Full Length Article

Short-term versus extended anticoagulant treatment for unprovoked venous thromboembolism: A survey on guideline adherence and physicians' considerations☆

Maria A. de Winter*, Gabriëlle C.P. Remme, Karin (H.A.H.) Kaasjager, Mathilde Nijkeuter

UMC Utrecht, Department of Internal Medicine, Utrecht, the Netherlands

A B S T R A C T

Background: In patients with unprovoked venous thromboembolism (VTE), anticoagulant treatment duration should be decided by weighing bleeding risk versus risk of recurrent VTE, considering patient's preference. Because both risks differ between individuals, this recommendation presumably leads to wide variation in clinical management.
Objectives: To identify physician's considerations when deciding between short-term and extended anticoagulation and to assess how current guidelines are put to practice.
Materials and methods: An online, 33-item survey was developed, containing questions on clinical management, considerations regarding treatment duration, risk scores, information tools and shared decision-making. It was distributed to internists, pulmonologists and residents treating patients with VTE in the Netherlands.
Results: 69 internists and 73 pulmonologists including 24 residents participated in the survey. Extended treatment was preferred by 73% (104/142) of participants. Most important reasons for extended treatment were, in descending order: patient's preference, active malignancy, low estimated bleeding risk, history of VTE and hemodynamic instability during previous VTE. Most important reasons for short-term treatment were frequent falls, history of major bleeding, previous bleeding during anticoagulation, patient's preference and thrombocytopenia. Although existing risk scores are infrequently used, physicians express their need for scores combining risks of recurrence and bleeding to aid individualized decision-making.
Conclusion: Our results confirm a wide variety of considerations regarding treatment duration in patients with unprovoked VTE. Although most participants followed guidelines' recommendations to prescribe indefinite treatment in absence of contraindications, rationale is not always supported by evidence. A clinical decision tool to estimate and weigh risks of recurrence and bleeding is warranted.

1. Introduction

Venous thromboembolism (VTE), comprising deep venous thrombosis (DVT) and pulmonary embolism (PE), is a global disease burden considering the annual incidence rate of 1–2 per 1000 individuals worldwide. This results in > 10 million new cases per year [1,2].

Guidelines unanimously recommend anticoagulant treatment for at least 3 months after diagnosis to prevent enlargement of the thrombus as well as early recurrence of VTE [3–5]. Anticoagulant treatment is limited to 3 months in VTE provoked by transient risk factors (short-term treatment), as recurrence risk is low when the initial risk factor is no longer present [3–5]. However, in unprovoked VTE, which involves one third to half of all VTE cases, recurrence risk is as high as 30% in 5 years [3,6]. Therefore, guidelines nowadays advise to treat patients with unprovoked VTE indefinitely (i.e. extended treatment) in the absence of a high bleeding risk.

In clinical practice, at three months after diagnosis, an important decision has to be made on continuation of anticoagulant treatment. According to guidelines, this needs to be done by weighing the risk of recurrent VTE versus the risk of bleeding, taking into account patient's

preferences [3–5]. However, there are 3 factors that complicate this advice. First, the risk of recurrent VTE cannot be calculated for an individual patient, but only general percentages can be given derived from population-based studies, such as the 30% in 5 years for unprovoked VTE [3,6]. It is known that several factors may lower this risk (e.g. female sex) or increase this risk (e.g. older age), but how this affects an individual risk is hard to translate into precise percentages. Second, guidelines recommend to use the American College of Chest Physicians (ACCP) risk score to classify patients at low or high risk of bleeding [3,4].However, this ACCP score has poor predictive performance and is therefore insufficiently reliable to guide decisions on extended treatment [7]. Other risk scores for bleeding are also considered insufficiently valid [3–5]. Although guidelines agree on the importance of individualized decision-making regarding treatment duration, concrete tools to calculate individual risks are non-existent [8–10]. Third, shared decision-making (SDM) should be used to discuss individual risks, treatment options, associated benefits and harms and individual preferences with the patient to decide jointly on treatment duration. However, guidelines do not advise what tools for SDM should be used.

