-2.7)	1.8 (1. 2.5)
Venous thromboembolism	0.8 (0.5-1.4)	0.5 (0.0-2.5)	0.5 (0.3-0.9)	0.6 (0.4-1.0)	0.7 (0.4-1.1)	0.1 (0.1-0.2)	0.4 (0. 0.8)
Arterial thromboembolism	3.0 (2.2-3.9)	7.1 (4.0-11.7)	1.7 (1.3-2.3)	2.1 (1.6-2.8)	2.9 (2.3-3.7)	3.1 (2.9-3.3)	2.9 (2. 3.7)
Myocardial infarction	0.7 (0.3-1.2)	2.8 (1.0-6.0)	0.4 (0.2-0.8)	0.5 (0.3-0.9)	0.8 (0.5-1.2)	1.2 (1.0-1.3)	0.7 (0. 1.2)
Stroke	1.8 (1.2-2.5)	3.7 (1.6-7.3)	1.0 (0.7-1.4)	1.3 (0.9-1.8)	1.7 (1.2-2.3)	1.6 (1.4-1.7)	1.8 (1. 2.5)
Other	0.5 (0.2-0.9)	0.9 (0.1-3.3)	0.4 (0.2-0.7)	0.4 (0.2-0.7)	0.5 (0.2-0.8)	0.4 (0.4-0.5)	0.4 (0. 0.8)

Cumulative incidences were computed taking the competing risk of death into account. Crude incidence rates (IR) of first bleeding and thromboembolic events were estimated as events per 100 person-years (PY), stratified by anticoagulant exposure. Abbreviations: AC = anticoagulation; CI = confidence interval; IR = incidence rate; PY = person-years.

Supplemental methods

Data sources

Data on personal characteristics: This dataset provides data on personal characteristics (i.e., year of birth, sex, and immigration background) collected from the Personal Records Database (in Dutch "Basisregistratie Personen", BRP)[1]. It includes all persons who have been registered in the BRP since October 1994, both residents (i.e., individuals who were registered in the population register of a Dutch municipality) and non-residents (i.e., individuals who had a relationship with the Dutch government)[2]. In the Netherlands, individuals who would stay in the Netherlands for more than four months are compulsory to register at a Dutch municipality and therefore their demographic characteristics would be recorded in the BRP. For the current study, data from the calendar years 2013 to 2019 were used.

Data on household income: Data on household income were collected from the Tax and Customs administration and the student grant registration of the Education Executive Agency (in Dutch "Dienst Uitvoering Onderwijs", DUO)[2,3].

Data on mortality and causes of death: Mortality data includes information on the dates of death for all persons who have been registered in the BRP since October 1994[4]. Data on underlying causes of death of persons who were registered in the BRP and died since the 2013 statistical year were collected from the nationwide Dutch Registry of Causes of Death statistics[5]. This registry also contains information on the most important injury and the location of the accident for those who died of non-natural death. For all deceased persons, the location of death and the statistical year, or the year in which the deceased was included in the statistics, are also present.

Data on diagnoses registered during hospitalizations: Data on diagnoses registered with hospital admissions in Dutch hospitals were collected from the Dutch Hospital Data registry, which includes all general and academic Dutch hospitals and two short-stay categorical hospitals (i.e., a cancer clinic and an eye hospital)[2] and includes data from individuals registered in the BRP[6-9]. The data contain diagnoses retrieved from discharge letters, length of hospital stay, and date of admission/discharge. The variable main diagnosis indicated which diagnosis was the main reason for the corresponding hospital admission, and the variable primary diagnosis indicated whether a diagnosis was the main reason for providing the corresponding care[10].

Data on outpatient medication prescriptions: Data on outpatient medication prescriptions for which costs were reimbursed under the basic health insurance in the Netherlands. The data included information on medications for individuals in residential homes for elderly, whereas information on medications in hospitals and in nursing homes were not included[10,11]. Only the prescription year was available.

Data on outpatient medication prescriptions of anticoagulants: Data on outpatient prescription of anticoagulants, identified by the codes from the World Health Organization's Anatomic-Therapeutic-Chemical (ATC) system (i.e., B01A*). Data contain information on the type of anticoagulant and the prescription date, but information on the amount of medication per dispensed prescription and the anticoagulant subtypes were not available[10].

Data from Dutch anticoagulation clinics: These data compromise information about VKA treatments managed by participating anticoagulation clinics, including information on start date, indication(s) for treatment, type of VKAs, dose, target INR ranges, INR values and measurement time, reason for stop and stop date (if available). These clinics are managed by the Dutch Federation of

Anticoagulation Clinics (in Dutch “Federatie Nederlandse Trombosediensten”, FNT). The following anticoagulation clinics participated in the study: Leiden Anticoagulation Clinic (Leiden), Atalmedial (Amsterdam), Saltro (Utrecht), Star-shl (Rotterdam), and Isala (Zwolle).

Netherlands Cancer Registry (NCR): The NCR is provided by the Netherlands Comprehensive Cancer Organization (in Dutch “Integraal Kankercentrum Nederland”, IKNL) and comprises individual-level data of newly diagnosed patients with cancer in the Netherlands, including cancer diagnosis, tumour staging (according to the TNM-classification developed and maintained by the Union for International Cancer Control (UICC)), tumour site (topography) and morphology (histology) (according to the WHO International Classification of Diseases for Oncology (ICD-O-3)), co-morbidity at diagnosis and treatment received directly after diagnosis (source: Netherlands Cancer Registry (NCR) (iknl.nl)).

Data linkage

Data from the anticoagulation clinics were linked to data from Statistics Netherlands by sex, date of birth, postal code, and last date known to be alive and >95% of records were successfully matched. Data from the NCR were also linked to Statistics Netherlands by sex, date of birth, and postal code with an 98.5% match.

Details about constructing treatment periods for anticoagulants

Dispensed anticoagulant prescriptions for vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs) and Low-molecular-weight heparins (LMWHs) from 2012 to 2020 were used to examine VKA and anticoagulant exposure after registered VKA end dates from the anticoagulation clinics, to account for possible switching to non-VKA anticoagulants and non-participating anticoagulation clinics. Both VKA and anticoagulant exposure were modelled by constructing treatment periods of person-time exposed according to dispensed prescriptions, only considering prescriptions after VKA end dates from anticoagulation clinics. As no data were available on the amount of anticoagulant dispensed nor the prescribed dose, treatment periods for the different types of anticoagulants were constructed assuming that a dispensing lasted a fixed number of days (i.e., the exposure time) unless a refill, death or end of follow-up occurred earlier. Whenever the period between two subsequent dispensed prescription dates exceeded this fixed number of days, the next prescription was considered to belong to a new treatment period. A predefined number of days was added to the last prescription date within the treatment period to construct the end of the corresponding treatment period (*Supplemental Figure 1*). For VKAs, the exposure time of a single prescription was based on a previously performed validation study (Kempers et al. 2024, unpublished data), which resulted in 180 days allowed between subsequent VKA prescription dates and the addition of 60 days to the last prescription date to construct the end date of the corresponding treatment period. For DOACs and LMWHs, exposure times were based on the number of days between two dispensed prescriptions studied in a random sample of patients with DOAC and/or LMWH prescriptions between 2013-2019 (*Supplemental Figure 2*). We applied an exposure time of 120 days for DOAC prescriptions and 30 days for LMWH prescriptions.

As sensitivity analyses, we varied the exposure time of anticoagulant prescriptions when constructing treatment periods: 100 days for LMWH prescriptions, 150 days combined with the addition of 100 days to the last prescription date within the treatment period for VKA prescriptions.

R packages used

The following packages were used for statistical analyses and preparing figures: tidyverse[12], dplyr[13], lubridate[14], stringr[15], tidyr[16], foreign[17], forcats[18], purrr[19], ggplot2[20], survival[21], prodlim[22], epiR[23], tidycmprks[24], ggsurvfit[25], and cowplot[26].

Supplemental Table 1. ICD-10 codes used to identify non-cancer life-limiting diseases

Life-limiting disease	**Restrictions**
Liver disease	
Esophageal varices	Primary diagnosis of hospital admission
Alcoholic cirrhosis of liver	Primary diagnosis of hospital admission
Secondary biliary cirrhosis	Primary diagnosis of hospital admission
Unspecified cirrhosis of liver	Primary diagnosis of hospital admission
Hepatorenal syndrome	Primary diagnosis of hospital admission
Hip fracture	
Fracture of neck of femur	Primary diagnosis of hospital admission in patients >
Pertrochanteric fracture	Primary diagnosis of hospital admission in patients >
Subtrochanteric fracture	Primary diagnosis of hospital admission in patients >
Heart disease	
Hypertensive heart disease with heart failure	Primary diagnosis of hospital admission
Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	Primary diagnosis of hospital admission
Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	Primary diagnosis of hospital admission
Ischemic cardiomyopathy	Primary diagnosis of hospital admission
Heart failure	Primary diagnosis of hospital admission
Lung disease	
Mixed simple and mucopurulent chronic bronchitis	Primary diagnosis of hospital admission
Other chronic obstructive pulmonary disease	Primary diagnosis of hospital admission
Other interstitial pulmonary diseases with fibrosis	Primary diagnosis of hospital admission
Diabetes mellitus	
Type 1 diabetes mellitus with kidney complications	Primary diagnosis of hospital admission in combinati of severity (see table S4)
Type 1 diabetes mellitus with circulatory complications	Primary diagnosis of hospital admission in combinati of severity
Type 1 diabetes mellitus with multiple complications	Primary diagnosis of hospital admission in combinati of severity
Type 2 diabetes mellitus with kidney complications	Primary diagnosis of hospital admission in combinati of severity
Type 2 diabetes mellitus with circulatory complications	Primary diagnosis of hospital admission in combinati of severity
Type 2 diabetes mellitus with multiple complications	Primary diagnosis of hospital admission in combinati of severity

Malnutrition-related diabetes mellitus with renal complications	Primary diagnosis of hospital admission in combinati of severity
Malnutrition-related diabetes mellitus with peripheral circulatory complications	Primary diagnosis of hospital admission in combinati of severity
Malnutrition-related diabetes mellitus with multiple complications	Primary diagnosis of hospital admission in combinati of severity
Other specified diabetes mellitus with kidney complications	Primary diagnosis of hospital admission in combinati of severity
Other specified diabetes mellitus with circulatory complications	Primary diagnosis of hospital admission in combinati of severity
Other specified diabetes mellitus with multiple complications	Primary diagnosis of hospital admission in combinati of severity
Unspecified diabetes mellitus with renal complication	Primary diagnosis of hospital admission in combinati of severity
Unspecified diabetes mellitus with peripheral circulatory complications	Primary diagnosis of hospital admission in combinati of severity
Unspecified diabetes mellitus with multiple complications	Primary diagnosis of hospital admission in combinati of severity
Dementia	
Creutzfeld-Jakob disease	Primary or secondary diagnosis of hospital admissior
Subacute sclerosing panencephalitis	Primary or secondary diagnosis of hospital admissior
Progressive multifocal leukoencephalopathy	Primary or secondary diagnosis of hospital admissior
Other atypical virus infections of central nervous system	Primary or secondary diagnosis of hospital admissior
Vascular dementia, unspecified severity	Primary or secondary diagnosis of hospital admissior
Vascular dementia, severe	Primary or secondary diagnosis of hospital admissior
Dementia in other diseases classified	Primary or secondary diagnosis of hospital admissior
Dementia in other diseases classified, severe	Primary or secondary diagnosis of hospital admissior
Unspecified dementia, unspecified severity	Primary or secondary diagnosis of hospital admissior
Unspecified dementia, severe	Primary or secondary diagnosis of hospital admissior
Delirium superimposed on dementia	Primary or secondary diagnosis of hospital admissior
Alzheimer's disease	Primary or secondary diagnosis of hospital admissior
Frontotemporal dementia	Primary or secondary diagnosis of hospital admissior
Senile degeneration of brain	Primary or secondary diagnosis of hospital admissior

Supplemental Table 2. ICD-10 codes used to identify any diagnosis of severity to indicate the severity of diabetes mellitus.

