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ORIGINAL ARTICLE

Use of antithrombotic therapy and the risk of cardiovascular outcomes and bleeding in cancer patients at the end of life: a Danish nationwide cohort study

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Abstract

Background: Despite uncertain benefit-risk profile near the end of life, antithrombotic therapy (ATT) is prevalent in patients with terminal cancer.

Objectives: To examine adherence and persistence with ATT in terminally ill cancer patients and investigate risks of major and clinically relevant bleeding, venous thromboembolism (VTE), and arterial thromboembolism (ATE) by ATT exposure.

Methods: Using a Danish nationwide cohort of terminal cancer patients, ATT adherence in the year following terminal illness declaration was measured by the proportion of days covered (PDC) by prescription. Discontinuation was defined as a treatment gap of ≥30

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days between prescription renewals. One-year cumulative incidences of bleeding complications, VTE, and ATE were calculated, considering the competing risk of death.

Results: During 2013-2022, 86 732 terminally ill cancer patients were identified (median age, 75 years; 47% female; median survival, 57 days). At terminal illness declaration, 37.5% were receiving ATT (66.6% platelet inhibitors, 23.0% direct oral anticoagulants, and 10.4% vitamin K antagonists [VKAs]). The mean PDC with ATT was 88% (SD, 30%), highest among platelet inhibitor users (mean PDC, 89%) and lowest among VKA users (73%). One-year ATT discontinuation incidence was 7.9% (95% CI, 7.7%-8.1%). Most patients continued ATT until death (74.8% platelet inhibitors, 58.8% direct oral anticoagulants, and 61.6% VKAs). Patients receiving ATT had a lower 1-year VTE risk but higher risks of ATE and major bleeding.

Conclusion: Despite uncertain benefit-risk profile, most terminally ill cancer patients continue ATT until the end of life. These findings provide insights into current ATT utilization and discontinuation dynamics in the challenging context of terminal illness.

KEYWORDS
anticoagulants, deprescription, neoplasms, palliative care, platelet aggregation inhibitors

1 | INTRODUCTION

Cancer remains a leading cause of death, accounting for approximately 10 million or nearly 1 in 6 deaths worldwide in 2020 [1]. As individuals approach their end of life, many medications, including antithrombotic therapy (ATT), are of questionable benefit [2–4]. Accordingly, advance care planning, which should become the standard of care in Europe, emphasizes the optimization of pharmacotherapy, with a focus on discontinuing medicines that are no longer useful and/or where potential harms outweigh existing benefits [5–7].

Approximately 5% to 15% of cancer patients receive anticoagulants at the end of life, most commonly for treatment of venous thromboembolism (VTE), stroke prevention due to atrial fibrillation (AF), or mechanical heart valves. A further 25% to 35% receive antiplatelet therapy for prevention of other arterial thromboembolic (ATE) complications [4,8]. Most clinical cancer guidelines contain clear recommendations regarding the initiation of ATT and the proposed length of time they should be taken. However, for most indications requiring "lifelong" ATT, there is little guidance on its management when approaching the end of life, and the risk of bleeding increases considerably [9–12].

The decision to discontinue ATT requires careful consideration of potential benefits and risks, incorporating the patient's clinical status, prognosis, preferences, and care goals. The paucity of data around the changing balance of risk and benefit from ATT near the end of life may pose a barrier to decision-making with respect to the appropriateness of ongoing ATT use. This is most acutely evident in the data that inform clinical guidelines where patients of poor prognosis (less than 3-6 months) were excluded from recruitment in the randomized trials. As such, healthcare professionals might overestimate the benefits and safety profile of ATT in advanced cancer patients, leading to potentially inappropriate treatment strategies [13]. Studies have shown that a majority of cancer patients continue their ATT throughout their final months of life [8,14–16], resulting in increased bleeding complications and reduced quality of life [17,18].

A large international collaboration, titled SERENITY (Towards cancer patient empowerment for optimal use of antithrombotic therapy at the end of life), is currently developing and evaluating a decision support tool for clinicians and patients to improve ATT optimization near the end of life [19]. The overarching aims and methodology of this program of work have already been described [19]. This includes a review of practice-based data from established databases to better inform the content and optimal use of the planned decision support tool. We therefore report the results of a nationwide cohort study to describe adherence to and persistence with ATT in the Danish population of cancer patients in their last phase of life and associated risks of major and clinically relevant bleeding, VTE, and ATE events according to ATT exposure.

2 | MATERIALS AND METHODS

A nationwide population-based cohort study based on registry data was conducted, including all cancer patients in Denmark who were declared terminally ill between January 1, 2013, and December 31, 2022. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies [20].

