Received: 18 November 2024 | Accepted: 14 March 2025

DOI: 10.1002/hem3.70135

ARTICLE

HemaSphere eha

Quality of vitamin K antagonist treatment during the last year of life

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Abstract

Limited data exist on the quality of anticoagulation in patients approaching the end of life. This study evaluated vitamin K antagonist (VKA) anticoagulation control during the last year of life, using nationwide data from Statistics Netherlands, linked to anticoagulation clinics' data and the Netherlands Cancer Registry. We included prevalent VKA users who were hospitalized with a severe medical condition and died between January 1, 2013, and December 31, 2019. Anticoagulation control was assessed using time in therapeutic range (TTR), time above therapeutic range (TAR), and time below therapeutic range (TBR) and the international normalized ratio (INR) variance growth rate (VGR), which reflects INR variability. Anticoagulation control was examined by two approaches: (1) over four intervals (0–12 months, 0–9 months, 0–6 months, and 0–3 months preceding death), and (2) in 3-month intervals (9–12, 6–9, 3–6, and 0–3 months before death) to describe temporal changes. Among 6874 VKA users in their last year of life (median age 82 [Interquartile range: 76–87] years, 46.9% female), the most prevalent severe medical conditions were heart disease (60.4%), cancer (16.2%), and hip fracture (15.2%). As death approached, TTR and TBR decreased, while TAR and mean VGR increased, particularly in the last 3 months of life. This decline was more pronounced in cancer patients and acenocoumarol users. In conclusion, the quality of VKA anticoagulation declined in the last year of life in severely ill patients, marked by reduced TTR and increased TAR and VGR, suggesting an increased bleeding risk. These findings highlight the importance of reassessing VKA use and considering discontinuation in patients approaching the end of life.

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INTRODUCTION

Anticoagulants are essential for treating venous thromboembolism (VTE) and preventing thromboembolic events, particularly in patients with atrial fibrillation (AF). Despite the availability of direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs) remain the first choice in patients with mechanical heart valves, extreme body weights, severe chronic kidney or liver disease, frail older patients who already use VKAs, or in situations where DOACs cannot be afforded.[1–3] Maintaining a high quality of anticoagulation control in patients using VKAs is challenging in specific settings due to their complex pharmacological properties.[4,5] These properties include a delayed onset of action, extensive drug and diet interactions, and a narrow therapeutic range. Regular monitoring of the international normalized ratio (INR) allows for timely adjustments of VKA doses to maintain the anticoagulant effect within the therapeutic range, thereby reducing the risks of bleeding and thromboembolic events.[6,7] INR fluctuations and prolonged periods with INRs outside the therapeutic range are associated with an increased risk of thrombotic and bleeding complications.[7,8]

In palliative care, where the focus shifts to symptom management and quality of life rather than prolonging life, the use of anticoagulants presents unique challenges.[9,10] In patients who receive palliative care, anticoagulants are commonly continued for stroke prevention in patients with AF and after VTE to prevent future thromboembolic events, rather than for immediate symptom relief.[11–14] Notably, patients receiving palliative care, particularly those with advanced cancer, are at higher risk of both thrombotic and bleeding complications.[15–19] Additionally, these patients often experience impaired oral intake, polypharmacy, impaired liver and kidney function, and other concurrent medical conditions and symptoms associated with limited life expectancy, such as vomiting, constipation, and cachexia, all of which can affect the pharmacokinetics and dynamics of VKAs, thereby further complicating anticoagulation control.[20–29] Poor anticoagulation control might require more frequent INR monitoring, which adds to the burden of care in patients approaching the end of life.[30,31]

Assessing the harm–benefit balance of anticoagulant use in this patient group is challenging. While anticoagulants may indeed prevent thrombotic events (stroke, recurrent VTE), they also directly increase the risk of serious bleeding. Clinicians may be hesitant to deprescribe anticoagulants, driven by concerns over the perceived risk of thromboembolic events following discontinuation, while underestimating the potential harms associated with bleeding complications.[32]

Given these complexities, healthcare professionals and patients should carefully weigh the benefits and risks of continuing VKA therapy in patients approaching the end of life. This decision is complicated by limited evidence on the effectiveness and safety of VKAs in this population. To provide more insights into the current management of VKA treatment during the last phase of life, this study aimed to evaluate anticoagulation control during the last 12 months of life in a large cohort of VKA users with severe medical conditions associated with limited life expectancy.

PATIENTS AND METHODS

This study used data from a previously published multicenter observational cohort, which described the characteristics, clinical outcomes, and anticoagulant use patterns in VKA users with a pre-specified life-limiting disease or who received a severe cancer diagnosis.[33] The study was judged exempt from ethical review according to Dutch law due to the use of pre-existing and de-identified data. The protocol was subsequently approved by the Scientific Committee of the Department of Clinical Epidemiology of the Leiden University Medical Centre (#A0178).

In short, data were obtained from five Dutch anticoagulation clinics and linked to individual-level data from Statistics Netherlands ("Centraal Bureau voor de Statistiek," CBS) and the Netherlands Cancer Registry (NCR). These data sources provide comprehensive information on demographic and clinical characteristics, mortality, and VKA treatment, including registered treatment indications, start and stop dates of VKA treatment, INR measurements and corresponding INR results, VKA type and dosages, and target INR ranges. Further details on variable identification and extraction are presented in Tables S1–S6.

Participants and setting

The original cohort consisted of prevalent VKA users with a severe medical condition,[34] identified between January 1, 2013, and December 31, 2019. To focus on patients with a limited life expectancy, we included VKA users with a severe medical condition associated with a median survival time of 2–4 years. Severe non-cancer conditions were identified based on hospitalization records from CBS, while cancer diagnoses were obtained from the NCR. If patients had multiple hospitalizations or cancer diagnoses during this period, the first recorded hospitalization or cancer diagnosis was used for inclusion.

For the current analysis, we selected all patients who died during the study period and studied a 12-month lookback period from their date of death to describe the anticoagulation control during their last year of life. For patients who were diagnosed with a severe medical condition within the year before their death, we used the available data from the time of diagnosis until death. Since acenocoumarol and phenprocoumon are the most used VKAs in the Netherlands, we excluded patients prescribed other types of VKA. Of note, VKA type is primarily determined by clinic preference rather than patient characteristics, with only a few clinics (i.e., Leiden) prescribing phenprocoumon to most of their patients.[35] Finally, patients with missing INR target ranges were excluded.