Any diagnosis of severity in combination with diabetes mellitus	**ICD-10 codes**
Peripheral vascular disease	
Diabetes mellitus due to underlying condition with circulatory complications	E08.5
Drug or chemical induced diabetes mellitus with circulatory complications	E09.5
Atherosclerosis of unspecified type of bypass graft(s) of the extremities	I70.3
Atherosclerosis of autologous vein bypass graft(s) of the extremities	I70.4
Atherosclerosis of nonautologous biological bypass graft(s) of the extremities	I70.5
Atherosclerosis of nonbiological bypass graft(s) of the extremities	I70.6
Atherosclerosis of other type of bypass graft(s) of the extremities	I70.7
Other and unspecified atherosclerosis	I70.9
Other arterial dissection	I77.7
Coronary artery disease	

Angina	I20.0; I20.1; I20.8; I20.9
ST elevation (STEMI) myocardial infarction involving other sites	I21.0; I21.1; I21.2; I21.3
Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	I22.0; I22.1; I22.8; I22.9
Other acute ischemic heart diseases	I24.0; I24.1; I24.8; I24.9
Atherosclerotic heart disease of native coronary artery	I25.1
Old myocardial infarction	I25.2
Coronary artery aneurysm and dissection	I25.4
Ischemic cardiomyopathy	I25.5
Silent myocardial ischemia	I25.6
Atherosclerosis of coronary artery bypass graft(s) and coronary artery of transplanted heart with angina pectoris	I25.7
Atherosclerosis of other coronary vessels without angina pectoris	I25.8
Chronic ischemic heart disease, unspecified	I25.9
Kidney failure	
Hypertensive renal disease with renal failure	I12.0
Hypertensive heart and chronic kidney disease without heart failure	I13.1
Chronic kidney disease, stage 4	N18.4
Chronic kidney disease, stage 5	N18.5
End stage renal disease	N18.6
Unspecified kidney failure	N19
Encounter for adequacy testing for haemodialysis	Z49.3
Dependence on renal dialysis	Z99.2

Supplemental Table 3. Survival rates of different cancer diagnoses

Cancer location	Stage	1 year survival	3 year survival	5 year survival	Reference
Pancreas	All stages	22%	6%	< 5%	van der Geest, L. et al. Alvleesklier in (2021).
Cervix					
	IIA2-IVA (locally advanced)	86%	66%	59%	van der Aa, M. et al. (no date) Baarm https://iknl.nl/cervixcarcinoom-in-ne
	IIIB	71%	42%	37%	
	IVA	47%	24%	21%	
	IVB	38%	13%	7%	
Endometrium[a]		90%	83%	80%	Soslow, Robert A et al. Clinicopatholo carcinomas of different histologic sub biologic differences. The American jo 979-87.
	III	80%		48%	
	IV	48%		15%	
Bladder					
	T2-4a			45,7%	Ripoll, J et al. Cancer-specific survival collected by Mallorca Cancer Registry 21,1 676. 7 Jun. 2021
	T3	60%	42%	41,0%	
	T4a+b	IV: 40%	IV:20%	21% ; 12%	
Breast					
	III	96%	83%	73%	IKNL 2023. Overleving borstkanker. A https://iknl.nl/kankersoorten/borstk September 2024).
	IV	70%	38%	22%	
Bone and soft tissue (sarcoma)					

	Bone	83%	69%	63%	IKNL 2024. Overleving bot- en weke
	Soft tissue sarcoma	79%	65%	59%	https://iknl.nl/kankersoorten/bot-en (Accessed: 17 September
	GIST	91%	84%	80%	
Colon					
	III	88-92%		71%	Araghi, Marzieh et al. Colon and rect
	IV	40-58%		12%	countries 2010-2014: variation by ag SURVMARK-2 project). Gut vol. 70,1
Rectal					
	III	91-96%		75%	Araghi, Marzieh et al. Colon and rect
	IV	52-66%		14%	countries 2010-2014: variation by ag SURVMARK-2 project). Gut vol. 70,1
Ovary					
	III	80%	40%	25%	Gaitskell, Kezia et al. Ovarian cancer
	IV	75%	25%	12%	diagnostic lifestyle factors, in the pro epidemiology vol. 76 (2022): 102074
Brain		54%	31%	26%	IKNL 2023. Overleving Hersentumore https://iknl.nl/kankersoorten/hersen 17 September 2024)
Hepatobiliary - liver		44%	24%	18%	IKNL 2023. Overleving HPB-tumoren. https://iknl.nl/kankersoorten/hpb-tu September 2024)
Hepatobiliary – gallbladder / bile duct		46%	22%	17	IKNL 2023. Overleving HPB-tumoren. https://iknl.nl/kankersoorten/hpb-tu September 2024)
Lung			34%		IKNL 2024. Overleving longkanker. Av https://iknl.nl/kankersoorten/longka September 2024)
	NSCLC III	78%	42%	30%	
	NSCLC IV	33%	< 10%	< 5%	
	SCLC III	78%	35%	24%	
	SCLC IV	25%	< 10%	< 5%	
NEC/NET (any location)[b]	All stages	73%	53%	39%	Man, Da et al. "Prognosis of patients database analysis." Cancer managem Nov. 2018. Dasari, Arvind et al. "Trends in the In in Patients With Neuroendocrine Tur vol. 3,10 (2017): 1335-1342.
Primary tumor unknown					
	Treated	40%		20%	IKNL 2024. Overleving Primaire Tumo
	Untreated	5%	< 5%	< 5%	https://iknl.nl/kankersoorten/primai (Accessed: 17 September 2024)
Esophagus					
	III	65%	33%	26%	IKNL 2023. Overleving slokdarm- en r
	IV	22%	4%	2%	https://iknl.nl/kankersoorten/slokda (Accessed: 17 September 2024)
Gastric					
	III	60%	25%	16%	IKNL 2023. Overleving slokdarm- en r
	IV	17%	2%	1%	https://iknl.nl/kankersoorten/slokda (Accessed: 17 September 2024)

First, all survival rates were collected by consulting the website of the Netherlands Comprehensive Cancer Organization ('IKNL' i not available on the IKNL website, epidemiological literature was used to identify the survival rates. Cancer types and stages wit included in the study.

a: Good quality epidemiological studies describing 1/3/5 year survival rates were found, hence this more pathology focused pap

b: 3 year survival rates for all NET/NECs in general were above 50%, however, as described in the paper from Dasari et. al, grade

than grade 1-2 patients. Looking at the overall 3-year survival rate of 53%, it was chosen to include the grade 3 and 4 patients b

Supplemental Table 4. Description of included severe cancer diagnoses

All stages	**Stage III + IV**	**Stage IV**
Pancreas	Cervix	Breast
Primary tumor unknown	Bladder	Colon and rectum
Brain	Ovary	Endometrium
Hepatobiliary (liver and gall bladder/duct)	Lung (NSCLC and SCLC)	
	Neuro-endocrine tumors	
	Esophagus	
	Gastric	
Cancer types with a median survival time of 3 years or less at the time of first diagnosis were selected.		

Supplemental Table 5. ICD codes used to identify comorbidities

Comorbidities	**Type of code**	**Code(s)**
Asthma	ICD-10	J45, J46
	ICD-9	493
Chronic obstructive pulmonary disease	ICD-10	J44
	ICD-9	491, 492, 496
Other chronic lung diseases	ICD-10	J41, J42, J43, J47, J6, J7
	ICD-9	494, 495, 50
Heart failure	ICD-10	I50
	ICD-9	428
Hypertension	ICD-10	I10, I11, I13, I15
	ICD-9	401, 402, 404, 405
Atrial fibrillation	ICD-10	I48
	ICD-9	4273
Atherosclerosis	ICD-10	I20, I250, I251, I255, I258, I259, I70
	ICD-9	413, 4140, 4143, 4144, 4148, 4149, 4292, 440
Myocardial infarction (history)	ICD-10	I21, I22, I252
	ICD-9	410, 412, 4142
Rheumatic Heart disease	ICD-10	I05, I06, I07
	ICD-9	3941, 395, 3971
Other valvular heart disease	ICD-10	I08, I34, I35, I36, I37, I38, I39, Z952
	ICD-9	3940, 3942, 3949, 396, 3970, 424, V433
Peripheral artery disease	ICD-10	I739
	ICD-9	4439
Liver disease	ICD-10	B15, B16, B17, B18, B19, D684, I982, I983, K70, K71, K72, K73, K74, K75, K76, K77, Z944
	ICD-9	070, 4560, 4561, 4562, 571, 5722, 5723, 5724, 5728, 5731, 5732, 5733, 5735, V427
Diabetes	ICD-10	E10, E11, E12, E13, E14
	ICD-9	250
Thyroid disease	ICD-10	E00, E01, E02, E03, E04, E05, E06, E07

