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ORIGINAL ARTICLE

Treatment and prevention of cancer-associated thrombosis in the Netherlands: A national survey

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Abstract

Background: In the recent years, numerous studies on the optimal treatment and prevention of cancer-associated venous thromboembolism (VTE) have been published, leading to updated (inter)national guidelines. These include direct oral anticoagulants (DOACs) as the first-line treatment agent in general and the recommendation of primary thromboprophylaxis in selected ambulatory patients.

Objectives: The objective of this study was to evaluate the clinical practice regarding treatment and prevention of VTE in patients with cancer in the Netherlands and practice variation among different specialties.

Methods: An online survey was conducted between December 2021, and June 2022, among Dutch physicians (oncologists, hematologists, vascular medicine specialists, acute internal medicine specialists, and pulmonologists) treating patients with cancer, in which we explored the treatment of choice for cancer-associated VTE, the use of VTE risk stratification tools, and primary thromboprophylaxis.

Results: A total of 222 physicians participated, of whom the majority (81%) used DOACs as a first-line agent for treating cancer-associated VTE. The treatment varied between the following specialties: hematologists and acute internal medicine specialists more often prescribed low-molecular-weight heparin than physicians of the other specialties (OR, 0.32; 95% CI, 0.13-0.80). The minimum duration of anticoagulant treatment was usually 3 to 6 months (87%), and treatment was extended when the malignancy was still active (98%). Regarding the prevention of cancer-associated VTE, no risk stratification tool was used. Three quarters of respondents never prescribed thromboprophylaxis to ambulatory patients, mostly because the thrombosis risk was not perceived high enough to justify prophylaxis.

Conclusion: Dutch physicians largely adhere to the updated guidelines regarding the treatment of cancer-associated VTE but less to the recommendations for its prevention.

Fleur H. J. Kaptein and Noori A. M. Guman contributed equally to this work.

KEYWORDS
anticoagulants, neoplasms, risk assessment, surveys and questionnaires, venous thromboembolism

Essentials

- Guidelines on the management of venous thromboembolism in cancer have recently been updated.
- We conducted a survey among Dutch physicians regarding their implementation.
- Treatment guidelines are largely adhered to, with the common use of direct oral anticoagulants.
- Recommendations on thromboprophylaxis in ambulatory patients with cancer are not broadly implemented.

1 | INTRODUCTION

Venous thromboembolism (VTE) is a common complication in patients with cancer, associated with increased morbidity and mortality [1,2]. Low-molecular-weight heparins (LMWH) have long been the standard therapy for cancer-associated VTE [3], but recently, multiple randomized controlled trials have demonstrated the efficacy and safety of direct oral anticoagulants (DOACs) for VTE treatment in patients with cancer [4–7], which are now incorporated in the guidelines as a first-line treatment (Supplemental Table 1) [8–12]. However, these guidelines include several recommendations based on low-quality data, extrapolated data, or expert opinion, for example, regarding treatment in specific subgroups such as patients with gastrointestinal or genitourinary malignancies (who possibly have a higher bleeding risk when using DOACs) or the type and dose of extended anticoagulation treatment beyond 3 to 6 months. This can result in heterogeneous management strategies in clinical practice based on local preferences [13].

Primary pharmacological thromboprophylaxis is routinely offered to surgical and hospitalized patients with cancer. In ambulatory patients, however, its risk benefit-ratio remains debated [14]. It is crucial to identify individual patients at high risk for VTE, leading to the development of risk stratification tools, of which the Khorana score is best validated [15]. Currently, most guidelines suggest that thromboprophylaxis with either LMWH or DOAC in ambulatory patients with a (intermediate to) high risk of VTE and low risk of bleeding, starting systemic anticancer therapy [10,11,16].

Given the recent changes in international guidelines on treatment and prevention of cancer-associated VTE and existing controversy, we explored their implementation in daily practice in the Netherlands. We conducted a survey among Dutch physicians treating patients with cancer with or without VTE to gain insight in their current practice regarding treatment and prevention of cancer-associated venous thrombosis.