To gain insight in the process of decision-making regarding treatment duration, we performed a survey on physicians' considerations when deciding between short-term and extended anticoagulant treatment and how current guidelines are put to practice.

2. Materials and methods

2.1. Study design

An online questionnaire was designed using Explora (http://www.explora-zorg.nl), a Dutch online questionnaire program, to assess current practice and considerations that physicians take into account when treating patients with unprovoked VTE. This study was, considering its non-invasive design, not subject to the Medical Research Involving Human Subjects Act. Upon approval, the questionnaire was pilot-tested and revised. Participation was voluntary and participants remained anonymous.

2.2. Study population

The study population consisted of specialists who treat patients with PE or DVT in the Netherlands, which are mainly internists (including vascular medicine specialists, hematologists and other subspecialists) and pulmonologists, including residents. To ensure a representative sample, participants were selected from all academic as well as general hospitals throughout the Netherlands. Between August and September 2018, a total of 135 internists, pulmonologists and medical residents received the questionnaire by email and were asked to distribute it to colleagues treating patients with VTE within their hospital. Moreover, the questionnaire was sent to all pulmonologists in the Netherlands via the Dutch association of pulmonologists ('Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose') in November 2018, and distributed among medical residents via the Dutch Young Internist Group ('Junior Nederlandse Internisten Vereniging') in December 2018. Cardiologists were not primarily approached as they are usually not involved in long-term treatment decisions for patients with unprovoked VTE.

2.3. Questionnaire

The questionnaire consisted of 31 questions, including multiple choice, rank order and open-ended questions. It was organized into 4 sections: 1) characteristics of survey participants, 2) considerations on treatment duration and current practice, 3) use of tools and 4) shared decision-making. Participants were offered a list of determinants that could potentially influence treatment duration consisting of 28 factors

favoring short-term treatment and 25 factors favoring extended treatment. Determinants were among others selected from risk scores for bleeding and recurrent VTE. Next, participants were asked to pick all relevant determinants and to formulate a top 5 in order of importance for deciding on treatment duration. Subsequently, statements were posed on the use of and need for risk scores for bleeding and recurrent VTE, information tools and practice of shared decision-making.

2.4. Data analysis

Participants' characteristics and survey results are shown as percentages or median and interquartile range as data were non-normally distributed. Differences in questionnaire results between groups by gender, level of training, type of healthcare facility, average number of unprovoked VTE patients treated and medical specialization were explored using Chi-square or Fisher's exact test, depending on size of subgroups, or Welch's *t*-test for continuous data. These subgroup analyses were planned prior to data collection. Bonferroni's correction was applied to reduce the probability of a type I error due to multiple testing when exploring reasons for extended and short-term treatment. Therefore, a *p*-value of 0.002 was considered significant. An overall ranking of determinants was performed by assigning points (0–5) according to their ranking by individual physicians, with 5 points for the determinant considered most important, 4 for the second most important determinant, etcetera, and 0 points for determinants that were not listed in the top 5. Per determinant, the points were added up and the overall ranking was determined by the total number of points assigned. Open-ended responses were analyzed thematically. All statistical analyses were performed using software IBM SPSS Statistics 25.

3. Results

3.1. Characteristics of survey participants

The survey was completed by 142 internists, pulmonologists and medical residents, including one physician assistant. Characteristics of survey participants are shown in Table 1.

3.2. Considerations on treatment duration and current practice

From a list of 28 potential determinants for prescribing extended treatment, participants chose a wide variety of determinants. Fig. 1 expresses the frequency of each determinant.

Subsequently, participants were asked to rank these determinants in descending order of importance. Combining top five lists of individual participants, the following top 10 emerged: patient's preference, active malignancy, low estimated risk of bleeding, history of PE or DVT, hemodynamic instability during previous VTE, known thrombophilia, immobilization, incomplete resolution of thrombi on ultrasound or computed tomography pulmonary angiography (CTPA), male sex and estrogen therapy.