	ICD-9	240, 241, 242, 243, 244, 245, 246
Kidney disease	ICD-10	I12, N01, N02, N03, N04, N05, N06, N07, N08, N11, N12, N14, N150, N158, N159, N16, N18, N19, N25, N26, Q60, Q611, Q612, Q613, Q614, Q615, Q618, Q619, Z49, Z940
	ICD-9	403, 581, 582, 583, 585, 586, 587, 588, 5900, 7530, 7531, V420, V451, V56
Anemia	ICD-10	D5, D60, D61, D63, D64
	ICD-9	280, 281, 282, 283, 2840, 2848, 2849, 2850, 2852, 2858, 2859
Coagulopathy	ICD-10	D65, D66, D67, D680, D681, D682, D683, D685, D686, D688, D689, D69
	ICD-9	286, 287
Stroke/TIA (history)	ICD-10	G45, G46, I63, I64
	ICD-9	3623, 434.1, 434.9, 435, 436
(Other) arterial thromboembolism	ICD-10	H340, H341, H342, I513, I74, K550
	ICD-9	3623, 444, 5570
Venous thromboembolism (history)	ICD-10	H348, I26, I636, I676, I801, I802, I803, I808, I809, I81, I820, I822, I823, I828, I829, K765, O225, O873
	ICD-9	4340, 4376, 4511, 4512, 4518, 4519, 452 , 4530, 4532, 4533, 4534, 4536, 4538, 4539, 6715
Major and clinically relevant bleeding (history)	ICD-10	D62, D683, H356, H431, I230, I312, I60, I61, I62, I850, I983, J942, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K661, K920, K921, K922, M250, N02, N837, N920, N921, N924, N938, N939, N950, R04, R31, R58, S064, S065, S066
	ICD-9	2851, 2865, 4230, 430, 431, 432, 4560, 4590, 5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5350, 5693, 578, 5967, 5997, 6207, 6262, 6266, 6268, 6269, 6270, 6271, 7191, 7847, 7848, 7863, 852
Parkinson's disease	ICD-10	F023, G20
	ICD-9	3320
Alzheimer's disease	ICD-10	F00, G30
	ICD-9	3310
Immune deficiency	ICD-10	D80, D81, D82, D83, D84, D89
	ICD-9	2790, 2791, 2792, 2793, 2798, 2799
Autoimmune/ autoinflammatory disease	ICD-10	D86, E271, G35, K50, K51, K900, M05, M06, M07, M08, M09, M30, M31, M32, M33, M34, M35
	ICD-9	135, 2554, 2794, 340, 556, 5790, 6960, 710, 714, 725
Malignant tumor	ICD-10	C
	ICD-9	14, 15, 16, 17, 18, 19, 20

Supplemental Table 6. ATC codes used to identify medication prescription at the pharmacological subgroup level at index date

Pharmacological subgroup	**ATC-code**

Antihypertensives	C02, C03, C07, C08, C09
Lipid lowering drugs	C10
Non-steroid anti-inflammatory and anti-rheumatic drugs	M01A
Steroids	H02A, H02B
Antidepressants	N06A
Antacids	A02B
Antiplatelet drugs	B01AC
Data on outpatient medication prescriptions covered by the Dutch statutory basic medical insurance were obtained from Statistics Netherlands. These included the year of prescription and Anatomical Therapeutic Chemical (ATC) code. Medications received in hospitals and nursing homes were not available. Only for anticoagulants, more detailed prescription data were provided, including dispending date and type of anticoagulant. The latter were used to identify prescriptions of antiplatelet drugs.	

Supplemental Table 7. ICD-10 codes used to identify bleeding and thromboembolic events

Major & clinically relevant bleeding		
D62: Acute posthaemorrhagic anaemia D683: Haemorrhagic disorder due to circulating anticoagulants H356: Retinal haemorrhage H431: Vitreous haemorrhage I230: Haemopericardium as current complication following acute myocardial infarction I312: Haemopericardium, not elsewhere classified I60: Subarachnoid haemorrhage I61: Intracerebral haemorrhage I62: Other nontraumatic intracranial haemorrhage I850: Oesophageal varices with bleeding I983: Oesophageal varices with bleeding in diseases classified elsewhere J942: Haemothorax K226: Gastro-oesophageal laceration-haemorrhage syndrome K250: Gastric ulcer, acute with haemorrhage K252: Gastric ulcer, acute with both haemorrhage and perforation K254: Gastric ulcer, chronic or unspecified with haemorrhage	K256: Gastric ulcer, chronic or unspecified with both haemorrhage and perforation K260: Duodenal ulcer, acute with haemorrhage K262: Duodenal ulcer, acute with both haemorrhage and perforation K264: Duodenal ulcer, chronic or unspecified with haemorrhage K266: Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation K270: Peptic ulcer, site unspecified, acute with haemorrhage K272: Peptic ulcer, site unspecified, acute with both haemorrhage and perforation K274: Peptic ulcer, site unspecified, chronic or unspecified with haemorrhage K276: Peptic ulcer, site unspecified, chronic or unspecified with both haemorrhage and perforation K280: Gastrojejunal ulcer, acute with haemorrhage K282: Gastrojejunal ulcer, acute with both haemorrhage and perforation K284: Gastrojejunal ulcer, chronic or unspecified with haemorrhage K286: Gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation K290: Acute haemorrhagic gastritis	K920: K921: K922: unspe M250 N02: R N837: N920: with r N921: with i N924: period N938: vagina N939: unspe N950: R04: H R31: U R58: H S064: S065: S066:

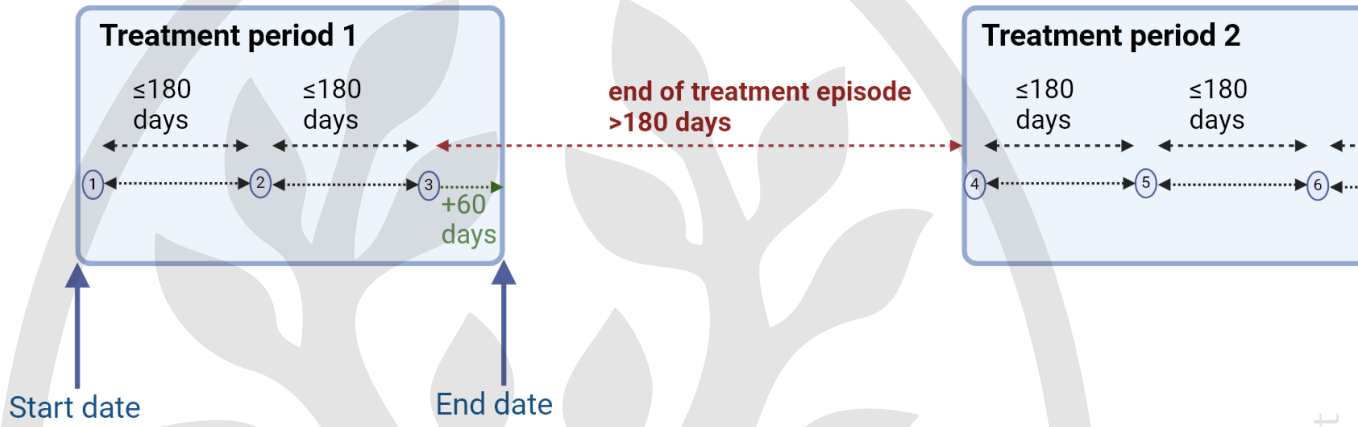
	K625: Haemorrhage of anus and rectum K661: Haemoperitoneum	

Venous thromboembolism		
PE/DVT+thrombophlebitis I26: Pulmonary embolism I801: Phlebitis and thrombophlebitis of femoral vein I802: Phlebitis and thrombophlebitis of other deep vessels of lower extremities (Deep vein thrombosis NOS) I803: Phlebitis and thrombophlebitis of lower extremities, unspecified (Embolism or thrombosis of lower extremity NOS)	**VTE other** H348: Other retinal vascular occlusions I808: Phlebitis and thrombophlebitis of other sites I809: Phlebitis and thrombophlebitis of unspecified site I820: Budd-Chiari I821: thrombophlebitis migrans I822: Embolism and thrombosis of vena cava I823: Embolism and thrombosis of renal vein I828: Embolism and thrombosis of other specified veins I829: Embolism and thrombosis of unspecified vein K765: Hepatic veno-occlusive disease O223: Deep phlebothrombosis in pregnancy (Deep-vein thrombosis, antepartum) O229: Venous complication in pregnancy, unspecified O871: Deep phlebothrombosis in the puerperium (Deep-vein thrombosis, postpartum/Pelvic thrombophlebitis, postpartum) O879: Venous complication in the puerperium, unspecified O882: Obstetric blood-clot embolism (Obstetric (pulmonary) embolism NOS/Puerperal (pulmonary) embolism NOS)	**Cerebral sinus thrombosis** I636: Cerebral infarction due to venous thrombosis, nonpyogen I676: Nonpyogenic thrombosis intracranial venous system O225: Cerebral venous thromb pregnancy O873: Cerebral venous thromb the puerperium

Arterial thromboembolism		
Ischemic stroke/TIA I63: Cerebral infarction G45: Transient cerebral ischaemic attacks and related syndromes G46: Vascular syndromes of brain in	**Other arterial thromboembolism** H340: Transient retinal artery occlusion H341: Central retinal artery occlusion H342: Other retinal artery occlusions I513: intracardial thrombosis	**Myo** I21: I22:

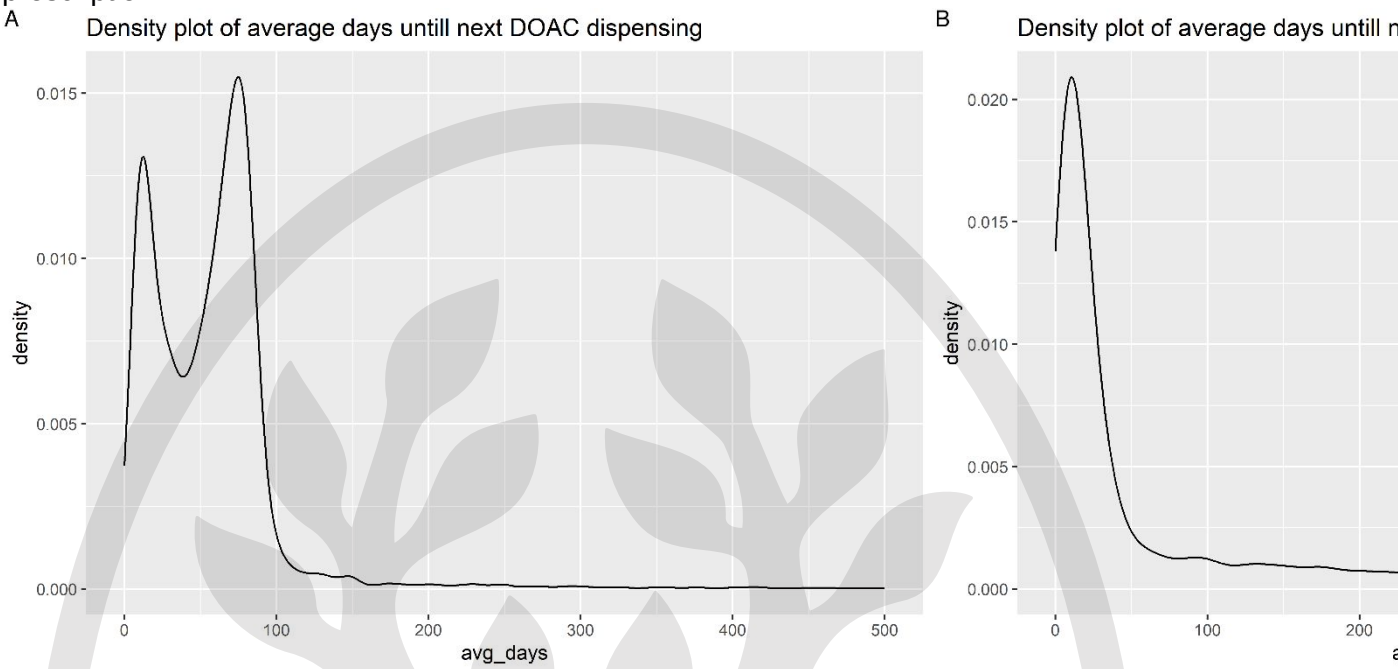
cerebrovascular diseases I64: Stroke, not specified as haemorrhage or infarction	I74: Arterial embolism and thrombosis K550: acute vascular disorder intestine	