Baseline characteristics

Collected baseline characteristics for the current analysis included sex, age, immigrant status (i.e., native Dutch, the first or second generation of migration background), registered treatment indications, type of VKA, and presence of comorbidities. Prespecified comorbidities were identified from ICD codes from hospitalizations within 3 years before severe medical condition diagnosis, restricted to the main and primary diagnoses of the hospital admission (Tables S2 and S6).

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TABLE 1 Baseline characteristics of VKA users with a severe medical condition between 2013 and 2019 who used VKA during their last year of life.

	Total (*N* = 6874)	Cancer patients (*n* = 1115)	Non-cancer patients (*n* = 5759)
Demographics			
Female sex, *n* (%)	3227 (46.9)	380 (34.1)	2847 (49.4)
Median age in years [Q1, Q3]	82.0 [76.0, 87.0]	77.0 [71.0, 82.0]	83.0 [77.0, 88.0]
Type of severe medical condition, *n* (%)[a]			
Cancer	1115 (16.2)	1115 (100)	
ILD	49 (0.7)		49 (0.9)
Liver disease	39 (0.6)		39 (0.7)
COPD	173 (2.5)		173 (3.0)
Dementia	183 (2.7)		183 (3.2)
Diabetes mellitus (complicated)	114 (1.7)		114 (2.0)
Hip fracture	1047 (15.2)		1047 (18.2)
Heart disease	4154 (60.4)		4154 (72.1)
Registered indications for VKA therapy, *n* (%)[b]			
Arterial embolus	68 (1.0)	14 (1.3)	54 (0.9)
Atrial fibrillation and other arrhythmias	5494 (79.9)	810 (72.6)	4684 (81.3)
Biological valve and other heart surgery	104 (1.5)	15 (1.3)	89 (1.5)
Cardiomyopathy or congestive heart failure	573 (8.3)	57 (5.1)	516 (9.0)
Cerebral vascular disease	108 (1.6)	16 (1.4)	92 (1.6)
Coronary syndrome and interventions	167 (2.4)	35 (3.1)	132 (2.3)
Mechanical heart valve	372 (5.4)	57 (5.1)	315 (5.5)
Peripheral arterial disease	61 (0.9)	10 (0.9)	51 (0.9)
Vascular surgery	157 (2.3)	44 (3.9)	113 (2.0)
VTE	334 (4.9)	107 (9.6)	227 (3.9)
Target INR levels, *n* (%)			
2.0–3.0	3881 (56.5)	585 (52.5)	3296 (57.2)
2.5–3.5	2568 (37.4)	475 (42.6)	2093 (36.3)
3.0–4.0	352 (5.1)	46 (4.1)	306 (5.3)
Type of VKA, *n* (%)			
Acenocoumarol	4999 (72.7)	756 (67.8)	4243 (73.7)
Phenprocoumon	1875 (27.3)	359 (32.2)	1516 (26.3)
≥1 Comorbidity present, *n* (%)[c]	3062 (44.5)	456 (40.9)	2606 (45.3)

Abbreviations: ATE, arterial thrombotic event; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; MI, myocardial infarction; Q1, Q3, interquartile range; TNM, tumor, nodes, and metastases; VKA, vitamin K antagonist; VTE, venous thrombotic event.

[a]Severe medical condition is defined as "a diagnosis that carries an increased risk of mortality, hospitalization and emergency room visits"[34] and was identified using ICD-10 codes of diagnosis registered as either the main or primary diagnosis of the hospital admission.

[b]All treatment indications for VKA treatment have been registered until the date of data export and were identified from the Dutch anticoagulation clinics. One or more indications can be present.

[c]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.

Outcomes

Anticoagulation control was assessed by several metrics, including the percentage of INRs within the target range, percentage of significant dose adjustments, INR variance growth rate (VGR) of Cannegieter,[8] and time spent in, above, and below target range (TTR, TAR, and TBR).[36] A significant dose adjustment was defined as a change of ≥10% in the average daily VKA dose prescribed at two consecutive INR measurements. The VGR reflects the variability between consecutive INR measurements. In this metric, a patient is most stable when the INR remains around the same value, even if the INRs are consistently outside the target range.[8] TTR, TAR, and TBR were calculated according to the Rosendaal method, which predicts daily INR values between two consecutive INR measurements through linear interpolation.[36] TTR was calculated by dividing the number of days with interpolated INR values within the target range by the total number of days observed. TAR and TBR were calculated similarly, representing the proportion of days with INR values above and below the target range, respectively.