2.1 | Setting and data sources

All Danish residents have access to tax-supported healthcare provided by the Danish National Health Service [21]. Comprehensive health

data for the entire Danish population of approximately 5.8 million inhabitants are registered in Danish nationwide registries. Data can be linked across these registries using the unique civil registration number assigned to all Danish residents at birth or upon immigration. For this study, we identified all patients diagnosed with primary cancer through the Danish Cancer Registry [22]. This registry has tracked all primary cancer diagnoses in Denmark since 1987, including information on stage and morphology at diagnosis. The reporting of new primary cancers is mandatory in Denmark, ensuring high coverage. We linked records in the Danish Cancer Registry with the Danish National Patient Register, which includes information on all admissions and discharges from nonpsychiatric hospitals since 1977 and emergency room and outpatient clinic visits since 1995 [23], providing detailed information on primary and secondary diagnoses coded according to the International Classification of Diseases 10th version. Data on ATT were retrieved from the National Prescription Register, which includes information regarding purchase date, Anatomical Therapeutic Chemical classification code, and package size for every prescription filled since 1994 [24]. This database also contains information on patients who are declared terminally ill by a physician (expected remaining lifetime <6 months), which entitles patients to full reimbursement of all prescription drug expenses, expenses for equipment used in-home care, and payment to informal caregivers [25]. Information on biological sex, date of birth, vital status, and migration status was retrieved from the Danish Civil Registration System [26]. Codes are provided in Supplementary Table S1.

2.2 | Ethical considerations and data availability

The study was based on data provided by the Danish Health Data Authority. According to Danish law, registry-based research does not require ethical approval or informed consent but only permission from the Danish Data Protection Board. This study was approved by the Danish Protection Agency through institutional registration (record number 2017-509-00006). Data sharing is not possible according to Danish laws. Danish researchers can file applications for data access to the Danish Health Data Authority.

2.3 | Study population

This study included all adult (>18 years) patients recorded in the Danish Cancer Registry with a solid tumor (except nonmelanoma skin cancer) who were formally registered with drug reimbursement due to terminal illness (DRTI) between 2013 and 2022 (ie, life expectancy <6 months) in the Danish National Prescription Registry. The index date was defined as the date of the first prescription received with DRTI. Patients with invalid information in the registers (ie, missing civil registration numbers), those who immigrated within 1 year before the index date, or those who emigrated and had not returned before the index date were excluded from the study population. The cancer type was classified according to the latest recorded primary diagnosis in the Danish Cancer Registry before the index date and grouped as primary lung cancer (including lung, pleura, and trachea), cancers of the male genital organs (including prostate, penile, etc.), female genital organs (uterus, ovaries, cervix, etc., including breast), gastrointestinal cancer, renal and urinary cancers, and other primary or unknown primary cancer type. Supplementary Table S1 displays the specification of cancer groups.

From the Danish National Patient Registry, we collected information on comorbidities included in the Charlson Comorbidity Index Score (except cancer diagnoses) diagnosed within 3 years before index (Supplementary Table S2). Based on registered diagnoses within 3 years before the index date, indications for ATT were defined as AF, cardiac valvular disease, VTE, stroke, and peripheral artery disease, allowing patients to have overlapping indications.

2.4 | ATT exposure

We extracted information on reimbursed prescription claims for ATT, including direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs), and platelet inhibitors. Treatment periods with ATT were estimated from information on drug package size, prescription frequency, and the defined daily dose. The end of a treatment period was defined as the last dispensed prescription date plus the number of dosages available since that dispensing. If the end of a treatment period exceeded the start of the next period, these periods were joined into 1 treatment period, taking into account the carry-over of tablets from previously dispensed prescriptions of the same drug class. A gap period of up to 30 days between purchases was allowed when defining joined treatment periods [27]. Patients were categorized as exposed if they had an ongoing ATT treatment period at the index date. Switching within drug classes was allowed when defining treatment periods (eg, from rivaroxaban to edoxaban in the DOAC group). Conversely, patients were categorized as unexposed to ATT if they had no treatment period overlapping the index date.

Warfarin is only available in 2.5 mg dose tablets in Denmark. Exposure to warfarin was defined as an individual variable dose based on the frequency and packet size of each claim. All individuals were assumed to initially receive 1 tablet (2.5 mg) per day, and this number was updated accordingly after each prescription claim. DOAC was included with the following dosages: dabigatran 110 mg and 150 mg twice a day, apixaban 2.5 mg and 5 mg twice a day, edoxaban 30 mg and 60 mg once daily (od), and rivaroxaban 15 mg and 20 mg od. Platelet inhibitors included aspirin od, clopidogrel od, ticagrelor twice a day, and prasugrel od.

2.5 | Outcomes

Outcomes included adherence to and discontinuation of ATT in the year following the index date of DRTI and the associated risk of major and clinically relevant bleeding, VTE, ATE, and all-cause death.

2.5.1 | Adherence to ATT

Adherence (ie, taking medications as prescribed [28]) to ATT was defined as the proportion of days covered (PDC), defining adherent patients as those with a PDC > 80%. We calculated the PDC for each individual patient as the ratio between the number of days treated with the respective drug following the index date and the total number of days following the index date. The calculation of PDC accounted for the package size of each prescription claim, assuming an intake according to the package label. Among ATT exposed at index, we estimated the PDC overall for the use of any ATT as well as for DOAC, VKA, and platelet inhibitor use, accommodating patients switching between medications within each treatment stratum. For patients who died within 1 year after the index date, the PDC was calculated until the date of death. Presupply of ATT covering the index date was included in the calculation of the number of tablets available after the index date. For the PDC, gap days were defined as days when ATT would be unavailable according to prescription claims and calculated tablets available.