Supplemental Figure 1. Construction of treatment periods for anticoagulants



Treatment episodes for anticoagulants were constructed assuming that a dispensed prescription lasted a fixed number of days, unless a refill, death or end of follow-up occurred earlier. Whenever the period between two subsequent dispensed prescription dates exceeded this fixed number of days, the next prescription was considered to belong to a new treatment period. A predefined number of days was added to the last prescription date within the treatment period to construct the end of the corresponding treatment period. Different exposure times were applied to the different types of anticoagulants: 180 days for VKA prescriptions, 120 days for DOAC prescriptions, and 30 days for LMWH prescriptions. The end date of each treatment period was constructed by adding a fixed number of days to the last dispensing date within the treatment period. This was 60 days for VKA prescriptions, 120 days for DOAC prescriptions and 30 days for LMWH prescriptions. Created in BioRender. Kruip, M. (2024) https://BioRender.com/y81a190

Supplemental Figure 2. Density plots of average days until next DOAC or heparin dispensed prescription



Density plots of average days until next DOAC (A) or heparin (B) dispensing per patient studied in two random samples of 10,000 patients with DOAC or heparin prescriptions between 2013-2019, respectively. For patients with DOAC prescriptions, the median number of days until the next DOAC dispensing per patient was 58 days with a 95th percentile of 117 days. For heparin the median was 22 days.

Supplemental Results

Supplemental Table 8. Additional baseline characteristics

	Total (N=18145)	**Cancer** (N=2457)	**Non-cancer** (N=15688)
Standardized household income, quintile[a], No. (%)			
First (lowest)	4207 (23.2)	589 (24.0)	3618 (23.1)
Second	6401 (35.3)	787 (32.0)	5614 (35.8)
Third	3009 (16.6)	471 (19.2)	2538 (16.2)
Fourth	1923 (10.6)	295 (12.0)	1628 (10.4)
Fifth (highest)	1408 (7.8)	261 (10.6)	1147 (7.3)
Institutional household/unknown	1197 (6.6)	54 (2.2)	1143 (7.3)
≥1 comorbidity present at index date[b], No. (%)	8195 (45.2)	956 (38.9)	7239 (46.1)
Autoimmune disease or immune deficiency	326 (1.8)	31 (1.3)	296 (1.9)
Thyroid disease	286 (1.6)	22 (0.9)	264 (1.7)
COPD	1696 (9.3)	162 (6.6)	1534 (9.8)
Asthma and other chronic lung diseases	338 (1.9)	25 (1.0)	313 (2.0)

History of major and clinically relevant bleeding	811 (4.5)	98 (4.0)	713 (4.5)
History of VTE	287 (1.6)	59 (2.4)	228 (1.5)
History of ATE	193 (1.1)	32 (1.3)	161 (1.0)
History of stroke	479 (2.6)	52 (2.1)	427 (2.7)
History of MI	1666 (9.2)	134 (5.5)	1532 (9.8)
Anemia	1440 (7.9)	136 (5.5)	1304 (8.3)
Coagulopathy	391 (2.2)	38 (1.5)	353 (2.3)
Heart failure	2380 (13.1)	93 (3.8)	2287 (14.6)
Valvular heart disease	1660 (9.1)	108 (4.4)	1552 (9.9)
Atrial fibrillation	4332 (23.9)	420 (17.1)	3912 (24.9)
Atherosclerosis	1622 (8.9)	161 (6.6)	1461 (9.3)
Peripheral artery disease	331 (1.8)	41 (1.7)	290 (1.8)
Diabetes mellitus	2292 (12.6)	198 (8.1)	2094 (13.3)
Hypertension	3119 (17.2)	295 (12.0)	2824 (18.0)
Kidney disease	1982 (10.9)	138 (5.6)	1844 (11.8)
Liver disease	247 (1.4)	31 (1.3)	216 (1.4)

ATE: Arterial Thrombotic Event; COPD: Chronic Obstructive Pulmonary Disease; MI: Myocardial Infarction; VTE: Venous Thromboembolic Event.
[a]Percentile groups were determined based on disposable income of private households of the complete Dutch population in the Statistics Netherlands database.
[b]Comorbidities were identified by examining data on hospitalizations within 3 years before the index date using ICD-10 codes and ICD-9 codes restricting to main or primary diagnosis of hospital admission. One or more comorbidities can be present.

Supplemental Table 9. Cancer-specific baseline characteristics

		Cancer (N=2457)
Differentiation grade[a], No. (%)		
	Grade I	36 (1.5)
	Grade II	286 (11.6)
	Grade III	380 (15.5)
	Grade IV	83 (3.4)
	Unknown or not applicable	1672 (68.1)
Treatment of cancer, No. (%)		
	Chemotherapy	675 (27.5)
	Radiotherapy	405 (16.5)
	Surgery[b]	321 (13.1)
	Hormonal therapy	49 (2.0)
	Targeted therapy	119 (4.8)

[a]The differentiation grade was identified by using the 6th number of the ICD-O-3 codes
[b]Surgery was defined as any surgical procedure involving the removal of (a portion of) an organ.

Supplemental Table 10. Median survival and follow-up times for different life-limiting diseases

	N at t=0	Number of deaths	Median survival time (95%CI)	Median follow-up time (IQR)
Total	18145	10948	2.03 (1.97, 2.10)	3.59 (1.95, 5.22)
Type of life-limiting disease				
Cancer	2457	2072	0.35 (0.32, 0.38)	3.41 (2.06, 5.07)
Non-cancer	15688	8876	2.50 (2.43, 2.59)	3.60 (1.95, 5.22)
Type of non-cancer life-limiting disease				
COPD	547	251	2.10 (1.72, 2.43)	1.93 (1.09, 2.64)
Dementia	387	275	2.14 (1.84, 2.57)	4.75 (2.80, 6.00)
Diabetes mellitus	327	203	2.28 (1.88, 2.94)	4.64 (2.20, 5.69)
Heart disease	10879	6185	2.57 (2.46, 2.68)	3.80 (2.07, 5.32)
Hip fracture	3277	1792	2.53 (2.40, 2.67)	3.20 (1.77, 4.80)
Interstitial lung disease	107	76	2.14 (1.26, 2.71)	3.58 (2.61, 5.62)
Liver disease	164	94	2.09 (1.09, 3.50)	3.57 (1.88, 5.57)

CI = confidence interval; COPD = Chronic obstructive pulmonary disease; IQR = Interquartile range. A life-limiting disease was defined according to the definition of a severe medical condition by Kelley et al. as "a diagnosis that carries an increased risk of mortality, hospitalization and emergency room visits"[27]. These diseases were identified by ICD-10 codes of diagnoses registered as either main or primary diagnosis of the hospital admission or registered cancer diagnosis by the Netherlands Cancer Registry.
Median survival and follow-up time were estimated by the Kaplan-Meier estimator.

Supplemental Table 11. Cumulative incidence and incidence rate of VKA and anticoagulant treatment discontinuation stratified by life-limiting disease

	VKA discontinuation				Anticoagulation discontinuation			
	IR / 100 PY (95% CI)	**6-month Cumulative incidence % (95%CI)**	**1-year Cumulative incidence % (95%CI)**	**3-year Cumulative incidence % (95%CI)**	**IR / 100 PY (95% CI)**	**6-month Cumulative incidence % (95%CI)**	**1-year Cumulative incidence % (95%CI)**	**3-year Cumulative incidence % (95%CI)**
Cancer	63.1 (59.3-67.0)	33.7 (31.9-35.6)	38.7 (36.7-40.6)	43.7 (41.7-45.8)	42.6 (39.7-45.7)	23.8 (22.1-25.5)	28.7 (26.9-30.5)	33.7 (31.7-35.6)
COPD	17.3 (14.1-21.0)	10.8 (8.3-13.7)	13.6 (10.8-16.7)	24.7 (20.3-29.3)	10.4 (8.0-13.2)	6.4 (4.6-8.8)	8.2 (6.0-10.7)	17.3 (13.0-22.1)

Dementia	21.7 (18.4-25.5)	16.8 (13.3-20.7)	23.2 (19.1-27.6)	35.6 (30.7-40.6)	19.9 (16.7-23.4)	15.5 (12.1-19.4)	22.2 (18.2-26.5)	33.5 (28.7-38.3)
Diabetes mellitus	17.1 (13.9-20.7)	12.3 (9.0-16.1)	14.9 (11.2-19.0)	27.0 (22.0-32.1)	14.1 (11.3-17.4)	10.8 (7.7-14.4)	12.7 (9.3-16.6)	23.6 (18.8-28.6)
Heart disease	13.8 (13.3-14.3)	11.0 (10.4-11.6)	14.4 (13.7-15.1)	23.8 (22.9-24.6)	9.4 (9.0-9.8)	7.4 (6.9-7.9)	10.1 (9.5-10.7)	17.4 (16.6-18.2)
Hip fracture	18.7 (17.6-19.9)	14.9 (13.7-16.1)	18.4 (17.1-19.8)	30.1 (28.4-31.9)	15.5 (14.4-16.5)	12.7 (11.6-13.9)	15.8 (14.6-17.1)	26.1 (24.4-27.7)
Interstitial lung disease	18.6 (12.7-26.2)	12.2 (6.8-19.2)	16.9(10.5-24.7)	29.4 (20.6-38.8)	12.0 (7.5-18.1)	9.4 (4.8-15.9)	11.3 (6.1-18.2)	19.1 (12.0-27.6)
Liver disease	29.6 (22.8-37.9)	22.1 (16.1-28.8)	29.9 (23.0-37.2)	36.5 (28.9-44.1)	21.0 (15.5-27.7)	17.9 (12.4-24.1)	24.4 (18.0-31.3)	30.5 (23.3-38.0)