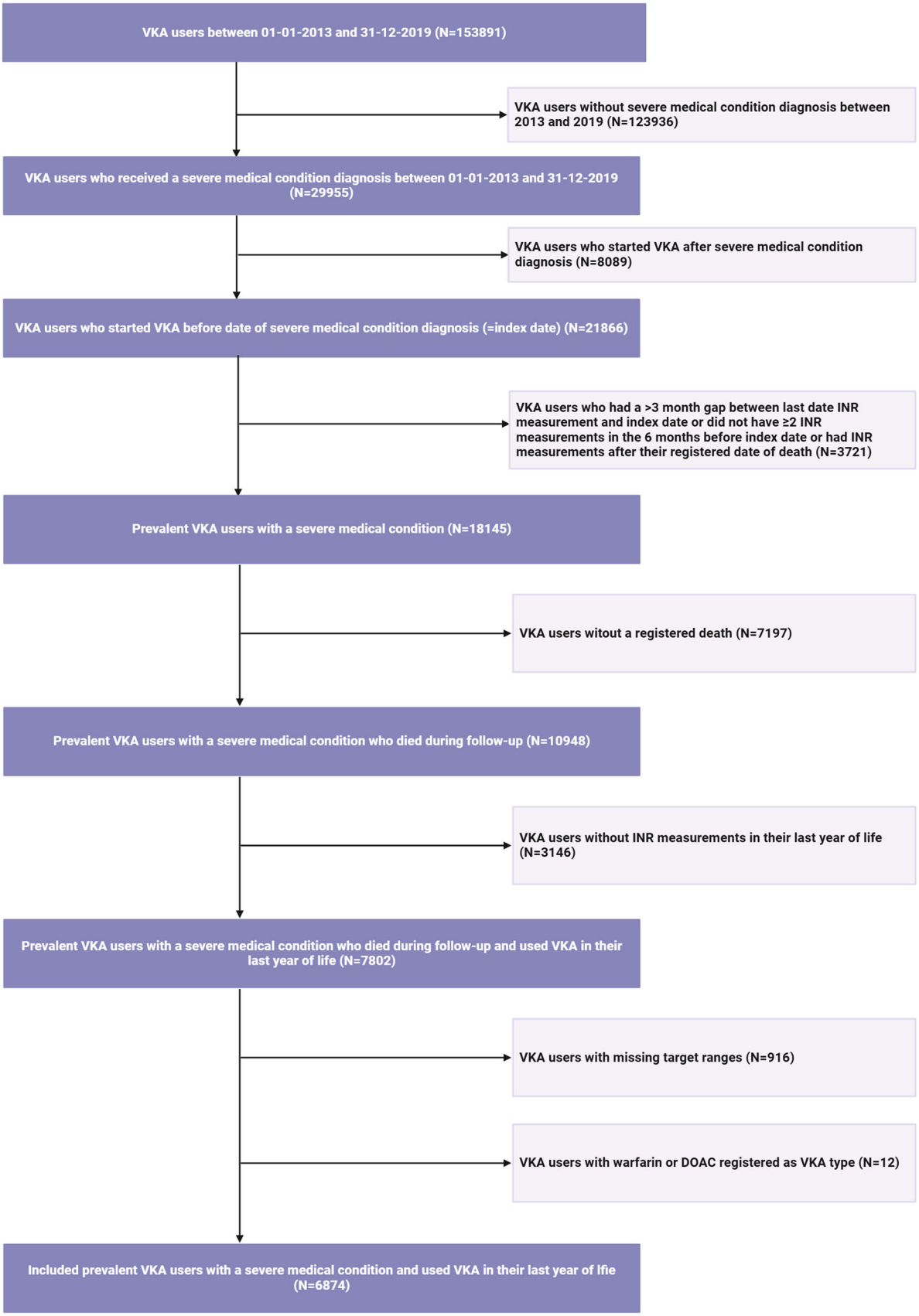

FIGURE 1 **Flowchart of the selection of our study cohort**. A severe medical condition is defined as "a diagnosis that carries an increased risk of mortality, hospitalization and emergency room visits."[34] DOAC, direct oral anticoagulant; INR, international normalized ratio; VKA, vitamin K antagonists. Created in BioRender. Kruip, M. (2025), https://BioRender.com/a20d177.

Statistical analyses

Continuous data were presented as mean with standard deviation (SD) or median with interquartile range (IQR), where appropriate. Categorical variables were presented as numbers and percentages, with categories containing fewer than 10 individuals masked in accordance with CBS privacy policy. The metrics of anticoagulation control were expressed as means with 95% confidence intervals (95% CI) or as percentages with 95% CI calculated using the Clopper–Pearson method.

Anticoagulation control was examined using two complementary approaches. First, we described the anticoagulation control during four specific time intervals preceding death: 0–12 months, 0–9 months, 0–6 months, and 0–3 months, as previously described by van Leeuwen et al.[8] (Figure S1). This analysis included patients who continued VKA treatment and had at least two INR measurements within the respective interval.

Second, we examined changes in anticoagulation control over time (Figure S2). Patients were stratified into subcohorts based on the time between their severe medical condition diagnosis and death: 365 days or more, 180–364 days, and 90–179 days. For each subcohort, the metrics were calculated for each 3-month period preceding death (i.e., 9–12 months, 6–9 months, 3–6 months, and 0–3 months). Patients were included if they had at least two INR measurements within the respective 3-month period.

All analyses were stratified by cancer versus non-cancer severe medical conditions (based on the first severe medical condition) and by the type of VKA first registered during the last year of life. Statistical analyses were performed using IBM SPSS Statistics (v.25) and R studio software (v.4.4.0)[37,38] with the packages stats,[38] dplyr,[39] lubridate,[40] stringr,[41] purrr,[42] table1,[43] tidyr,[44] foreign,[45] haven,[46] and xlsx.[47]

Sensitivity analyses

We performed three sensitivity analyses. First, we excluded patients who died from non-natural causes (i.e., slip and fall, traffic collision, or accidental poisoning), identified by data on the cause of death. Second, we excluded patients who switched between VKA types (i.e., from acenocoumarol to phenprocoumon or vice versa) during their last year of life. Finally, periods of hospitalization were excluded from the calculation of the various anticoagulation control metrics to assess the effect of not observing INR measurements during hospitalization, which could potentially introduce time-related bias.

RESULTS

Participants and baseline characteristics

Of the identified cohort of 18,145 prevalent VKA users with a severe medical condition, 10,948 (60.3%) patients died during study follow-up. Of these 10,948 patients, 7802 (71.3%) had >1 INR measurement during their last phase of life. After applying the additional eligibility criteria, our final cohort included 6874 patients (Figure 1). The median age at diagnosis was 82.0 years (IQR: 76.0–87.0), with 46.9% being female. Acenocoumarol was the most frequent VKA type, and most patients were treated with an INR target range between 2.0 and 3.0 (Table 1). The most common severe medical condition was heart disease, followed by cancer and hip fracture. Among those with cancer, bronchus and lung cancers were the most prevalent cancer types, followed by pancreatic and colorectal cancers (Table S7).

Quality of anticoagulation control in the last year of life

Anticoagulation control was generally poor across the four time intervals, with poorer anticoagulation control observed in the last 3 months of life (Table 2). The median INR values and advised average doses were relatively stable, while the INR variability was highest in the final 3 months. The mean TTR ranged from 53.6 (95% CI: 52.9–54.3) in the year before death to 44.8 (95% CI: 43.9–45.7) during the last 3 months (Figure 2). The TBR was relatively consistent across the intervals, while the TAR ranged from 23.1 (22.6–23.7) during the entire year before death, to 33.2 (95% CI: 32.3–34.1) in the final 3 months.