2.5.2 | Discontinuation of ATT

Persistence (ie, continuation without interruption or discontinuation [29]) with ATT was defined as the duration of time exposed to ATT in the year following the index date until treatment discontinuation or death. Discontinuation of ATT was defined as the estimated end of a treatment period with no new treatment period within the next 30 days. To calculate the length of the period covered by medication, all tablets carried over from early prescription claims were considered.

2.5.3 | Bleeding and cardiovascular outcomes

Finally, we investigated the occurrence of major and clinically relevant bleeding, VTE, ATE, myocardial infarction, stroke/transient ischemic attack (TIA), and other ATE events identified by primary or secondary hospital inpatient and outpatient clinic diagnoses recorded in the National Patient Registry. ATE was defined as a composite of stroke/TIA, myocardial infarction, and other ATE events. The International Society for Thrombosis and Haemostasis9 has agreed on criteria for the reporting of major bleeds and clinically relevant nonmajor bleeds [30,31]. Since all bleeds recorded were those requiring hospital admission, they met the criteria for clinically relevant nonmajor bleeding as a minimum. We further assessed all-cause death in the year following the index date according to ATT exposure at index. Patients were followed until the earliest event of the clinical outcome of interest, emigration, death, 365 days, or January 31, 2022.

2.6 | Statistical analyses

Patient characteristics were described as medians with IQRs and mean with SD for continuous variables and as proportions for discrete and categorical variables, stratified according to ATT exposure at the index date.

We calculated the PDC with any DOAC, VKA, and platelet inhibitors separately and as the PDC with any ATT in the year following index. The total number of days was defined as the earliest occurrence of death or emigration 365 days after the index date, or January 31, 2022.

Next, among ATT-exposed patients at index, we estimated the crude incidence rate of discontinuation (as a measure of persistence) as events per 100 person-years overall and for each group of ATT (ie, DOAC, VKA, and platelet inhibitors). We further calculated the cumulative incidence of discontinuation using the Aalen–Johansen estimator, assuming death as a competing risk. We similarly calculated the rate and cumulative incidence at 3, 6 months, and 1 year of major and clinically relevant bleeding, VTE, and ATE, stratified by ATT exposure at index, accounting for death as a competing risk. Survival in the year after index was computed by the Kaplan–Meier plot.

To allow for a thorough evaluation of ATT treatment patterns and associated clinical outcomes, stratified analyses were conducted for cancer subtypes and ATT indications.

All analyses were conducted using STATA version 17.0 (StataCorp LLC).

3 | RESULTS

3.1 | Baseline characteristics according to ATT exposure at index

The study population comprised 86 732 patients with solid tumors who were formally declared terminally ill in Denmark from 2013 to 2022. Within this cohort, 62.5% were unexposed to ATT at index, while 37.5% had an ongoing treatment period with ATT at the time of terminal illness declaration. The median age at DRTI was 75 years (IQR, 67-82 years), with the highest median age observed for ATT-exposed patients (78 years vs 72 years among unexposed). Among patients exposed to ATT, 66.6% were treated with platelet inhibitors, 23.0% received DOAC therapy, and 10.4% received VKAs (Table 1). The mean duration from cancer diagnosis to DRTI was 3.4 years (SD, 5.7 years), with a slightly longer duration among patients exposed to ATT at index compared with unexposed (3.8 years vs 3.2 years). The most prevalent cancer types were gastrointestinal cancers (34%) and lung cancers (26%), with no significant variation in cancer type based on ATT exposure. This distribution remained relatively stable over time (Supplementary Table S2). The prevalence of AF, peripheral artery disease, and stroke was notably higher among ATT-exposed patients.

The median time from DRTI to death was 57 days (IQR, 19-151) for ATT unexposed at index and 47 days for exposed patients (IQR, 14-132); median follow-up was 48 days (IQR, 14-135) for platelet inhibitor users, 34 days (IQR, 9-97) for DOAC users, and 52 days (IQR, 16-140) for VKA users.

TABLE 1 Characteristics of 86 732 patients with cancer at the time of first drug reimbursement due to terminal illness in Denmark, according to ongoing antithrombotic therapy usage at index, 2013-2022.