Cumulative incidences were computed taking the competing risk of death into account. Crude incidence rates (IR) were estimated as events per 100 person-years (PY). Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IR = incidence rate; PY = person-years; VKA = vitamin K antagonist

Supplemental Table 12. Mean proportion of days covered with anticoagulants during follow-up

	Number of patients, No.	**Mean PDC % (SD)**	**Adherent* patients %**
Total	18145	91.8 (22.2)	88.0
Type of life-limiting disease			
Cancer	2457	87.2 (26.4)	81.0
Non-cancer	15688	92.6 (21.4)	89.2
Type of non-cancer life-limiting disease			
COPD	547	95.3 (17.3)	93.6
Dementia	387	83.9 (30.2)	75.5
Diabetes mellitus	327	88.0 (26.4)	82.9

Heart disease	10879	94.1 (18.8)	91.3
Hip fracture	3277	88.9 (26.3)	84.3
Interstitial lung disease	107	92.7 (21.2)	87.9
Liver disease	164	82.3 (32.2)	76.8
Sex			
Females	8841	91.0 (23.4)	86.8
Males	9304	92.6 (21.1)	89.2

*Adherent was defined as a proportion of days covered (PDC) with anticoagulants >80%. Abbreviations: COPD = chronic obstructive pulmonary disease; PDC = proportion of days covered; SD = standard deviation.

Supplemental Table 13. Cumulative incidence and incidence rate of VKA and anticoagulant treatment discontinuation in sensitivity analysis VKA exposure time

	VKA discontinuation				**Anticoagulation discontinuation**			
	IR / 100 PY (95%CI)	**6-month Cumulative incidence % (95%CI)**	**1-year Cumulative incidence % (95%CI)**	**3-year Cumulative incidence % (95%CI)**	**IR / 100 PY (95%CI)**	**6-month Cumulative incidence % (95%CI)**	**1-year Cumulative incidence % (95%CI)**	**3-year Cumulative incidence % (95%CI)**
Total	17.7 (17.2-18.2)	14.9 (14.4-15.5)	18.6 (18.1-19.2)	27.7 (27.0-28.4)	12.7 (12.3-13.1)	10.8 (10.4-11.3)	14.0 (13.5-14.5)	21.4 (20.7-22.0)
Type of life-limiting disease								
Cancer	62.8 (59.0-66.7)	33.7 (31.8-35.5)	38.5 (36.6-40.5)	43.6 (41.6-45.6)	42.4 (39.5-45.4)	23.7 (22.0-25.4)	28.5 (26.7-30.4)	33.5 (31.6-35.5)
Non-cancer	15.0 (14.5-15.5)	12.0 (11.5-12.5)	15.5 (15.0-16.1)	25.3 (24.5-26.0)	10.8 (10.4-11.2)	8.8 (8.4-9.3)	11.7 (11.2-12.2)	19.5 (18.8-20.2)
Type of non-cancer life-limiting disease								
COPD	17.1 (14.0-20.8)	10.6 (8.2-13.4)	13.4 (10.6-16.5)	24.5 (20.1-29.2)	10.2 (7.9-13.0)	6.3 (4.4-8.5)	8.0 (5.8-10.5)	17.2 (12.9-22.0)
Demen	21.7	16.8	23.2	35.6	19.9	15.5	22.2	33.5

tia	(18.4-25.5)	(13.3-20.7)	(19.1-27.6)	(30.7-40.6)	(16.7-23.4)	(12.1-19.4)	(18.2-26.5)	(28.7-38.3)
Diabetes mellitus	16.7 (13.6-20.3)	12.3 (9.0-16.1)	14.9 (11.2-19.0)	26.6 (21.7-31.8)	13.7 (11.0-17.0)	10.8 (7.7-14.4)	12.7 (9.3-16.6)	23.2 (18.5-28.2)
Heart disease	13.5 (13.0-14.1)	10.9 (10.3-11.5)	14.3 (13.7-15.0)	23.4 (22.5-24.2)	9.2 (8.8-9.6)	7.4 (6.9-7.9)	10.1 (9.5-10.7)	17.0 (16.3-17.8)
Hip fracture	18.5 (17.4-19.7)	14.8 (13.6-16.1)	18.3 (16.9-19.6)	29.8 (28.1-31.5)	15.2 (14.2-16.3)	12.6 (11.5-13.8)	15.7 (14.5-17.0)	25.7 (24.1-27.4)
Interstitial lung disease	18.0 (12.2-25.6)	11.3 (6.1-18.1)	16.9(10.5-24.7)	28.1 (19.5-37.4)	11.4 (7.1-17.5)	8.4 (4.1-14.7)	11.3 (6.1-18.2)	17.8 (11.0-26.0)
Liver disease	29.6 (22.7-37.8)	22.1 (16.1-28.8)	29.9 (23.0-37.2)	36.5 (28.9-44.2)	21.0 (15.5-27.7)	17.9 (12.4-24.1)	24.4 (18.0-31.3)	30.5 (23.3-38.0)
Sex								
Females	17.8 (17.1-18.5)	14.9 (14.1-15.6)	18.9 (18.0-19.7)	28.7 (27.7-29.7)	13.1 (12.6-13.7)	11.1 (10.4-11.7)	14.4 (13.6-15.1)	22.6 (21.7-23.6)
Males	17.6 (16.9-18.3)	15.0 (14.3-15.7)	18.4 (17.6-19.2)	26.8 (25.9-27.8)	12.3 (11.7-12.9)	10.6 (10.0-11.3)	13.6 (12.9-14.3)	20.2 (19.4-21.1)

This table displays the cumulative incidences and incidence rates of vitamin K antagonist (VKA) and anticoagulant treatment discontinuation calculated in a sensitivity analysis where we varied the exposure time of a VKA prescription when constructing treatment periods (150 days + 100 days added versus 180 days + 60 days added in the main analysis).
Cumulative incidences were computed taking the competing risk of death into account. Crude incidence rates (IR) were estimated as events per 100 person-years (PY). Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IR = incidence rate; PY = person-years; VKA = vitamin K antagonist.

Supplemental Table 14. Cumulative incidence and incidence rate of anticoagulant treatment discontinuation in sensitivity analysis heparin exposure time

Anticoagulation discontinuation

	IR / 100 PY (95%CI)	6-month Cumulative incidence % (95%CI)	1-year Cumulative incidence % (95%CI)	3-year Cumulative incidence % (95%CI)
Total	12.7 (12.3-13.1)	10.7 (10.3-11.2)	13.8 (13.3-14.3)	21.2 (20.6-21.9)
Type of life-limiting disease				
Cancer	39.9 (37.1- 42.8)	22.9 (21.3-24.6)	27.2 (25.5-29.0)	31.4 (29.5-33.3)
Non-cancer	10.9 (10.6-11.3)	8.8 (8.4-9.3)	11.7 (11.2-12.2)	19.7 (19.0-20.3)
Type of non-cancer life-limiting disease				
COPD	10.1 (7.8-12.9)	6.4 (4.6-8.8)	7.9 (5.8-10.5)	15.9 (12.2-20.1)
Dementia	19.9 (16.7-23.4)	15.5 (12.1-19.4)	22.2 (18.2-26.5)	33.5 (28.7-38.3)
Diabetes mellitus	13.9 (11.1-17.2)	10.8 (7.7-14.4)	12.7 (9.3-16.6)	22.8 (18.1-27.7)
Heart disease	9.3 (8.9-9.7)	7.3 (6.9-7.8)	10.0 (9.5-10.6)	17.2 (16.5-18.0)
Hip fracture	15.4 (14.4-16.4)	12.7 (11.6-13.9)	15.7 (14.5-17.0)	26.0 (24.3-27.6)
Interstitial lung disease	12.0 (7.5-18.1)	9.4 (4.8-15.9)	11.3 (6.1-18.2)	19.1 (12.0-27.6)
Liver disease	20.9 (15.5- 27.7)	17.9 (12.4-24.1)	24.4 (18.0-31.3)	29.5 (22.5-36.9)
Sex				
Females	13.1 (12.6-13.7)	11.0 (10.4-11.7)	14.3 (13.6-15.1)	22.5 (21.6-23.5)
Males	12.2 (11.6-12.8)	10.5 (9.9-11.1)	13.3 (12.6-14.0)	20.0 (19.2-20.9)

This table displays the cumulative incidences and incidence rates of anticoagulant treatment discontinuation calculated in a sensitivity analysis where we varied the exposure time of a heparin (i.e. LMWH) prescription when constructing treatment periods (100 days added versus 30 days in the main analysis).
Cumulative incidences were computed taking the competing risk of death into account. Crude