Temporal changes in the quality of anticoagulation control in the last year of life

Anticoagulation control progressively declined as patients approached their end of life (Figure 3 and Tables 3 and 4). Among patients surviving ≥365 days following their severe medical condition diagnosis ($n = 3597$), the TTR remained relatively stable from 12 to

TABLE 2 Quality of anticoagulation control in the last year of life.

Anticoagulation control metric	0–12 months before death ($n = 2326$)	0–9 months before death ($n = 2732$)	0–6 months before death ($n = 3156$)	0–3 months before death ($n = 3698$)
Median INR values [Q1, Q3]	2.6 [2.0, 3.3]	2.6 [2.0, 3.4]	2.6 [2.0, 3.5]	2.7 [2.1, 3.7]
Mean percentage INRs in range (95% CI)	47.7 (47.1–48.4)	46.6 (46.0–47.3)	45.1 (44.5–45.8)	43.3 (42.5–44.1)
Median advised average dose [Q1, Q3][a]	1.1 [0.6, 1.7]	1.1 [0.6, 1.7]	1.1 [0.6, 1.6]	1.0 [0.6, 1.6]
Mean time in therapeutic range (95% CI)[b]	53.6 (52.9–54.3)	51.9 (51.2–52.6)	49.3 (48.6–50.1)	44.8 (43.9–45.7)
Mean time above therapeutic range (95% CI)[b]	23.1 (22.6-23.7)	25.0 (24.5–25.6)	27.7 (27.1–28.4)	33.2 (32.3–34.1)
Mean time below therapeutic range (95% CI)[b]	23.3 (22.6-23.9)	23.1 (22.4–23.7)	22.9 (22.2–23.6)	22.0 (21.2–22.8)
Mean VGR (95% CI)[c]	3.2 (3.0-3.4)	3.6 (3.4–3.8)	4.1 (3.8–4.3)	5.0 (4.7–5.3)

Abbreviations: CI, confidence interval; INR, international normalized ratio; Q1, first quartile; Q3, third quartile; VGR, variance growth rate; VKA, vitamin K antagonist.

[a]Advised average dose is expressed as the number of tablets, where one tablet acenocoumarol contains 1 mg and one tablet phenprocoumon 3 mg.

[b]Calculated using the Rosendaal method.

[c]Variance growth rate is calculated using the Cannegieter method. Stability is assumed when the INRs are around the same value every time, even if they are consistently outside the target range.

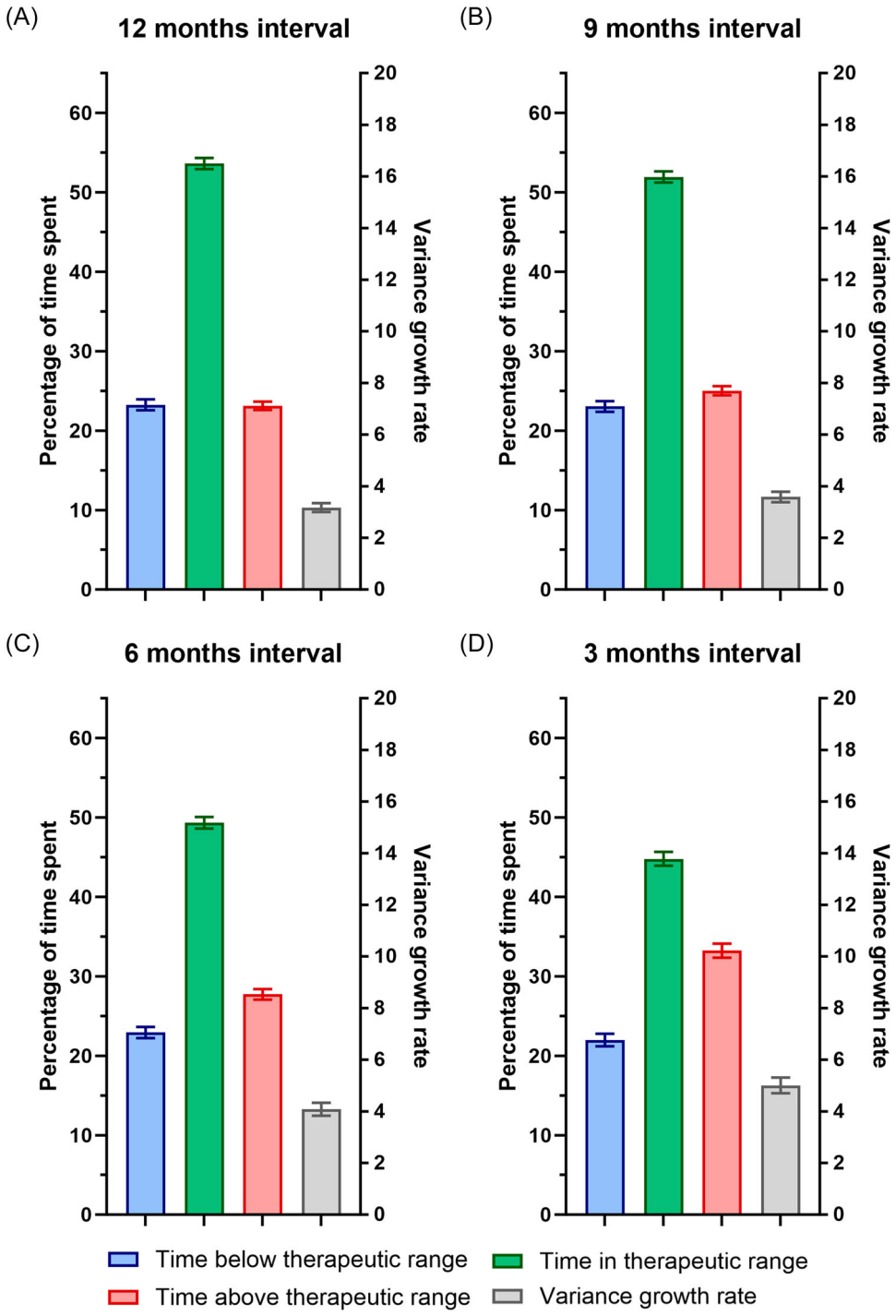

FIGURE 2 **Anticoagulation control in the last year of life.** Bar charts with 95% confidence intervals of the mean time below therapeutic range, time in therapeutic range, and time above therapeutic range, along with the mean variability of INR measurements expressed as the variance growth rate, calculated across four distinct intervals leading up to death: 0–12 months **(A)**, 0–9 months **(B)**, 0–6 months **(C)**, and 0–3 months **(D)** before death.