2 | METHODS

We conducted a cross-sectional online survey in the Netherlands. The questionnaire was developed by 4 Dutch experts in cancer-associated thrombosis and subsequently piloted by an independent vascular internist, pulmonologist, and oncologist and an expert in survey design. No formal validation of the survey was undertaken.

The survey was in Dutch and consisted of 2 main sections (Supplemental Table 2): (I) treatment of cancer-associated VTE (including the standard treatment and duration and reasons to withhold DOACs) and (II) prevention of cancer-associated VTE (including the use of the Khorana score, thromboprophylaxis in ambulatory patients, and rationales for not prescribing this). Regarding the VTE prevention section, we focused on solid tumors and lymphomas because these were included in the derivation study of the Khorana score. The survey consisted of thirteen multiple-choice questions, with branch logic used for certain follow-up questions. Participants could answer "other" on some occasions and were then able to provide free text explanations.

The survey was published online by using the Tool for Anonymous Castor Surveys (Castor electronic data capture). The target population included oncologists, hematologists, vascular medicine specialists, acute internal medicine specialists, and pulmonologists involved in the treatment and prevention of VTE in adult patients with cancer in the Netherlands. Surveys were distributed between December 2021 and June 2022 electronically through email or in newsletters by the national professional networks of the respective specialties, using a convenient sampling method, and all emails/newsletters were sent once (for details and number of approached clinicians, see Supplemental Table 3). These professional networks sometimes included physicians not involved in the treatment and prevention of cancer-associated VTE, and these members were identified based on the respondent characteristics and excluded from the analysis. No financial or other incentives were provided for completion of the survey. Survey responses were collected anonymously. Respondents were urged to participate only once, and identical cases were removed with the statistical software application.

In addition to the national guideline on antithrombotic management [8], it was assumed that oncologists primarily follow the ASH/ASCO guidelines [11]; pulmonologist, vascular, and acute internal medicine specialists, mainly the ACCP guidelines [12]; and hematologists use both.

The results of the survey were summarized as proportions of the total number of respondents per question. The percentages were

presented with a corresponding 95% CI. In addition, the proportions were calculated separately for different specialties, for academic medical centers (tertiary referral centers) vs nonacademic, regional teaching hospitals (predominantly secondary referral centers), and for increasing years of experience (with the group with 10-20 years' experience as the reference group). Differences between these groups were estimated by using Pearson's chi-square test and univariate binary logistic regression. For the latter, when independent variables contained more than 2 categories, odds ratios were calculated as the group of interest vs the other groups combined as the reference group. All statistical analyses were performed by using SPSS Statistics version 25.0.

3 | RESULTS

3.1 | Respondents

Of the 1685 members of the professional networks who were reached out to, 235 physicians participated, corresponding to a response rate of 14%. Thirteen surveys (6%) were excluded because only respondent characteristics were completed. Surveys of the 7 respondents (3%) who worked in a specialty other than the target specialties were excluded additionally, resulting in 215 responses available for evaluation. Pulmonologists were best represented (n = 98, 44%), followed by oncologists (n = 46, 21%), vascular medicine specialists (n = 30, 14%), hematologists (n = 25, 11%), and acute internal medicine specialists (n = 16, 7%). Most of them practiced in a regional teaching hospital (n = 150, 70%). Most respondents had less than 10 years of experience in their specialties (n = 118, 55%), whereas 29 respondents (14%) had more than 20 years of experience. The completion per question ranged between 88% and 98% in the section on treatment and between 79% and 100% in the section on prevention of cancer-associated VTE.