Characteristics	No ATT *n* = 54 210	ATT *n* = 32 522	Overall *N* = 86 732
Inclusion year, % (*n*)			
2013-2015	32.3 (17 507)	27.6 (8977)	30.5 (26 484)
2016-2018	32.5 (17 593)	30.5 (9917)	31.7 (27 510)
2019-2022	35.3 (19 110)	41.9 (13 628)	37.7 (32 738)
Mean years since cancer diagnosis, (SD)	3.2 (5.4)	3.8 (6.2)	3.4 (5.7)
Females	50.5 (27 381)	41.7 (13 558)	47.2 (40 939)
Age (y), median (IQR)	72 (64-80)	78 (72-84)	75 (67-82)
Age groups (y), % (*n*)			
<60	16.7 (9079)	3.5 (1136)	11.8 (10 215)
60-79	57.8 (31 319)	51.2 (16 663)	55.3 (47 982)
≥80	25.5 (13 812)	45.3 (14 723)	32.9 (28 535)
Cancer type[a], grouped % (*n*)			
Airways	24.6 (13 346)	27.8 (9049)	25.8 (22 395)
Female genital organs and breast	13.6 (7385)	11.9 (3859)	13.0 (11 244)
Male genital organs and prostate	8.6 (4650)	12.8 (4177)	10.2 (8827)
Gastrointestinal cancer	35.0 (18 982)	31.7 (10 310)	33.8 (29 929)
Genito-urinary tract	5.5 (2988)	5.9 (1920)	5.7 (4908)
Other	12.7 (6859)	9.9 (3207)	11.6 (10 066)
Charlson Comorbidity Index Score[b]			
0	54.8 (29 723)	19.0 (6194)	41.4 (35 917)
1	25.1 (13 633)	29.7 (9654)	26.8 (23 287)
2	10.9 (5919)	22.1 (7201)	15.1 (13 120)
3+	9.1 (4935)	29.1 (9473)	16.6 (14 408)
Indication for ATT, % (*n*)			
AF	7.8 (4242)	31.6 (10 279)	16.7 (14 521)
Cardiac valvular disease	0.5 (268)	2.8 (924)	1.4 (1192)
VTE	2.8 (1525)	3.6 (1163)	3.1 (2688)
Stroke	4.2 (2288)	24.7 (8022)	11.9 (10 310)
Peripheral artery disease	3.1 (1679)	15.4 (4996)	7.7 (6675)

AF, atrial fibrillation; ATT; antithrombotic therapy; VTE, venous thromboembolism.

[a] Last recorded cancer type in the Danish Cancer Registry before the date of drug reimbursement for terminal illness.

[b] Excluding cancer diagnoses.

3.2 | Adherence to ATT

Table 2 shows the mean 1-year PDC with ATT in ATT users following DRTI. The overall mean PDC following DRTI was 88% (SD, 30%), with 92.5% of patients being classified as adherent to ATT, defined by a PDC > 80%. Stratification by ATT type revealed the highest adherence among users of platelet inhibitors (mean PDC of 89%) and the lowest for VKA users (mean PDC of 73%). However, across all ATT types, >90% of patients were classified as adherent, meeting the threshold of a PDC > 80%. Adherence varied according to cancer type but remained above 90% in all classes. Adherence according to indication for ATT remained high but had a lower PDC ranging from 84.2% (cardiac valvular disease) to 89.2% (VTE; Table 2).

3.3 | Discontinuation of ATT

Following DRTI, the overall 1-year discontinuation rate of any ATT was 24.6 per 100 person-years, with a 1-year cumulative incidence of 7.9% (95% CI, 7.7%-8.1%) among ATT users at index (Table 3, Figure 1). Conversely, only a few ATT nonusers initiated ATT therapy in the year following DRTI, with a cumulative incidence of 4.4% (95% CI, 4.2%-4.6%; Supplementary Figure S1). Stratification by ATT type showed varying rates of discontinuation, with platelet inhibitors exhibiting the highest rate at 15.5 per 100 person-years and a cumulative incidence of 5.2% (95% CI, 5.0%-5.3%; Table 3). Discontinuation also varied by cancer type and indication for ATT, with the highest incidences observed among patients with cancers of the male genital organs and prostate (10.8%) and for AF (17.6%), respectively.

3.4 | ATT at the time of death

At the date of death, a substantial proportion of patients still had an active ATT treatment period. Specifically, the treatment period covered the date of death in 74.8% of patients treated with platelet inhibitors, 58.8% of patients exposed to DOAC, and 61.6% exposed to VKA. Among patients who were untreated at the time of death, the majority had discontinued treatment close to the time of death (Supplementary Figure S2). The mean time from the end of the last treatment period to death was 0.91 months (SD, 5.0) for platelet inhibitors, 0.33 (SD, 2.2) for DOAC, and 2.48 (SD, 7.8) for VKA exposed.

3.5 | Incidence of cardiovascular and bleeding outcomes according to ATT exposure at index

Table 4 displays the number of events, rate per 100 person-years, and the cumulative incidence of cardiovascular and bleeding outcomes according to ATT exposure at the time of DRTI. As shown, the rate

TABLE 2 Mean proportion of days covered with antithrombotic therapy in the year following first drug reimbursement for terminal illness in cancer patients in Denmark, 2013-2022.