3 months, until dropping in the final 3 months. The TAR showed a pronounced increase, especially in the last 3 months, while the TBR slightly decreased. Additionally, more than one-third of VKA users required at least one significant dose adjustment, and the variability of the INR increased from 1.7 to 5.1 in the last 3 months.

Among patients surviving 180–364 days ($n = 1256$), a similar trend was observed, but overall anticoagulation control was poorer compared with those with longer survival times (Table 4). The mean TTR and TBR decreased from 3–6 months to 0–3 months before death, while the TAR increased. Despite relatively constant INR monitoring frequency over time, the INR variability rose, increasing from 3.3 to 5.2.

Patients surviving only 90–179 days ($n = 810$) exhibited the poorest anticoagulation control during the last 3 months of life (Table S8). Nearly half required significant dose adjustments, and INR was measured almost weekly. Despite this frequent monitoring, the target range was achieved for only one-third of the time.

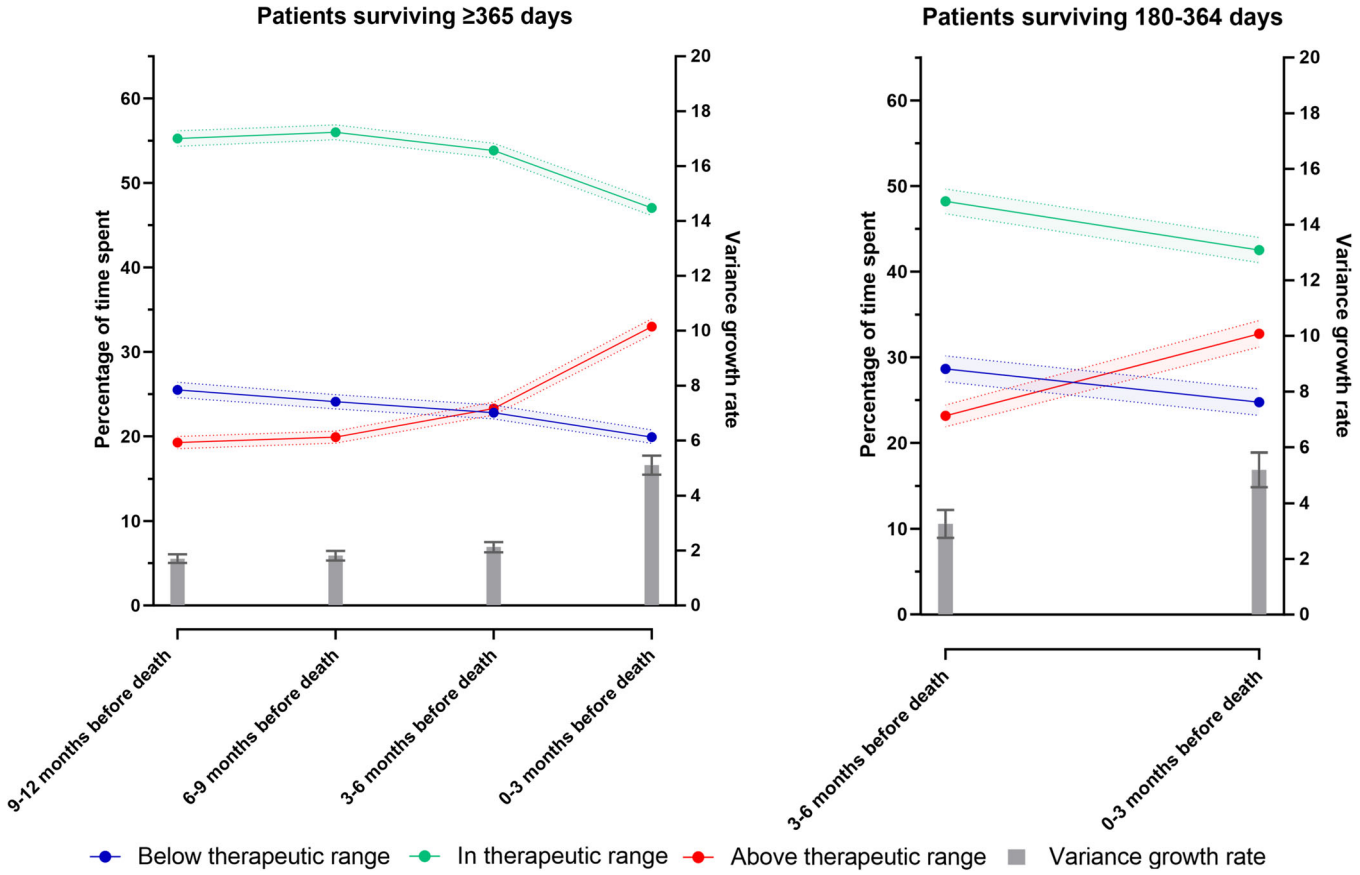

FIGURE 3 **Anticoagulation control in two subcohorts of VKA users stratified based on survival time since severe medical condition diagnosis.** Anticoagulation control is expressed as the percentage of time spent within the therapeutic range (green line), above the therapeutic range (red line), and below the therapeutic range (blue line). The dotted lines represent the 95% confidence intervals for each metric. The variance growth rate is depicted with gray bars, accompanied by 95% confidence intervals.

Cancer and non-cancer patients

Anticoagulation control was generally poorer in patients with cancer compared to those with non-cancer severe medical conditions (Figures S3–S6, and Table S9), with cancer patients experiencing a more pronounced decline in anticoagulation control (Figure 4 and Tables S8, S10, and S11). In patients surviving ≥365 days following cancer diagnosis, the mean TTR began to decline earlier, starting at 6 months before death, whereas non-cancer patients maintained more stable TTR levels until the final 3 months of life, when a significant decline occurred (Figure 4 and Table S10). The frequency of INR measurements increased for both groups, with a larger increase observed in cancer patients. These trends were consistent across subcohorts with patients surviving 180–364 and 90–179 days after diagnosis, with cancer patients consistently exhibiting poorer anticoagulation control compared to non-cancer patients (Figure 4 and Tables S8 and S11).