3.2 | Treatment of cancer-associated venous thromboembolism

The current first-line treatment of choice for cancer-associated venous thrombosis was predominantly DOACs (161 of the 198 respondents, 81% [95% CI, 75-86]), of which rivaroxaban (n = 79, 49% [95% CI, 41-57]) and apixaban (n = 64, 40% [95% CI, 33-47]) were most commonly prescribed (Table). Among different specialties, hematologists more often treated with LMWH as the first choice (OR, 0.32 [95% CI, 0.13-0.80] for DOAC use; Figure). Acute medicine specialists numerically preferred LMWH more often as well, although not significant (OR, 0.38 [95% CI, 0.12-1.2]). On the other hand, pulmonologists almost exclusively prescribed DOACs (OR, 5.8 [95% CI, 2.3-14.6]). Furthermore, physicians in academic hospitals more often prescribed LMWH as the first choice than in the regional teaching hospitals (OR, 2.5 [95% CI, 1.2-5.2]). In general, the main reasons not to prescribe DOACs were renal dysfunction (eGFR <30 mL/min; n = 110), the presence of a gastrointestinal malignancy (n = 101), and thrombocytopenia (platelet count <50 x10^9/L; n = 97). Notably, respondents who reported LMWH as a standard treatment for cancer-associated VTE more often withheld DOACs in gastrointestinal and genitourinary malignancies, than respondents using DOACs as a first-line therapy (70% vs 44% [OR, 3.0; 95% CI, 1.4-6.5] and 38% vs 15% [OR, 3.5; 95% CI,1.6-7.7], respectively). Hematologists more often reported withholding DOACs in patients with a primary brain tumor (28% vs 6% [OR, 5.8; 95% CI, 2.0-16.5]) or gastrointestinal malignancy (64% vs 43% [OR, 2.4; 95% CI, 1.0-5.7]) compared with other physicians.

Minimal treatment duration was 6 months in most cases (n = 105, 55% [95% CI, 48-62]), although 3 months (n = 61, 32% [26-39]) and 12 months (n = 25, 13% [95% CI, 9-19]) were also reported. Nearly all treating physicians continued anticoagulation when the malignancy was not cured or when patients received anticancer therapy (185 of 189, 98% [95% CI, 95-99]). Most respondents continued the initial anticoagulation; however, some changed from LMWH to DOACs (n = 15, 8% [95% CI, 5-13]) and some lowered the DOAC dose from therapeutic to a half-therapeutic dose (n = 29, 16% [95% CI, 11-21]).

3.3 | Prevention of cancer-associated venous thromboembolism

Of the 169 respondents who were involved in outpatient cancer treatment, only 7 (4% [95% CI, 2-8]) always discussed the risk of VTE with their patients, whereas 22 (13% [95% CI, 9-19]) discussed this "often," 115 (68% [95% CI, 61-75]) "sometimes," and 25 (15% [95% CI, 10-21]) "never." A minority of respondents were familiar with the Khorana score (n = 98, 46% [95% CI, 39-52]), with vascular medicine specialists being best aware of the score (OR, 4.8 [95% CI, 2.0-11.8]). Only 8 respondents (4% [95% CI, 2-7]) used this score in their decision-making regarding primary VTE prophylaxis, including 2% (n = 1) of the oncologists and 8% (n = 2) of the hematologists. Fifty-four respondents (25% [95% CI, 20-31]) "sometimes" or "often" prescribed pharmacological thromboprophylaxis in ambulatory patients with cancer, with either LMWH (45% [95% CI, 33-59]) or DOACs (55% [95% CI, 41-67]). Among different specialties, hematologists most often prescribed prophylaxis (56% [OR, 4.8; 95% CI, 2.0-11.3]; Figure). Prophylaxis was generally prescribed throughout systemic anticancer therapy (n = 31, 58% [95% CI, 45-71]) or depending on (not further specified) individual risk factors (n = 10, 19% [95% CI, 24-49]), rather than a fixed treatment duration (n = 4, 8% [95% CI, 3-18]). Of the respondents not prescribing primary prophylaxis (n = 161, 75% [95% CI, 69-80]) to ambulatory patients with cancer, 130 physicians reported their rationale: the most frequently reported argument was that the VTE risk was not considered high enough to justify prophylaxis (n = 79, 61% [95% CI, 52-69]), whereas 35% (95% CI, 27-43) regarded thromboprophylaxis as too burdensome for patients, and 22% (95% CI, 16-30) evaluated the bleeding risk as too high. Thirteen respondents (10% [95% CI, 6-16]) reported that they were not aware of the indication or that it was not recommended in the guidelines.

TABLE Management pattern of cancer-associated VTE in the total of respondents and per hospital type and years of experience.