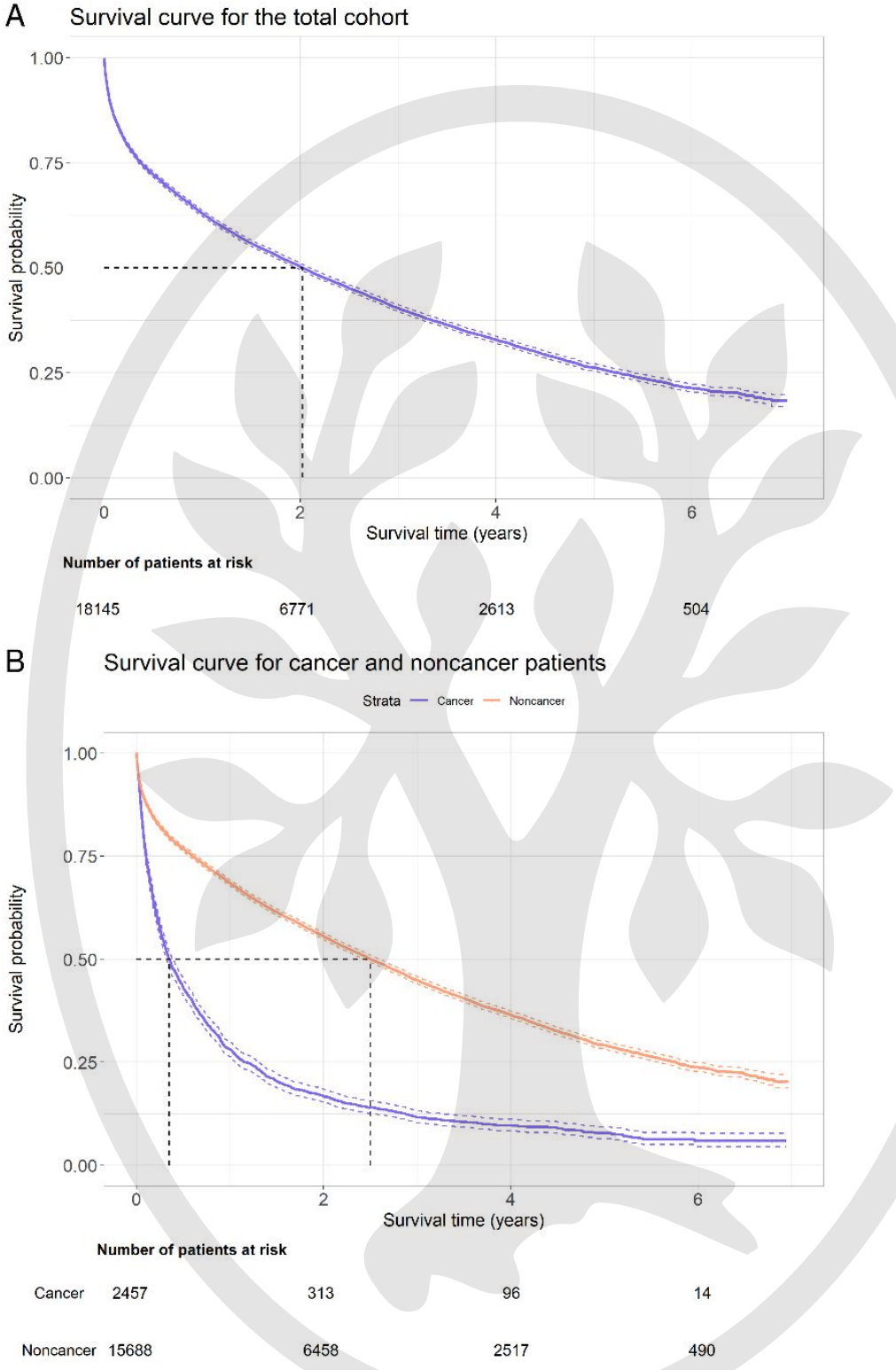
incidence rates (IR) were estimated as events per 100 person-years (PY). Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IR = incidence rate; PY = person-years.

Supplemental Table 15. Incidence rates of bleeding and thromboembolic events stratified by anticoagulation exposure in sensitivity analyses

	Extending AC exposed period by 7 days		**Sensitivity analysis heparin exposure time**	
	IR/100 PY AC exposed (95%CI)	**IR/100 PY unexposed (95%CI)**	**IR/100 PY AC exposed (95%CI)**	**IR/100 PY unexposed (95%CI)**
Major and clinically relevant bleeding	2.6 (2.4-2.8)	1.9 (1.4-2.7)	2.6 (2.4-2.8)	2.1 (1.5-2.8)
Venous thromboembolism	0.2 (0.1-0.2)	0.4 (0.2-0.8)	0.2 (0.1-0.2)	0.4 (0.2-0.7)
Arterial thromboembolism	3.1 (2.9-3.3)	3.0 (2.3-3.8)	3.1 (2.9-3.3)	3.2 (2.5-4.1)
Myocardial infarction	1.1 (1.0-1.3)	0.8 (0.5-1.3)	1.1 (1.0-1.3)	0.8 (0.5-1.3)
Stroke	1.6 (1.5-1.7)	1.8 (1.3-2.4)	1.6 (1.4-1.7)	2.0 (1.5-2.7)
Other	0.4 (0.4-0.5)	0.5 (0.2-0.8)	0.4 (0.4-0.5)	0.4 (0.2-0.8)

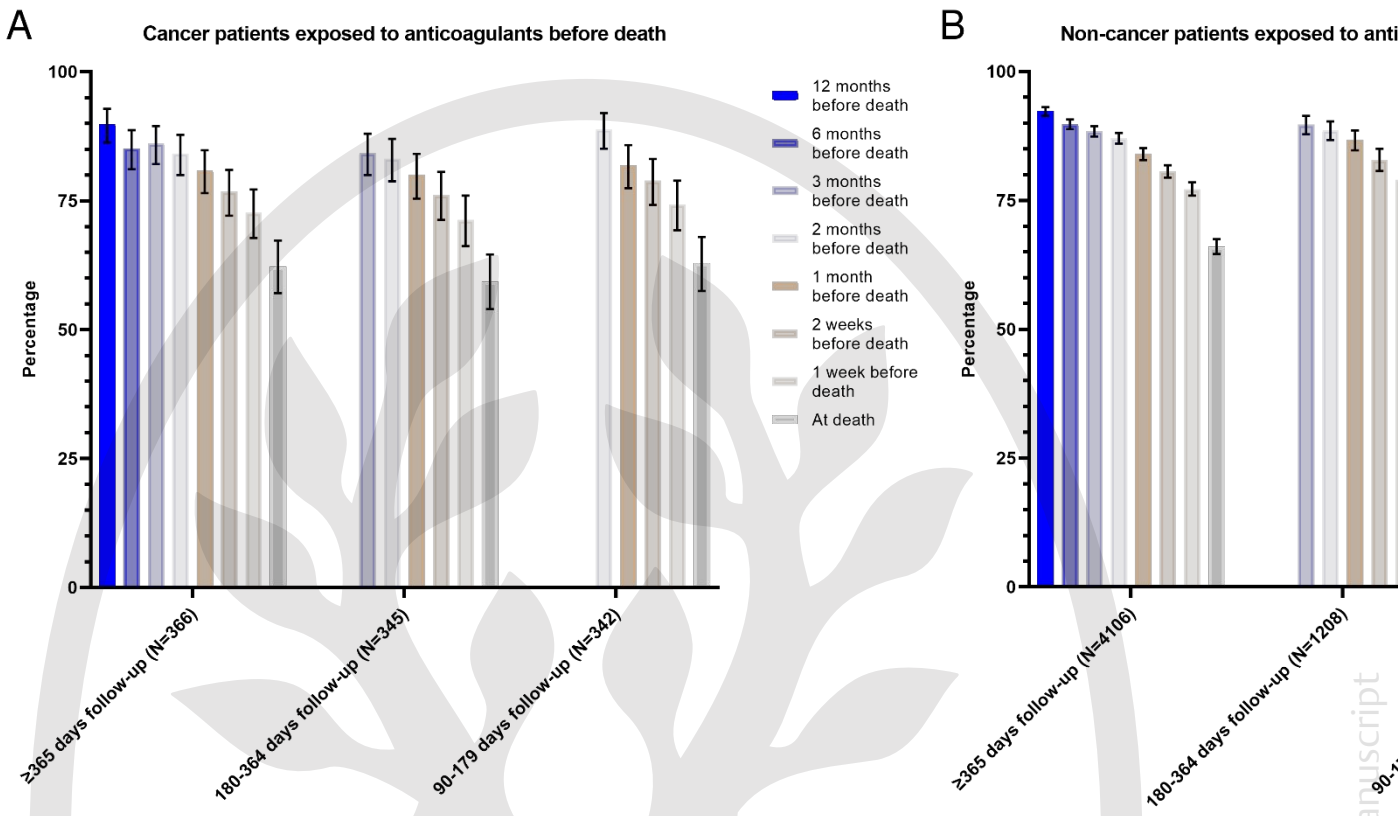
This table displays the incidence rates of first bleeding and thromboembolic events stratified by anticoagulant exposure, estimat sensitivity analyses were performed: (1) extending the period exposed to anticoagulants by seven days, (2) varying the exposure when constructing treatment periods (100 days added versus 30 days in the main analysis), (3) varying the exposure time of a VI periods (150 days + 100 days added versus 180 days + 60 days added in the main analysis). Incidence rates were estimated as ev was categorized according to anticoagulant exposure. AC = anticoagulant; CI = confidence interval; IR = incidence rate; PY = pers

Supplemental Figure 3. Kaplan-Meier survival curve for the total cohort and for patients with cancer versus non-cancer diseases



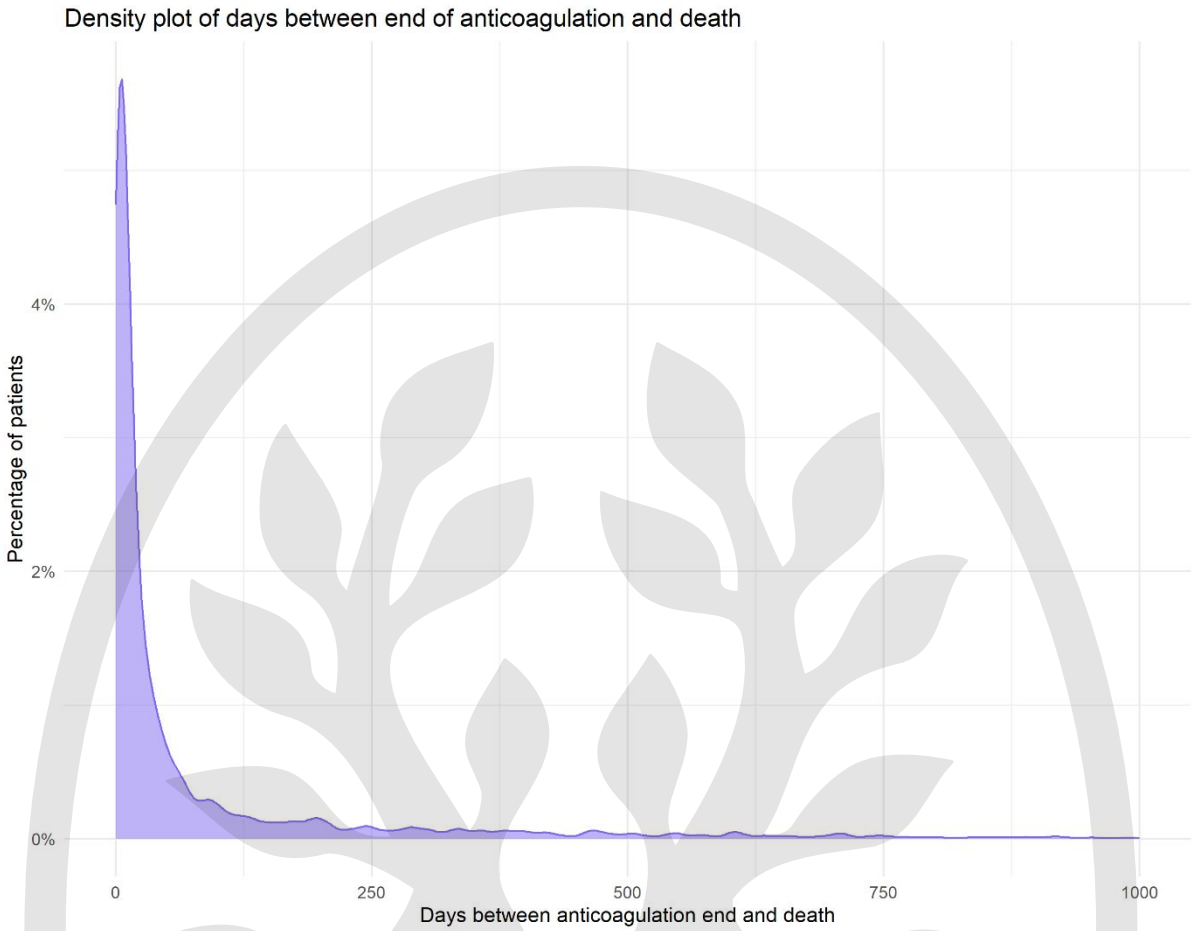
Kaplan-Meier survival curves for the total cohort (A) and patients with cancer versus non-cancer diseases separately (B). Median survival was estimated by the Kaplan-Meier estimator.