Acenocoumarol and phenprocoumon users

Anticoagulation control was overall better in phenprocoumon users compared to acenocoumarol users, as reflected by higher TTR and lower VGR (Table S12). As end of life approached, both groups experienced a decline in anticoagulation control, although phenprocoumon users consistently maintained better anticoagulation control (Figure S7 and Tables S13–S14). Among patients surviving ≥365 days after diagnosis, phenprocoumon users showed a more gradual decline in TTR, while acenocoumarol users experienced a sharper drop. These trends were also observed in patients surviving 180–364 days and 90–179 days after diagnosis, with phenprocoumon users consistently showing higher mean TTR values and less INR fluctuation compared to acenocoumarol users.

Sensitivity analyses

The results of the sensitivity analyses excluding patients dying from non-natural causes ($n = 377$) and those who switched VKA type during their last year of life ($n = 53$) closely mirrored those of the main analysis (Tables S15–S21). Metrics from the sensitivity analysis that accounted for hospital admissions were slightly lower compared with the main analysis (Tables S18 and S22–S24). However, the overall trend observed in this sensitivity analysis remained consistent with the main analysis.

DISCUSSION

This study evaluated anticoagulation control during the last year of life in a large cohort of VKA users with limited life expectancy. We consistently observed a decline in anticoagulation control as patients approached their end of life, characterized by a reduced TTR due to

TABLE 3 Quality of anticoagulation control in vitamin K antagonists (VKA) users surviving ≥365 days following severe medical condition diagnosis.

Anticoagulation control metric	9-12 months before death (*n* = 3544)	6-9 months before death (*n* = 3479)	3-6 months before death (*n* = 3404)	0-3 months before death (*n* = 3272)
Median INR values [Q1, Q3]	2.5 [2.0, 3.2]	2.5 [2.0, 3.2]	2.5 [2.0, 3.3]	2.7 [2.1, 3.7]
Mean number of INR measurements (95% CI)	6.4 (6.2–6.5)	6.3 (6.2–6.4)	6.6 (6.5–6.7)	7.0 (6.7–7.2)
Mean percentage INRs in range (95% CI)	52.9 (52.0–53.8)	52.7 (51.8–53.7)	50.8 (49.9–51.7)	44.0 (43.1–44.9)
Median advised average dose [Q1, Q3][a]	1.2 [0.7, 1.8]	1.2 [0.7, 1.8]	1.1 [0.7, 1.7]	1.0 [0.6, 1.6]
Number VKA users with >1 significant dose adjustment (% [95% CI])[b]	643 (18.1% [16.9%–19.5%])	615 (17.7% [16.4%–19.0%])	762 (22.4% [21.0%-23.8%])	1244 (38.0% [36.4%–39.7%])
Mean time in therapeutic range (95% CI)[c]	55.3 (54.4–56.2)	56.0 (55.1–56.9)	53.8 (53.0–54.7)	47.1 (46.1–48.0)
Mean time above therapeutic range (95% CI)[c]	19.3 (18.5–20.0)	19.9 (19.2–20.6)	23.3 (22.5–24.1)	33.0 (32.1–33.9)
Mean time below therapeutic range (95% CI)[c]	25.5 (24.6–26.4)	24.1 (23.2–24.9)	22.9 (22.1–23.7)	20.0 (19.2–20.8)
Mean VGR (95% CI)[d]	1.7 (1.6–1.9)	1.8 (1.6–2.0)	2.1 (1.9–2.3)	5.1 (4.8–5.5)

Abbreviations: CI, confidence interval; INR, international normalized ratio; Q1, first quartile; Q3, third quartile; VGR, variance growth rate; VKA, vitamin K antagonist.

[a]Advised average dose is expressed as the number of tablets, where one tablet acenocoumarol contains 1 mg and one tablet phenprocoumon 3 mg.

[b]Significant dose adjustment is defined as a change of more than 10% between consecutive VKA doses.

[c]Calculated using the Rosendaal method.

[d]Variance growth rate is calculated using the Cannegieter method. Stability is assumed when the INRs are around the same value every time, even if they are consistently outside the target range.

TABLE 4 Quality of anticoagulation control in vitamin K antagonists (VKA) users surviving 180–364 days following severe medical condition diagnosis.

Anticoagulation control metric	3–6 months before death (*n* = 1157)	0–3 months before death (*n* = 1088)
Median INR values [Q1, Q3]	2.5 [2.0, 3.3]	2.7 [2.0, 3.8]
Mean number of INR measurements (95% CI)	7.4 (7.3–7.6)	7.5 (7.3–7.7)
Mean percentage INRs in range (95% CI)	45.0 (43.5–46.5)	39.9 (38.4–41.3)
Median advised average dose [Q1, Q3][a]	1.2 [0.6, 1.8]	1.1 [0.6, 1.6]
Number VKA users with >1 significant dose adjustment (% [95% CI])[b]	334 (28.9% [26.3%–31.6%])	447 (41.1% [38.1%–44.1%])
Mean time in therapeutic range (95% CI)[c]	48.2 (46.8–49.7)	42.5 (41.0–44.0)
Mean time above therapeutic range (95% CI)[c]	23.2 (21.9–24.4)	32.7 (31.2–34.3)
Mean time below therapeutic range (95% CI)[c]	28.6 (27.1–30.2)	24.8 (23.2–26.3)
Mean VGR (95% CI)[d]	3.3 (2.8–3.8)	5.2 (4.6–5.8)

Abbreviations: CI, confidence interval; INR, international normalized ratio; Q1, first quartile; Q3, third quartile; VGR, variance growth rate; VKA, vitamin K antagonist.

[a]Advised average dose is expressed as the number of tablets, where one tablet acenocoumarol contains 1 mg and one tablet phenprocoumon 3 mg.

[b]Significant dose adjustment is defined as a change of more than 10% between consecutive VKA doses.

[c]Calculated using the Rosendaal method.

[d]Variance growth rate is calculated using the Cannegieter method. Stability is assumed when the INRs are around the same value every time, even if they are consistently outside the target range.

an increased time spent above therapeutic range, more frequent significant dose adjustments, and higher INR variability. Notably, anticoagulation control was particularly poor in the final 3 months of life, with a more pronounced decline observed in cancer patients compared with non-cancer patients, and in acenocoumarol users compared to phenprocoumon users.