	Total respondents	Academic medical center	Regional teaching hospital	*P* value[a]	Experience <10 y	Experience 10-20 y	Experience >20 y	*P* value[b] (ref.: 10-20 y)
Treatment of cancer-associated VTE (*n*, %)								
Standard treatment of VTE in cancer	*N = 198*	*N = 62*	*N = 136*		*N = 107*	*N = 65*	*N = 26*	
- LMWH	37 (19)	18 (29)	19 (14)		18 (17)	11 (17)	8 (31)	
- Apixaban	64 (32)	25 (40)	39 (29)	*0.001*	38 (36)	20 (31)	6 (23)	vs <10 y: 0.37
- Rivaroxaban	79 (40)	11 (18)	68 (50)		41 (38)	28 (43)	10 (39)	
- Edoxaban	16 (8)	7 (11)	9 (7)		10 (9)	4 (6)	2 (8)	vs >20 y: 0.55
- Dabigatran	2 (1)	1 (2)	1 (1)		-	2 (3)	-	
Minimum duration of treatment	*N = 191*	*N = 59*	*N = 132*		*N = 103*	*N = 63*	*N = 25*	
- 3 mo	61 (32)	17 (29)	44 (33)		38 (37)	16 (25)	7 (28)	vs <10 y: 0.31
- 6 mo	105 (55)	33 (56)	72 (55)	*0.13*	51 (50)	37 (59)	17 (68)	
- 12 mo	25 (13)	9 (15)	16 (12)		14 (14)	10 (16)	1 (4)	vs >20 y: 0.31
Extended anticoagulation therapy	*N = 189*	*N = 59*	*N = 130*		*N = 102*	*N = 62*	*N = 25*	
- No	4 (2)	3 (5)	1 (1)		2 (2)	2 (3)	-	
- Continue initial treatment	141 (75)	41 (70)	100 (77)	*0.29*	76 (75)	50 (81)	15 (60)	vs <10 y: 0.49
- Switch to different agent/dose	44 (21)	15 (25)	29 (22)		24 (24)	10 (16)	10 (40)	vs >20 y: 0.04
Prevention of cancer-associated VTE (*n*, %)								
Discussing VTE risk with patients	*N = 169*	*N = 49*	*N = 120*		*N = 86*	*N = 58*	*N = 25*	
- Never	25 (15)	6 (12)	19 (16)		12 (14)	8 (14)	5 (20)	
- Sometimes	115 (68)	36 (73)	79 (67)	*0.75*	62 (72)	37 (64)	16 (64)	vs <10 y: 0.62
- Often	22 (13)	6 (12)	16 (13)		10 (12)	11 (19)	1 (4)	
- Always	7 (4)	1 (2)	6 (5)		2 (2)	2 (3)	3 (12)	vs >20 y: 0.15
Familiar with the Khorana score	*N = 215*	*N = 65*	*N = 150*		*N = 118*	*N = 68*	*N = 29*	
- No	117(56)	35 (54)	82 (55)		65 (55)	37 (54)	15 (52)	vs <10 y: 0.72
- Yes, but do not use it	90 (41)	29 (45)	61 (41)	*0.50*	49 (42)	30 (44)	11 (38)	
- Yes, and I use it	8 (4)	1 (2)	7 (5)		4 (3)	1 (2)	3 (10)	vs >20 y: 0.13
Prophylaxis in ambulatory patients	*N = 215*	*N = 65*	*N = 150*		*N = 118*	*N = 68*	*N = 29*	
- Never	161 (75)	48 (74)	113 (75)		94 (80)	48 (71)	19 (66)	vs <10 y: 0.30
- Sometimes	48 (22)	16 (25)	32 (21)	*0.68*	20 (17)	18 (27)	10 (35)	
- Often	6 (3)	1 (2)	5 (3)		4 (3)	2 (3)	-	vs >20 y: 0.50

(Continues)

TABLE (Continued)