Proportion of days covered, mean % (SD)	PDC % (SD)	Adherent PDC %	Nonadherent PDC %
Use of any ATT	88 (30)	92.5	7.5
ATT group			
DOAC	83 (30)	96.9	3.1
VKA	73 (30)	98.2	1.8
Platelet inhibitor	89 (20)	95.3	4.7
Cancer type			
Airways	90 (20)	92.8	7.2
Female genital organs and breast	85 (30)	91.8	8.2
Male genital organs and prostate	89 (20)	92.5	7.5
Gastrointestinal cancer	87 (30)	91.2	8.8
Genito-urinary tract	89 (20)	93.0	7.0
Other	88 (30)	93.6	6.4
Indication for ATT			
AF	88 (30)	86.8	13.2
Cardiac valvular disease	88 (30)	84.2	15.8
VTE	86 (30)	89.8	10.2
Cerebrovascular disease: stroke	91 (20)	88.1	11.9
Peripheral artery disease	91 (20)	88.7	11.3

AF, atrial fibrillation; ATT, antithrombotic therapy; DOAC, direct oral anticoagulant; PDC, proportion of days covered; VKA, vitamin K antagonist; VTE, venous thromboembolism.

and risk of VTE were lower among ATT exposed compared with unexposed at all follow-up times (1-year risk of 2.9% [95% CI, 2.7%-3.1%] vs 3.8% [95% CI, 3.7%-4.0%]), while the rates and 1-year risks of major bleeding were higher among ATT exposed (5.5% [95% CI, 5.0%-5.6%] vs 4.0% [95% CI, 3.8%-4.2%]; Table 4, Figure 2). Throughout follow-up, the risk of ATE was also higher among ATT exposed (1-year risk of 2.5% [95% CI, 2.3%-2.7%] vs 1.2% [95% CI, 1.1%-1.3%]). The same applied to stroke/TIA, myocardial infarction, and other ATE events (Table 4). However, few events of myocardial infarction and other ATE events occurred, and the risk was generally low regardless of ATT exposure. Figure 3 illustrates Kaplan–Meier survival curves according to ATT exposure at index. The overall 1-year cumulative all-cause mortality was 82.6% (95% CI, 82.1%-83.1%) among ATT exposed at index date and 84.4% (95% CI, 84.1%-84.8%) among ATT unexposed (Table 4).

4 | DISCUSSION

Several findings emerged from this nationwide cohort study of ATT and cardiovascular and bleeding outcomes in terminally ill cancer patients with solid tumors. First, the data reveal that ATT is prevalent among terminally ill cancer patients, with nearly 40% having an active prescription period at the time of DRTI. This confirms that the management of thrombosis and subsequent ATT, which has previously been considered largely outside the remit of palliative care, is indeed an area of clinical interest and relevance for this specialty. Conversely, it was rare for patients to be commenced on ATT following DRTI. Rather, most patients already used ATT for preexisting indications. Second, regardless of cancer type and ATT indication, most patients remained on ATT until death. For those who discontinued treatment, this usually occurred just before death. Third, ATT was associated with a higher risk of major bleeding, while those not receiving ATT had a greater risk of VTE. The risk of ATE was generally low regardless of ATT exposure, although ATT was surprisingly associated with a higher risk of ATE, likely due to confounding by indication; the numbers were too small to draw firm conclusions.

Despite recommendations to reassess the risk-benefit ratio of continuing ATT when entering the last phase of life [32], our findings align with several previous studies indicating that ATT is often continued into the last months of life, with many patients continuing ATT use even in hospices [8,15,33,34]. Previous studies have reported that ATT use near the end of life ranges from 9% to 60% of patients, depending on patient population, healthcare environment, and clinical course [4,8,15,16,35]. Similarly, we found that 37.5% of cancer patients in Denmark were treated with ATT at the time of DRTI. Furthermore, data from Sweden and the United Kingdom reported that most ATT users continued treatment until death [15,18]. Common indications for continuing ATT into the last phase of life include stroke prevention in patients with AF and primary or secondary prevention of VTE [36,37].

Patients with cancer also often continue to receive systemic cancer treatment during the last phase of life [38–41]. In Denmark, 16% of all patients dying from cancer received cancer therapy in the final month leading up to death, despite doubtful survival benefits and potential side effects that could compromise the quality of life [42]. This underscores the challenges faced by physicians in balancing the benefits and risks of continuing or deprescribing medications, leading to prescribing inertia at the end of life. Current guidelines offer limited direction in the role of ATT in this last phase of life, with only cursory

TABLE 3 One-year cumulative incidence of antithrombotic therapy discontinuation following drug reimbursement for terminal illness in cancer patients in Denmark, 2013-2022.

Strata	Discontinuation, *n*	Person-time in 100 PY	Rate/100 PY (95% CI)	Cumulative incidence % (95% CI)
Use of any ATT	5688	231.1	24.6 (24.0-25.3)	7.9 (7.7-8.1)
ATT group				
DOAC	1494	244.6	6.1 (5.8-6.4)	2.1 (2.0-2.2)
VKA	1496	244.8	6.1 (5.8-6.4)	2.0 (1.9-2.1)
Platelet inhibitor	3696	237.8	15.5 (15.1-16.1)	5.2 (5.0-5.3)
Cancer type				
Airways	1376	58.9	23.4 (22.2-24.6)	7.0 (6.6-7.3)
Female genital organs and breast	725	33.9	21.4 (19.9-23.0)	8.5 (8.0-9.2)
Male genital organs and prostate	697	23.6	29.6 (27.4-31.9)	10.8 (10.0-11.6)
Gastrointestinal cancer	1996	78.0	25.6 (24.5-26.7)	8.0 (7.6-8.3)
Genito-urinary tract	322	11.2	28.9 (25.9-32.2)	8.0 (7.2-8.9)
Other	572	25.6	22.3 (20.6-24.3)	6.7 (6.2-7.3)
Indication for ATT				
AF	2008	31.3	64.2 (31.5-67.1)	17.6 (16.9-18.3)
Cardiac valvular disease	197	2.7	73.9 (64.3-85.0)	21.5 (18.8-24.2)
VTE	236	6.9	34.4 (30.3-39.1)	11.0 (9.7-12.4)
Stroke	1277	23.4	54.7 (51.8-57.8)	15.8 (15.0-16.6)
Peripheral artery disease	782	15.8	49.6 (46.3-53.2)	14.5 (13.6-15.5)