The quality of anticoagulation control observed in patients nearing the end of life was notably lower than that described in the general Dutch population of VKA users, where the TTR typically exceeds 70%.[35,48–52] Additionally, the values observed in our study were below the quality standards set by the Federation of Dutch Anticoagulation Clinics during the years of inclusion.[35,48–52] This observation aligns with previous research on VKA therapy in an end-of-life setting.[30,53] For instance, a study comparing warfarin users receiving hospice or palliative care (HPC) showed that, while HPC patients were monitored more frequently than non-HPC warfarin users, they had a higher proportion of INRs outside the therapeutic range, mainly due to INRs above range.[30]

The suboptimal anticoagulation control observed in our cohort raises concerns about elevated bleeding risks in patients nearing the end of life. Low TTR, particularly an increase in time above the therapeutic range, is dose-dependently associated with higher bleeding rates.[54–56] For instance, the estimated bleeding rate per 100 patient-years is 2.7 (95% CI: 1.0–7.3) when the INR is between 4.0 and 4.5, and 9.4 (95% CI: 5.2–16.9) when the INR exceeds 4.5.[55] Given these risks, clinicians may need to consider reassessing VKA therapy in patients with limited life expectancy, particularly in cancer patients and acenocoumarol users.

Switching from acenocoumarol to phenprocoumon, might address some of these challenges, as phenprocoumon may improve

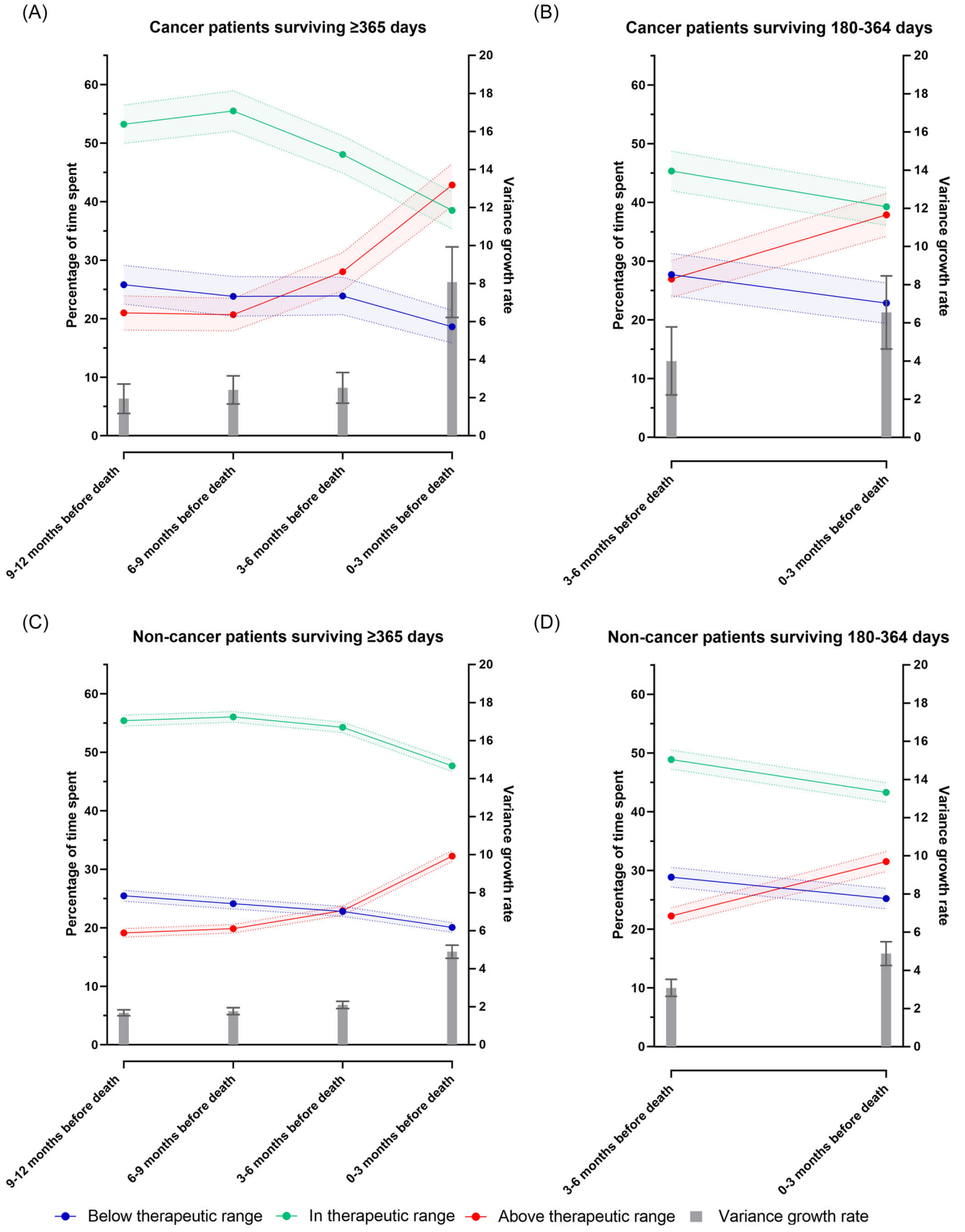

FIGURE 4 **Anticoagulation quality in two subcohorts of VKA users stratified based on survival time since severe medical condition diagnosis and type of severe medical condition.** Anticoagulation quality is expressed as the percentage of time spent within the therapeutic range (green line), above the therapeutic range (red line), and below the therapeutic range (blue line). The dotted lines represent the 95% confidence intervals for each metric. The variance growth rate is depicted with gray bars, accompanied by 95% confidence intervals. Anticoagulation quality is displayed in patients with cancer surviving ≥365 days **(A)** and 180–364 days **(B)** following cancer diagnosis and in patients with non-cancer severe medical conditions surviving ≥365 days **(C)** and 180–364 days **(D)** following severe medical condition diagnosis.