	Total respondents	Academic medical center	Regional teaching hospital	*P* value[a]	Experience <10 y	Experience 10-20 y	Experience >20 y	*P* value[b] (ref.: 10-20 y)
Agent of prophylaxis	*N* = 53	*N* = 17	*N* = 36		*N* = 23	*N* = 20	*N* = 10	
- LMWH	24 (45)	10 (59)	14 (39)	0.17	11 (48)	10 (50)	3 (30)	vs <10 y: 0.89
- DOAC	29 (55)	7 (41)	22 (61)		12 (52)	10 (50)	7 (70)	vs >20 y: 0.30
Duration of prophylaxis	*N* = 53	*N* = 17	*N* = 36		*N* = 23	*N* = 20	*N* = 10	
- During systemic therapy	31 (58)	12 (71)	19 (53)		13 (57)	12 (60)	6 (60)	
- 3 mo	2 (4)	-	2 (6)	0.45	-	1 (5)	1 (10)	vs <10 y: 0.70
- 6 mo	2 (4)	1 (6)	1 (3)		1 (4)	1 (5)	-	vs >20 y: 0.86
- Other	18 (34)	4 (23)	14 (39)		9 (39)	6 (30)	3 (30)	

N, total number of respondents per question, n: number of respondents per answer (percentages are proportions of the total number of respondents per question), ref.: reference; VTE, venous thromboembolism, LMWH, low-molecular-weight heparin; DOAC, direct oral anticoagulant.

[a]Difference between academic and regional teaching hospitals with Pearson's chi-square tests.

[b]Difference between years of experience-groups with Pearson's chi-square tests, with "10 to 20 years" experience' as reference group ("vs <10 y": compared with <10 years' experience and "vs >20 y": compared with >20 years' experience).

There were no notable differences between hospital setting or years of experience (Table) with respect to this survey section.

4 | DISCUSSION

This survey among Dutch treating physicians of different medical backgrounds, who are responsible for the anticoagulant treatment of patients with cancer and VTE, demonstrates that in the Netherlands the updated guidelines on cancer-associated VTE treatment are widely adopted because most respondents reported they prescribed DOACs as the first-line therapy. By contrast, adherence to guideline recommendations regarding the VTE risk assessment and the use thromboprophylaxis in ambulatory patients was limited.

Variations in VTE treatment practices were noted between the different medical specialties, with more hematologists routinely starting treatment with LMWH. This is most likely related to the cancer type they are treating, with hematological patients experiencing severe thrombocytopenia more often. Contrarily, pulmonologists treat lung patients with cancer with a relatively low bleeding risk compared with several other cancer types, which might be reflected in the high rate of pulmonologists starting DOACs by default. Furthermore, a few respondents reported to use dabigatran as the first choice for cancer-associated VTE, which is not recommended by guidelines because it has not been specifically studied in a randomized trial for this indication.

The current Dutch guideline prefers LMWH over DOACs as a first-line treatment of patients with a gastrointestinal or urogenital tract malignancy because the initial clinical trials and meta-analyses showed a higher bleeding risk in these patients [5,17,18]. However, 44% and 78% of the survey respondents used DOACs in gastrointestinal and urogenital tract malignancies, respectively. International guidelines do not strictly discourage the use of DOACs in these patient subgroups (Supplemental Table 1) but do recommend using caution in these patients, especially in upper gastrointestinal and/or (unresected) luminal tumors.

Regarding the duration of anticoagulation in cancer-associated VTE, guidelines are consistent in advising a minimum treatment of 3 to 6 months [8,10,11], although in our survey, 13% of the respondents indicated a minimum duration of 12 months. The decision about continuing anticoagulation beyond 3 to 6 months of the initial treatment has to be made on an individual patient level because the optimal type and dose of anticoagulation for the extended therapy is unknown. Nearly all respondents continued anticoagulation therapy if there was still an active malignancy or anticancer treatment in concordance with the current guidelines, usually with the same agent and dose as the initial treatment. However, 18% of the physicians who initiated treatment with DOACs continued with a reduced dose. The efficacy of the latter approach has not been properly evaluated yet in patients with cancer; however, supporting data have been published [19] and large randomized controlled trials are ongoing (the API-CAT study, NCT03692065 [20] and the EVE trial, NCT03080883 [21]).