AF, atrial fibrillation; ATT, antithrombotic therapy; DOAC, direct oral anticoagulant; PY, person-year; VKA, vitamin K antagonist; VTE, venous thromboembolism.

acknowledgment of patient choice and shared decision-making. Physicians report the lack of evidence around ATT near the end of life as a major barrier to decision-making, leading to varied and inconsistent approaches to ATT use among patients with limited life expectancy [8,43]. This profound clinical uncertainty may lead to the avoidance of proactive decision-making on deprescribing and default to medication continuation.

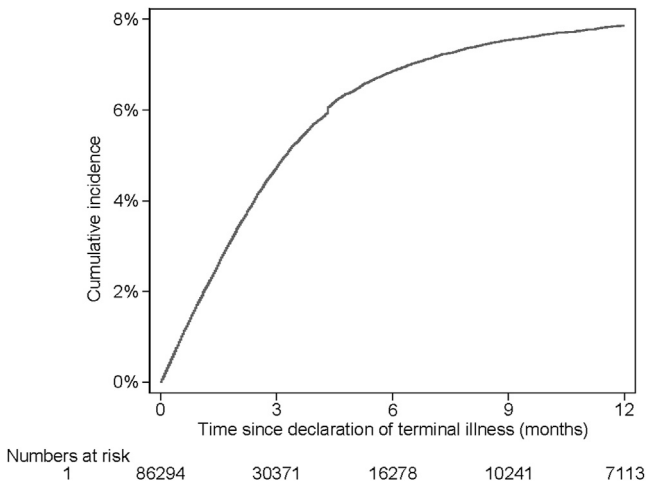

FIGURE 1 Cumulative incidence of antithrombotic therapy discontinuation before death in the year following first drug reimbursement due to terminal illness among cancer patients in Denmark, 2013-2022.

4.1 | Strengths and limitations

All large cohort studies have acknowledged strengths and limitations, and our results must be viewed within this context. Our study was strengthened by the large national sample of patients with terminal cancer with detailed and precise data on drug dispensations and minimal loss to follow-up. The challenges of defining what constitutes a palliative care patient are well documented, particularly in the context of setting criteria for inclusion in a clinical trial. This is largely due to the broad heterogeneity of the cancer population and recognized inaccuracy among clinicians in prognostication [44]. In Denmark, a unique reimbursement system allowed us to employ the DRTI as a proxy for entry into the terminal phase of cancer [45]. The DRTI grants patients full reimbursement for prescription medication. Prior to issuing a DRTI, the attending physician is required to actively assess the patient as having a terminal illness with a prognosis of death within 6 months [45]. With a median life expectancy of 57 days following a DRTI, it is clear that the cohort truly represents a cancer

TABLE 4 Clinical outcomes in terminally ill cancer patients, stratified by antithrombotic therapy usage at index.