Supplemental Figure 4. Patients exposed to anticoagulants before death stratified by cancer versus non-cancer diseases



Percentage of patients exposed to anticoagulants with corresponding 95% confidence intervals at different time points before death, stratified according to the amount of follow-up time between index date and date of death and by cancer versus non-cancer diseases. This analysis was restricted to patients who died during follow-up.

Supplemental Figure 5. Density plot of days between end of anticoagulant treatment and death



Calculated among patients who died during follow-up and discontinued anticoagulant treatment before death (N=3372).

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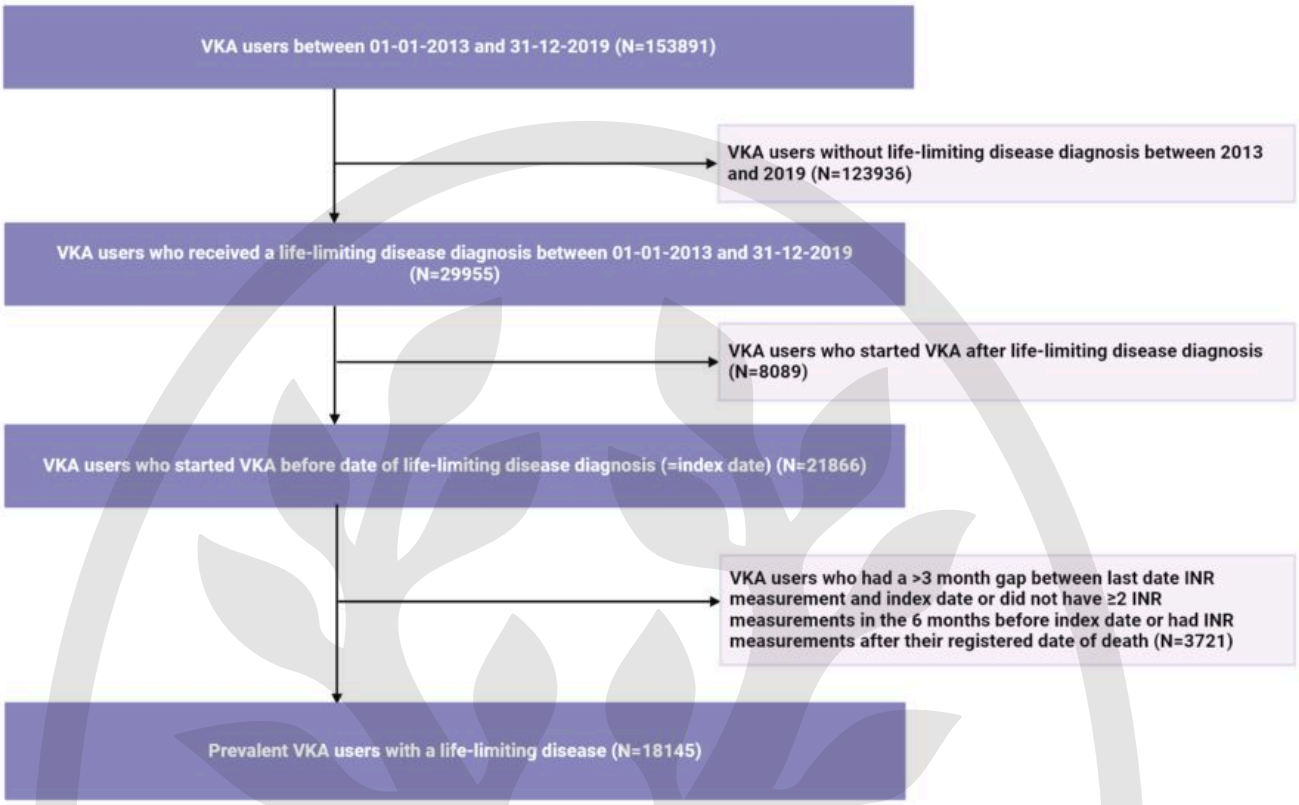
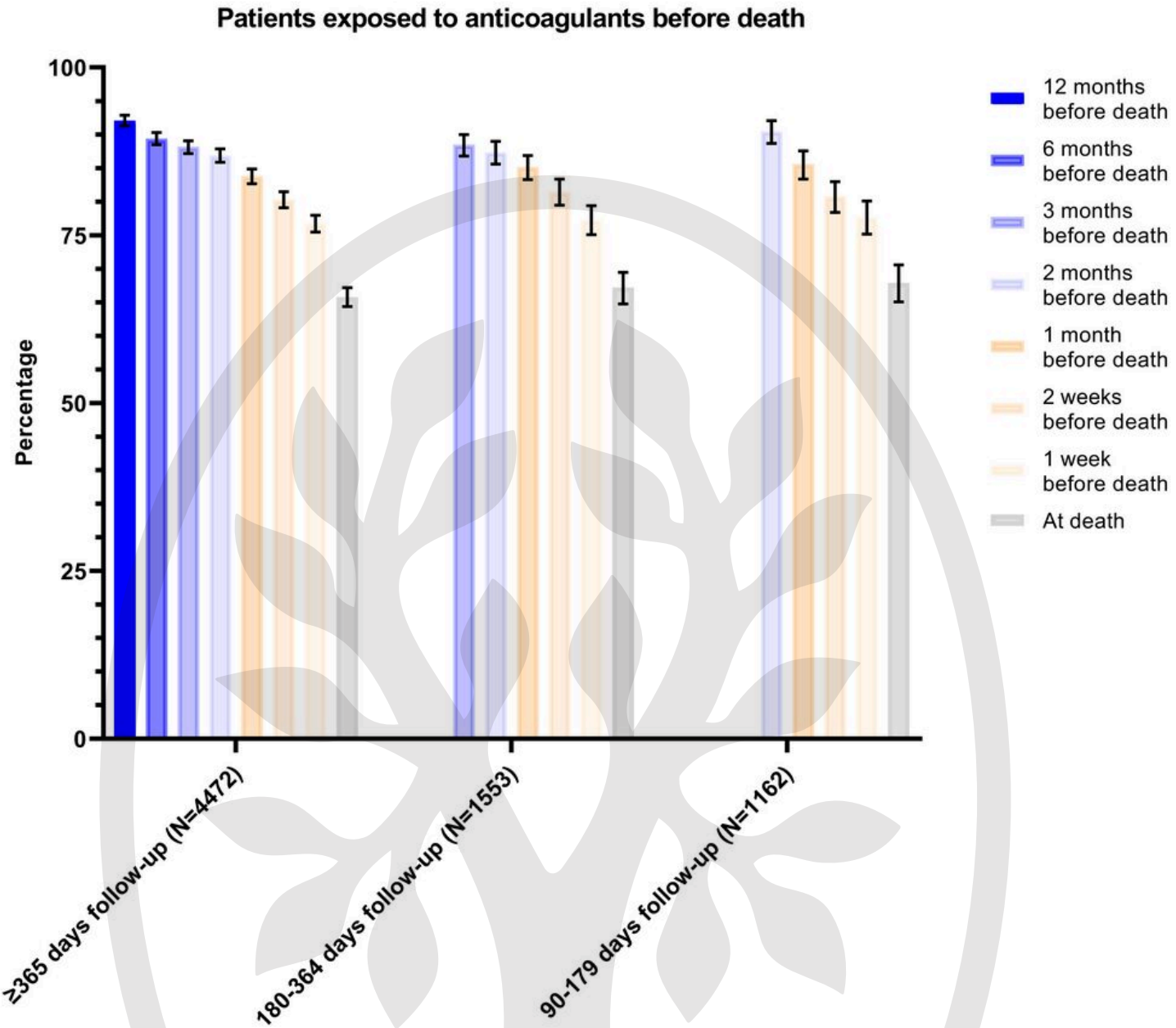
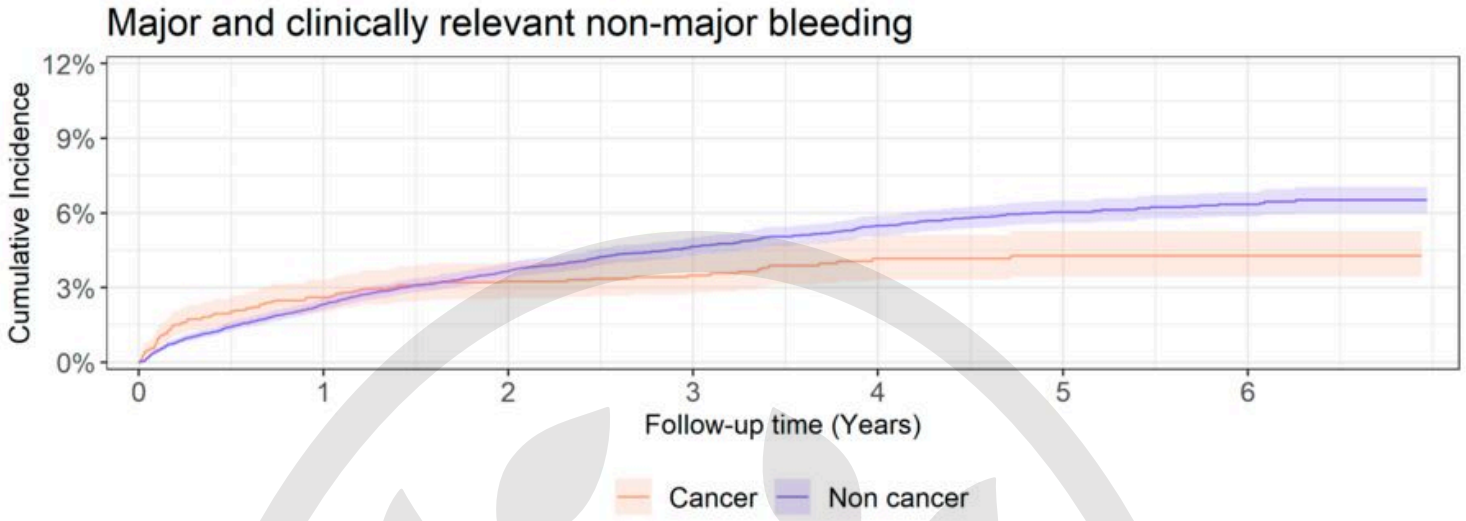
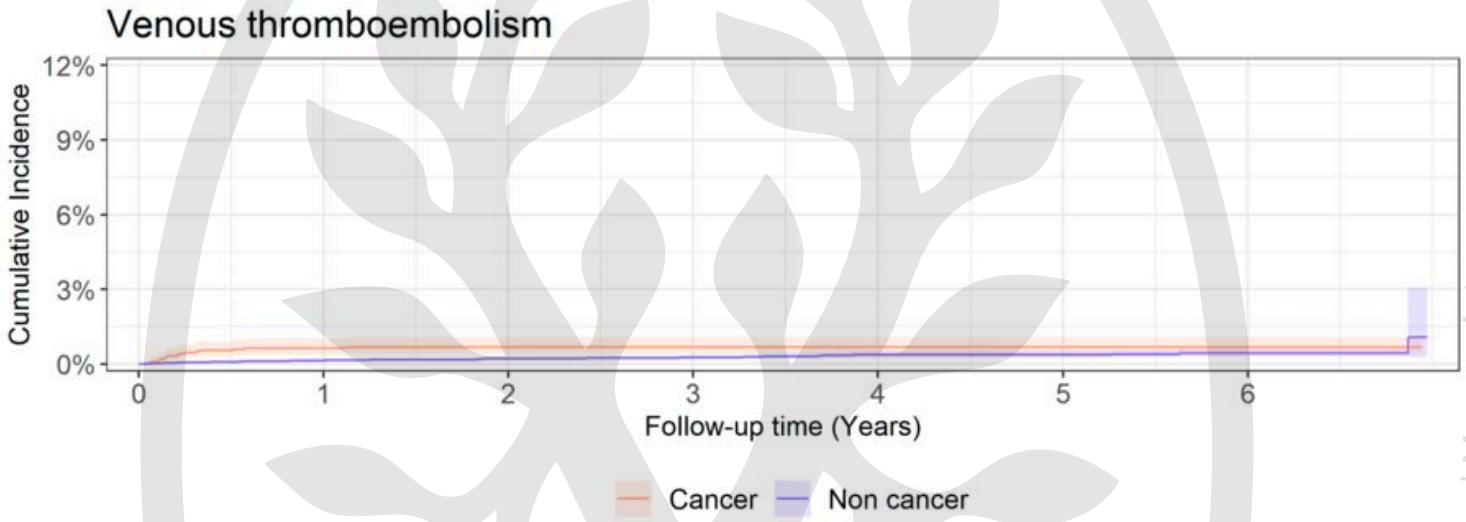
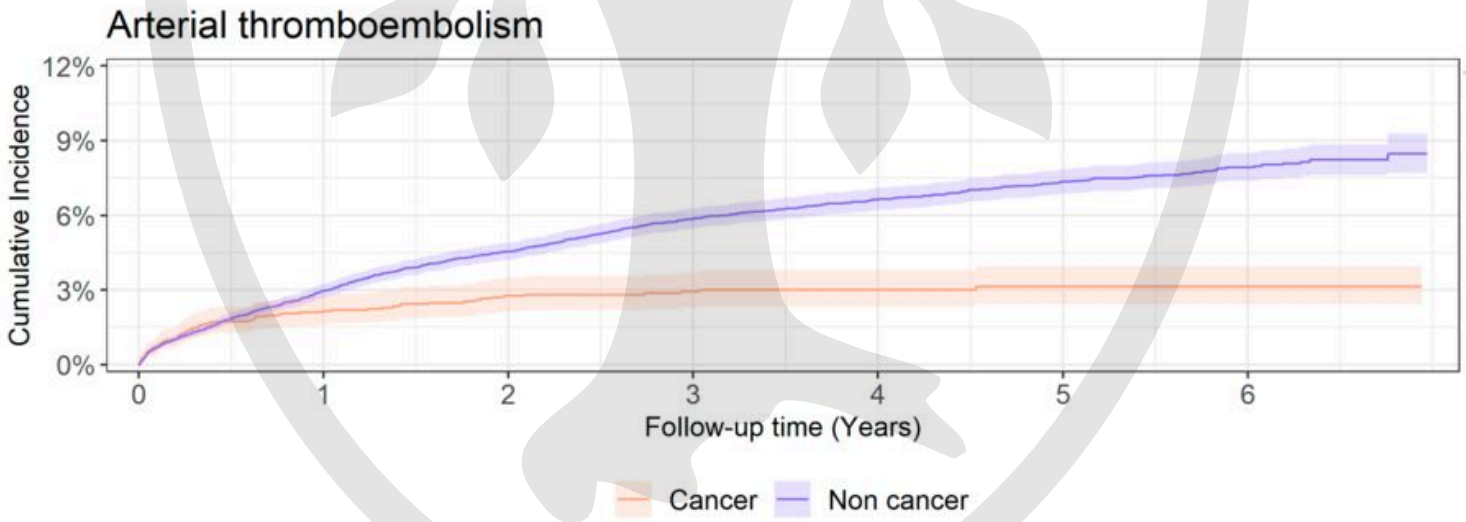