The risk of thrombosis during outpatient anticancer treatment was rarely discussed with patients. This is in line with the results of a

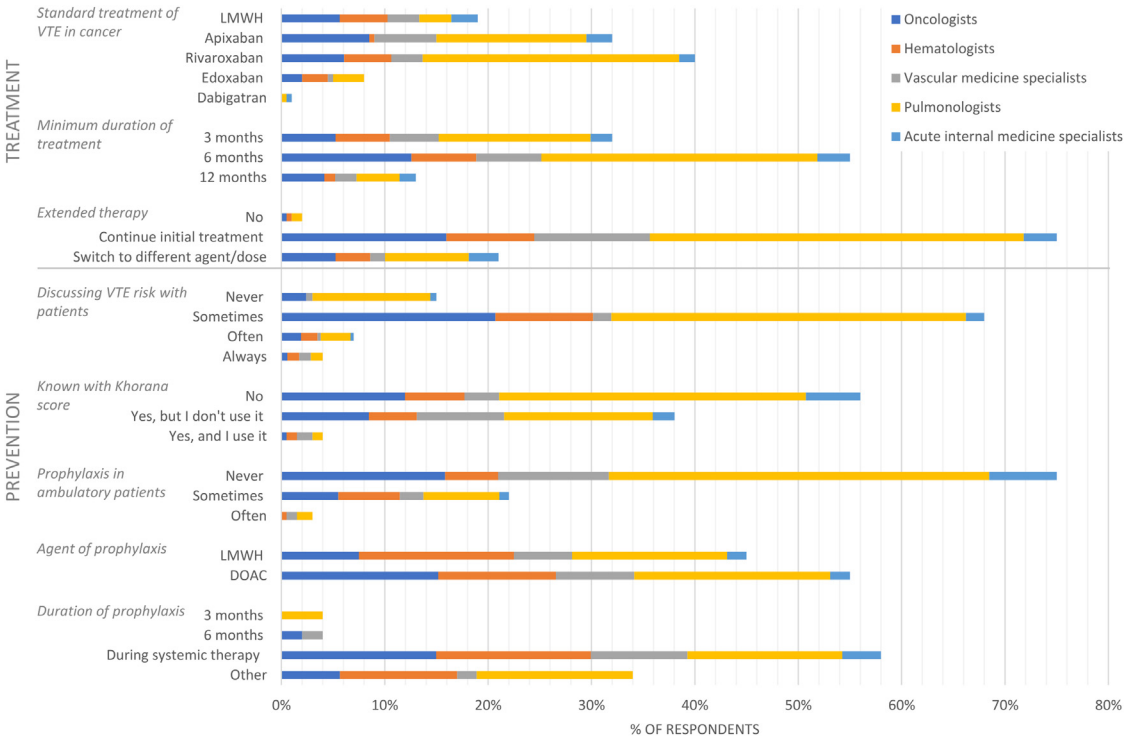

FIGURE Management pattern of cancer-associated VTE per specialty

large European survey among patients, indicating that 72% of patients with cancer were unaware of their higher risk to develop thrombosis. Moreover, of the patients who did receive information about cancer-associate VTE, 26% noted that this education only occurred at the time they developed thrombosis [22].