INR stability due to its longer half-life.[57–61] However, switching near the end of life could cause INR instability during the transition period and complicate the management of elevated INRs due to phenprocoumon's slower dose adjustment effect.[57] Finally, as this study is descriptive, we cannot establish causal comparisons between acenocoumarol and phenprocoumon users. The observed differences may not only be due to the VKA type itself but also to variations in patient characteristics, center-specific treatment approaches, or other unmeasured factors. Therefore, while chronic use of phenprocoumon shows potential advantages, further investigation is needed before recommending a switch from VKA type in this setting.

Similarly, DOACs are not necessarily a better alternative in this setting, as factors such as impaired organ function, altered drug metabolism, and interactions with concurrent medications affect both VKAs and DOACs. Additionally, switching frail, long-term VKA users to DOACs has been associated with increased bleeding risks.[2] Thus, neither phenprocoumon nor DOACs fully address the complex anticoagulation needs of patients nearing the end of life, highlighting the need to optimize treatment strategies for this population. In this regard, the SERENITY consortium is committed to providing the necessary evidence and developing a patient-centered framework and decision support tool to optimize antithrombotic therapy in advanced cancer patients facing the end of their lives.[62]

The key strength of our study is the use of nationwide, routinely collected health data linked to anticoagulation clinic data. This approach enabled us to study anticoagulation control in a large, diverse cohort of VKA users with limited life expectancy, encompassing a broad spectrum of life-limiting diseases and including both phenprocoumon and acenocoumarol users.

However, some limitations should be considered. First, as our aim was to describe the 12 months before death, we had to select patients based on a future event (i.e., death) and retrospectively analyze the period leading up to death. This approach hindered time-to-event analyses and made it impossible to assess the impact of poor anticoagulation control on thromboembolic and bleeding complications due to inherent selection bias. This method also inadvertently included patients with non-natural or acute deaths, although sensitivity analyses excluding these cases yielded comparable results. Additionally, because patients were selected based on death, our findings describe anticoagulation control in the last year of life but do not imply that these patients could have been prospectively identified as being in their final phase of life. This inherent uncertainty should be considered when interpreting our results.

Second, the use of routinely collected healthcare data introduces potential misclassification and measurement errors. For example, INR values were not recorded during hospital stays, in hospices or nursing homes managing VKAs themselves, or when care was transferred to non-participating anticoagulation clinics. However, sensitivity analyses excluding periods of hospital admission showed consistent results, suggesting this limitation had minimal impact.

Third, anticoagulation clinic data were only available until 2020, which may have affected the generalizability of our findings to current VKA users. While the increased use of DOACs in recent years may have altered the patient profile of VKA users, the major shift toward DOACs occurred between 2013 and 2019 and was captured by our study period.[63,64] Therefore, despite changes in the anticoagulation landscape, we believe our findings remain applicable to contemporary VKA-treated patients.

Finally, increased INR monitoring near the end of life may have contributed to increased INR variability, particularly in patients with prior bleeding complications, who are monitored more frequently. However, in our study, the overall increase in INR monitoring was minimal and unlikely to have significantly influenced our findings.

In conclusion, our study provides evidence about the challenges of managing VKA therapy in patients with limited life expectancy, showing a gradual decline in anticoagulation control during the last 12 months of life, particularly in the final 3 months. This decline was more pronounced in cancer patients and acenocoumarol users. These findings suggest that clinicians may need to carefully assess and re-assess the risks and benefits of continuing VKA therapy as patients approach the end of life and consider deprescribing when appropriate. If VKA is continued, close monitoring of the INR can be warranted.

ACKNOWLEDGMENTS

The authors thank the Federation of Dutch Anticoagulation Clinics, the Netherlands Comprehensive Cancer Organization, and Statistics Netherlands for making the data available. The study is part of the research project SERENITY—"Towards Cancer Patient Empowerment for Optimal Use of Antithrombotic Therapy at the End of Life" (https://serenity-research.eu/).

Views and opinions expressed are, however, those of the author(s) 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 can be held responsible for them.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology: Chantal Visser, Eva K. Kempers, Jamilla Goedgebuur, Qingui Chen, Suzanne C. Cannegieter, Eric C. T. Geijteman, and Marieke J. H. A. Kruip. Data curation: Chantal Visser, Eva K. Kempers, and Qingui Chen. Formal analysis, investigation, validation, and visualization: Chantal Visser and Eva K. Kempers. Funding acquisition: Simon I. R. Noble, Frederikus A. Klok, Suzanne C. Cannegieter, Eric C. T. Geijteman, and Marieke J. H. A. Kruip. Writing—original draft preparation: Chantal Visser. Writing—review and editing: All authors.

CONFLICT OF INTEREST STATEMENT

C. V. has received travel support from the International Society on Thrombosis and Haemostasis (ISTH) for attending the ISTH Congress in 2024. I. M. has received research support from BMS and Pfizer, and has received speaker fees from LEO Pharma, BMS, Pfizer, and AstraZeneca, paid to her institution. S. S. has received speaker fees from Bayer, BMS, and Pfizer. S. I. R. N. has received a payment for a lecture at LEO Pharma and is a Medical Director of Thrombosis UK (non-remunerated charity work). F. A. K. has received research support from Bayer, BMS, BSCI, AstraZeneca, MSD, LEO Pharma, Actelion, Farm-X, The Netherlands Organization 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. C. 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 has received travel support from the ISTH for attending the ISTH Congress between 2022 and 2024. 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 article.

DATA AVAILABILITY STATEMENT

This study used non-public microdata from Statistics Netherlands, Federation of Dutch Anticoagulation Clinics, and the Netherlands

Cancer Registry from the Netherlands Comprehensive Cancer Organization. The authors cannot directly share these data. Under certain conditions, these data are accessible for statistical and scientific research. For additional information, please contact microdata@cbs.nl, fnt@fnt.nl, and/or gegevensaanvraag@iknl.nl.

ETHICS STATEMENT

This study received ethical approval from the Scientific Committee of the Department of Clinical Epidemiology of the Leiden University Medical Centre (#A0178). A waiver of participant consent was granted due to the use of the pre-existing and de-identified data. This study was performed on behalf of the SERENITY consortium.

FUNDING

This project has received funding from the European Union's Horizon Europe Research and Innovation Action under grant agreement no. 101057292. Additionally, UK Research and Innovation (UKRI) has provided funding under the UK government's Horizon Europe funding guarantee (grant agreement no. 10039823 for Cardiff University and 10038000 for Hull York Medical School).

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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