	ATT[a]			No ATT		
Outcome	Events *N*	Rate[b] (95% CI)	Cumulative incidence % (95% CI)	Events *N*	Rate[a] (95% CI)	Cumulative incidence % (95% CI)
3-mo follow-up						
Major bleeding	904	20.0 (18.7-21.3)	3.1 (2.9-3.3)	1194	14.8 (14.0-15.6)	2.4 (2.3-2.5)
VTE	516	11.3 (10.4-12.4)	1.8 (1.7-2.0)	1226	15.2 (14.4-16.1)	2.5 (2.3-2.6)
Any arterial thrombotic events	424	9.3 (8.4-10.2)	1.5 (1.3-1.6)	363	4.5 (4.0-4.9)	0.7 (0.7-0.8)
Stroke/TIA	290	6.3 (5.6-7.1)	1.0 (0.9-1.1)	243	3.0 (2.6-3.4)	0.5 (0.4-0.5)
Myocardial infarction	85	1.9 (1.5-2.3)	0.3 (0.2-0.4)	64	0.8 (0.6-1.0)	0.1 (0.1-0.2)
Other arterial thrombotic events	55	1.2 (0.9-1.6)	0.2 (0.1-0.2)	58	0.7 (0.6-0.9)	0.1 (0.1-0.1)
All-cause death	15 786	342.8 (337.5-348.2)	54.6 (54.0-55.1)	27 143	331.6 (327.7-335.5)	54.3 (53.9-54.8)
6-mo follow-up						
Major bleeding	1173	17.8 (16.8-18.8)	4.3 (4.0-4.5)	1558	13.2 (12.5-13.8)	3.2 (3.1-3.4)
VTE	645	9.7 (9.0-10.5)	2.3 (2.2-2.5)	1543	13.1 (12.5-13.8)	3.2 (3.0-3.4)
Any arterial thrombotic events	543	8.1 (7.5-8.8)	2.0 (1.8-2.1)	465	3.9 (3.5-4.3)	1.0 (0.9-1.0)
Stroke/TIA	375	5.6 (5.0-6.2)	1.4 (1.2-1.5)	311	2.6 (2.3-2.9)	0.6 (0.6-0.7)
Myocardial infarction	112	1.7 (1.4-2.0)	0.4 (0.3-0.5)	80	0.7 (0.5-0.8)	0.2 (0.1-0.2)
Other arterial thrombotic events	63	0.9 (0.7-1.2)	0.2 (0.2-0.3)	77	0.6 (0.5- 0.8)	0.2 (0.1-0.2)
All-cause death	19 455	287.5 (283.4-291.5)	70.0 (69.5-70.6)	34 341	285.1 (282.1-288.2)	71.1 (70.7-71.5)
1-y follow-up						
Major bleeding	1376	15.8 (15.0-16.6)	5.3 (5.0-5.6)	1851	11.6 (11.3-12.4)	4.0 (3.8-4.2)
VTE	748	8.5 (7.9-9.1)	2.9 (2.7-3.1)	1787	11.5 (11.0-12.1)	3.8 (3.7-4.0)
Any arterial thrombotic events	650	7.3 (6.8-7.9)	2.5 (2.3-2.7)	549	3.5 (3.2-3.8)	1.2 (1.1-1.3)
Stroke/TIA	453	5.1 (4.6-5.6)	1.7 (1.6-1.9)	365	2.3 (2.1-2.5)	0.8 (0.7-0.9)
Myocardial infarction	137	1.5 (1.3-1.8)	0.5 (0.4-0.6)	104	0.7 (0.5-0.8)	0.2 (0.2-0.3)
Other arterial thrombotic events	72	0.8 (0.6-1.0)	0.3 (0.2-0.3)	85	0.5 (0.4-0.7)	0.2 (0.1-0.2)
All-cause death	21 964	244.0 (240.8-247.2)	82.6 (82.1-83.1)	39 392	246.7 (244.3-249.1)	84.4 (84.1-84.8)

ATT, antithrombotic therapy; TIA, transient ischemic attack; VTE, venous thromboembolism.
[a] Defined by active treatment period at the time of terminal illness declaration.
[b] Rate is estimated per 100 person-years.

population in the advanced stages of terminal illness. However, it should be noted that patients with a high income and those living with a partner are more likely to receive a DRTI [46], suggesting we may not have fully captured all cancer patients entering the last phase of life.

Several limitations should also be considered. The use of administrative health registries has inherent limitations, particularly during the terminal phase of life. Bleeding complications and thromboembolic events may be underrecorded if patients were primarily managed in a primary care setting, thus not seeking hospital care for these events during the last phase of life. This likely has led to an underestimation of these clinical events as primary care registry data are currently not captured in the Danish nationwide registries. Similarly, if the event immediately caused death, it may not have been recorded. In addition, we relied on filled prescriptions for estimating ATT adherence and persistence, leading to potential misclassification of adherence and persistence in instances where ATT was collected but not consumed. Moreover, over-the-counter medications and medications administered in hospitals are not recorded in the prescription registry. Due to this, we lacked data on prescriptions of low-molecular-weight heparin, which is dispensed from the hospital and not recorded in the prescription registry. It is likely, therefore, that our data underreport the prevalence of ATT in terminally ill cancer patients. It is also