The occurrence of VTE has important consequences for a patient with cancer including the need for therapeutic anticoagulation (with associated high bleeding risk), possible delays in cancer treatment, and decreased quality of life [23]. Prevention of cancer-associated venous thrombosis with pharmacological thromboprophylaxis during hospital admission and in the postoperative setting is widely adopted in standard practice. However, in ambulatory patients with cancer, the use of thromboprophylaxis remains a matter of debate. Previous trials in unselected patients with cancer showed that primary prophylaxis with LMWH was effective and safe, although the absolute risk reduction was relatively small (number needed to treat [NNT] 30-50), and the evidence regarding the incidence of (major) bleeding complications was inconsistent [24]. Together with the costs and patient burden to daily subcutaneous injections of LMWH, the benefit-risk balance remained uncertain [25]. Because the VTE risk differs widely between different cancer types, cancer stages, and anticancer therapy, identifying high-risk patients who can benefit from thromboprophylaxis is crucial but challenging, especially considering the sudden changes of risk factors characteristics during the cancer journey [26]. In the prophylaxis trials with DOACs, the selection of patients based on the Khorana score resulted indeed in a higher 6-month VTE rate in the placebo arms of approximately 10% [27,28]. Although only the AVERT-trial demonstrated a statistically significant difference between DOACs and placebo, a pooled analysis showed an absolute VTE risk reduction of 4% (NNT 25) at the cost of a 1% increase in major bleeding (number needed to harm 100) [25,29]. More than half of the survey respondents were not familiar with the Khorana score, which did not differ between the hospital setting or the years of experience. Only 4% of the respondents used the score for risk assessment, possibly explained by the fact that the utility of this tool remains controversial because different studies report varying results about the discriminatory performance of the score, particularly in different cancer types [30,31]. Most of the respondents who never prescribed primary thromboprophylaxis in ambulatory patients reported that they did not consider the VTE risk high enough to justify prophylaxis. Considering the Khorana score was rarely used and, although we did not assess this, it is also unlikely that other risk assessment tools were commonly used, this suggests that physicians base their VTE risk evaluation in these patients on other (non-standardized) factors. The underuse of both assessing VTE risk and anticoagulation prophylaxis is in line with previous publications, indicating that also accumulating studies and guideline updates in recent years have not resulted in a change in clinical practice [32,33]. An explanation for the low physicians' adherence might be that they draw different conclusions from the clinical trials and may disagree with international guideline recommendations. Furthermore, a small proportion of respondents reported that they were not aware of the indication for thromboprophylaxis in these patients or that it was not included in the guideline. The latter could refer to the Dutch antithrombotic management guideline [8] because it indeed does not address primary prophylaxis in ambulatory patients with cancer.

Some limitations merit consideration. First, we did not undertake formal validation of our developed survey. The results of this study may be biased because of the relatively low response rate (14%), which is probably the result of our strategy to reach the eligible physicians, i.e., through (newsletters from) the national professional networks, which also impeded the sending of reminders. National privacy regulations precluded direct email contact with all physicians. We cannot exclude that physicians who responded to our survey are more interested in the management of cancer-associated VTE (and subsequently more up-to-date on guidelines) than those who did not respond. Furthermore, the different specialties were not evenly distributed, with an excess of pulmonologists. This might have influenced our overall results, although we have provided the results that differed per specialty separately. The small subgroups led however to large confidence intervals. In addition, we do not have information available on the race or ethnicity of the participants. Finally, the questions were designed to be pan-cancer, which precludes conclusions about single tumor types.

In conclusion, this survey shows that most Dutch physicians treating cancer-associated VTE prescribe DOACs and continue treatment after 3 to 6 months when the cancer or treatment is still active, which is in accordance with (inter)national guidelines. Discussing the risk of VTE in patients with cancer is uncommon and can be improved. Currently, in the Netherlands, the Khorana score is hardly ever used, and primary prophylaxis in ambulatory patients is rarely prescribed in contrast to the international guideline recommendations. This could be the result of lack of awareness, disagreement with the guideline recommendations, or absence of national guidelines on this topic. There appears to be a potential to better educate Dutch physicians in this regard, which may improve the management of cancer-associated VTE in the Netherlands.

AUTHOR CONTRIBUTIONS

F.H.J. Kaptein: substantial contribution to concept and design, analysis and interpretation of data; critical writing the intellectual content; and final approval of the version to be published. N.A.M. Guman: substantial contribution to concept and design, interpretation of data; critical revising the intellectual content; and final approval of the version to be published. N. van Es: substantial contribution to concept and design, interpretation of data; critical revising the intellectual content; and final approval of the version to be published. P.W. Kamphuisen: substantial contribution to concept and design, interpretation of data; critical revising the intellectual content; and final approval of the version to be published. F.A. Klok: substantial contribution to concept and design, interpretation of data; critical revising the intellectual content; and final approval of the version to be published. A.T.A. Mairuhu: substantial contribution to concept and design, interpretation of data; critical revising the intellectual content; and final approval of the version to be published. M.V. Huisman: substantial contribution to concept and design, interpretation of data; critical writing and revising the intellectual content; and final approval of the version to be published.

RELATIONSHIP DISCLOSURE

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SUPPLEMENTARY MATERIAL

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