Discontinuation of anticoagulants is uncommon in vitamin K antagonist users with a life-limiting disease

Large-scale cohort study

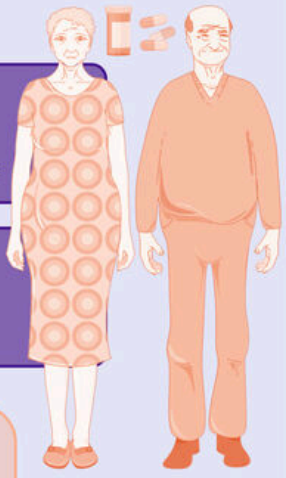
2013-2019

3 linked nationwide data sources

Statistics Netherlands

KNL Netherlands comprehensive cancer organisation

FEDERATIE VAN NEDERLANDSE TROMBOSEDIENSTEN



18,145 prevalent VKA users with a life-limiting disease

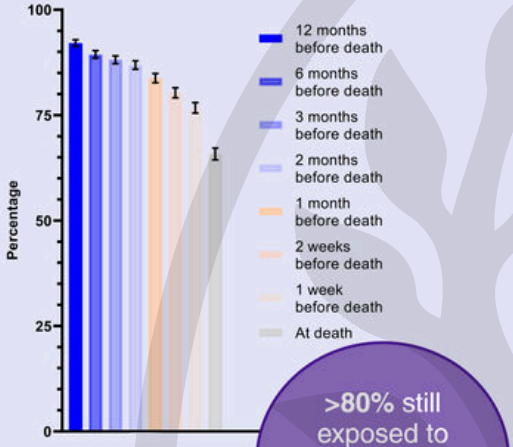
Median age 81 years

49%

Median survival time 2.03 years

Life-limiting diseases

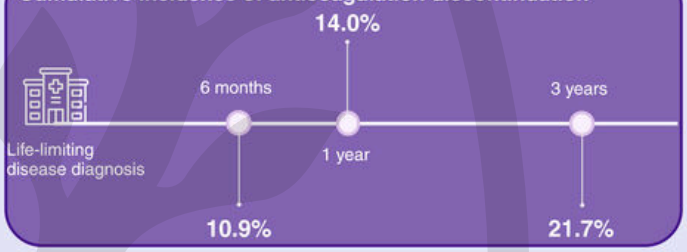
60% 18% 14%



>80% still exposed to anticoagulants 1 month prior to death

Median 14 days between end of anticoagulant treatment and death

Cumulative incidence of anticoagulation discontinuation

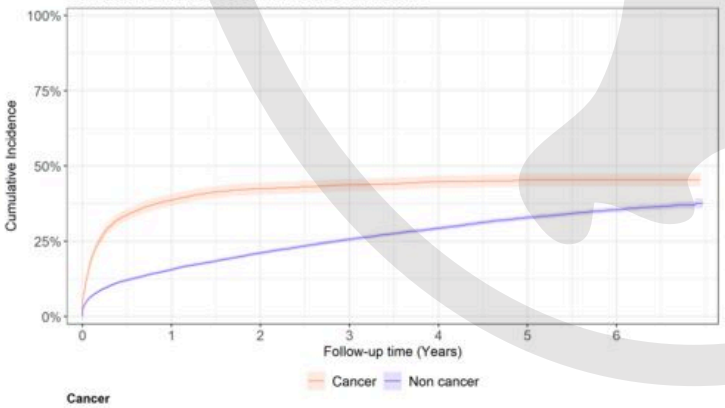


Crude incidence rates of hospital admission for **bleeding** and **thromboembolism comparable** during **anticoagulant use** and after **discontinuation**

vs

A

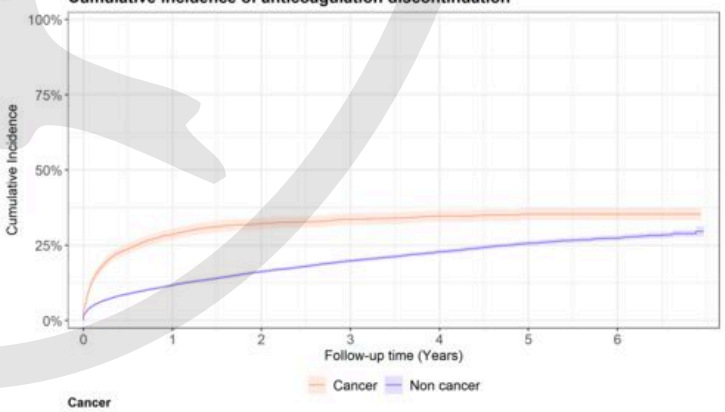
Cumulative incidence of VKA discontinuation



Cancer							
At Risk	2457	479	250	139	81	41	13
Events	0	928	1006	1028	1041		1047
Non cancer							
At Risk	15688	8603	5763	3622	2146	1066	397
Events	0	2378	3099	3592	3911	4135	4229

B

Cumulative incidence of anticoagulation discontinuation



Cancer							
At Risk	2457	552	288	161	88	44	13
Events	0	685	756	781	794		799
Non cancer							
At Risk	15688	9007	6079	3862	2319	1179	447
Events	0	1786	2368	2747	2989	3157	3218