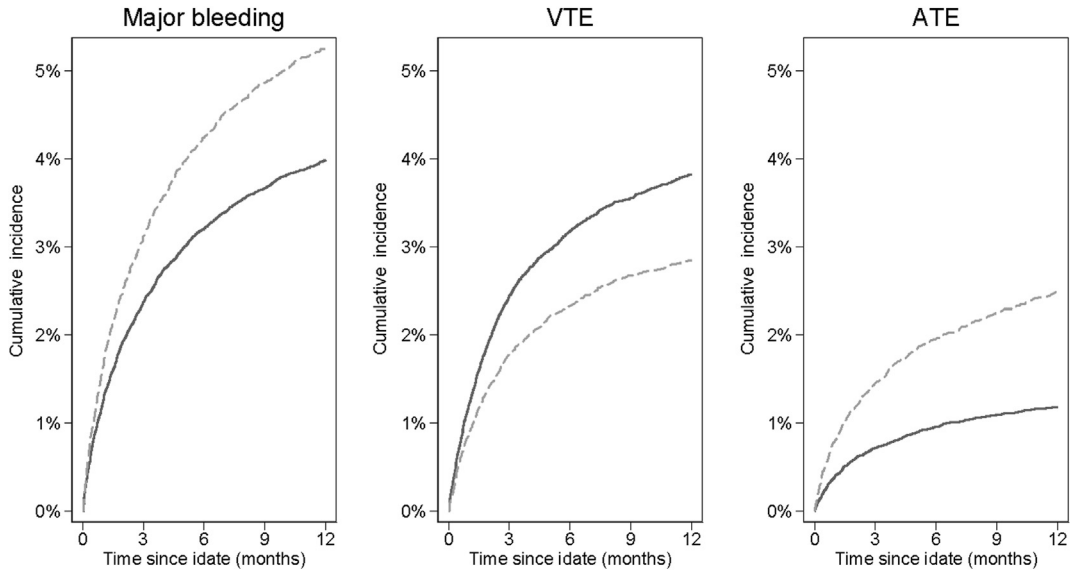

FIGURE 2 One-year cumulative incidence of clinical outcomes in cancer patients at first drug reimbursement for terminal illness in Denmark, 2013-2022, according to antithrombotic therapy (ATT) exposure. The solid line represents patients unexposed to ATT, while the dashed line represents patients exposed to ATT at terminal illness declaration. ATE, arterial thromboembolism; VTE, venous thromboembolism.

conceivable that a proportion of patients who experienced bleeding yet were not exposed to ATT were in fact receiving low-molecular-weight heparin. This would infer an overestimation of bleeding complications in patients classified as unexposed to ATT. While it is not currently possible to access these missing data, it is important to note that the addition of this information would only further emphasize the current take-home messages from this study, namely the high prevalence of ATT use in terminal cancer patients and the lower rate of bleeding in those who no longer receive ATT.

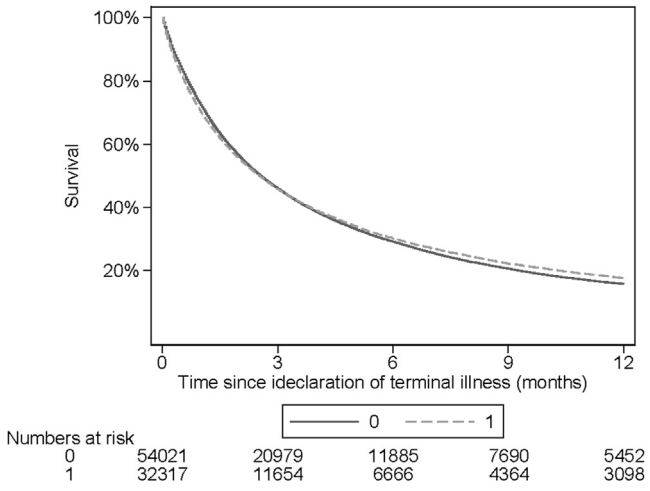

FIGURE 3 Kaplan–Meier survival curve of terminally ill cancer patients according to antithrombotic therapy (ATT) exposure at first drug reimbursement for terminal illness in Denmark, 2013-2022. The solid line represents patients unexposed to ATT, while the dashed line represents patients exposed to ATT at index.

5 | CONCLUSION

This nationwide cohort study showed that the large majority of terminally ill cancer patients receiving ATT continued these medicines until death. Among the small proportion of patients who discontinued ATT, this usually occurred only shortly before death. The risk of VTE was lower among the ATT users, while the risk of ATE and major bleeding was marginally higher among nonusers. Thus, ATT may prevent VTE events even in the last phase of life but at the expense of an increase in major bleeding. These findings contribute to our understanding of ATT utilization, discontinuation dynamics, and consequences in the complex context of terminal illness among cancer patients. Our study further offers insights into factors to consider when rationalizing medicines at the end of life and, as such, will inform the design of the SERENITY shared decision-making support tool.

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AUTHOR CONTRIBUTIONS

M.S.: conception and design of the study; interpretation of data; drafting the article; final approval. M.Ø.: analysis and interpretation of data; drafting the article; critical revision; final approval. M.J.: analysis and interpretation of data; critical revision; final approval. J.G.: conception and design of the study; interpretation of data; critical revision; final approval. E.K.K.: conception and design of the study; interpretation of data; critical revision; final approval. C.V.: conception and design of the study; interpretation of data; critical revision; final approval. E.C.T.G.: conception and design of the study; interpretation of data; critical revision; final approval. D.A.: conception and design of the study; interpretation of data; critical revision; final approval. G.-J.G.: conception and design of the study; interpretation of data; critical revision; final approval. J.P.: conception and design of the study; interpretation of data; critical revision; final approval. A.E.: conception and design of the study; interpretation of data; critical revision; final approval. S.J.A.: conception and design of the study; interpretation of data; critical revision; final approval. A.A.: conception and design of the study; interpretation of data; critical revision; final approval. A.A.H.: critical revision; final approval. F.A.K.: conception and design of the study; funding acquisition; critical revision; final approval. S.N.: conception and design of the study; funding acquisition; critical revision; final approval. S.C.: conception and design of the study; interpretation of data; critical revision; final approval. A.G.O.: conception and design of the study; interpretation of data; drafting the article; critical revision; final approval.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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