Likewise, a wide variety of determinants were chosen as rationale for short-term treatment (Fig. 2). The following top 10 could be constructed based on the participants' rankings: history of frequent falls, history of major bleeding, previous bleeding during use of anticoagulation, patient's preference, thrombocytopenia ($< 80 \times 10^9$/L), alcohol abuse, anemia (hemoglobin < 10 g/dL), use of platelet aggregation inhibitors, recent surgery and renal insufficiency (creatinine clearance of < 40 mL/min).

The ranking of determinants differed between medical specialists. Pulmonologists more often considered residual clot on computed tomographic pulmonary angiography (CTPA) a reason for extended treatment compared to internists (41% versus 9%, $p < 0.001$). Internists more often chose male sex as rationale for extended treatment (25% versus 6%, p 0.002). The number of patients with unprovoked VTE that physicians treat per month nor the stage of training of

Table 1
Characteristics of participants.

Characteristics	N (%)
Type of healthcare facility	
Academic hospital	40 (28)
General hospital	102 (72)
Type of specialist[a]	
Internist	69 (49)
Differentiation vascular medicine[b]	37/69 (54)
Differentiation hematology	12/69 (18)
Other	32/69 (46)
Pulmonologist	73 (51)
Level of training	
Specialist; years of experience	118 (83)
0–5	29/118 (25)
5–10	38/118 (32)
> 10	50/118 (43)
Medical resident; years of training	24 (17)
0–4[c]	14/24 (58)
5–6	10/24 (42)
Gender	
Male	75 (53)
Number of patients with VTE per month	
0–5	53 (37)
> 5	89 (63)
Number of patients with unprovoked VTE per month	
0–5	84 (59)
> 5	58 (41)

[a] Other specialists included: geriatricians, cardiologists, dermatologists, intensivists and other.

[b] Other differentiations included: general internal medicine, endocrinology, infectious disease, intensive care, oncology, nephrology, allergy-immunology and pharmacology.

[c] One participant checked zero for being a physician assistant.

residents influenced the choice of determinants. However, physicians with > 10 years of experience less often considered previous major bleeding as a reason for short-term treatment compared to those with less experience (91% versus 67%, p 0.002). There was a trend towards an influence of gender on the choice of determinants. Compared to male

participants, female participants selected several determinants for short-term treatment more frequently (frequent falls, history of major bleeding, previous bleeding during anticoagulation, thrombocytopenia, liver disease, anemia, uncontrolled hypertension), although after applying Bonferroni correction, associated p-values were not considered significant ($p > 0.002$).

The majority of participants (73%) generally prescribe extended treatment for unprovoked VTE. Answers to the question "In what percentage of patients with unprovoked VTE do you prescribe extended treatment?" resulted in a median of 70% (interquartile range 40–82). This did not differ across gender, medical specialization, level of training and experience with unprovoked VTE Participants who prescribe extended treatment in general were significantly more likely to choose patient's preference as rationale for either extended or short-term treatment ($p < 0.001$ for both). Moreover, low estimated risk of bleeding was more frequently mentioned as reason for extended treatment by those who prefer to prescribe extended treatment ($p < 0.001$). No other differences between participants who generally prescribe extended or short-term treatment were found.

The majority of participants (63%) found morbidity and mortality due to recurrent VTE most important when deciding on treatment duration compared to morbidity and mortality due to bleeding (19%) or consequences for quality of life in general.

Considering choice of anticoagulant when deciding on extended treatment, 64/142 (45%) of participants stated to always prescribe direct oral anticoagulants (DOAC), namely Apixaban (20), Rivaroxaban (35), Dabigatran (2) or Edoxaban (1), among whom twenty physicians (20/64, 31%) mentioned to switch to reduced dose DOACs. Six participants did not specify their preference of DOAC. None of the participants always prescribes VKA. In addition, 58/142 (41%) stated that they do not routinely prescribe DOACs, but decide on medication based on patient-related factors, including but not limited to patient's preferences, bleeding risk factors, renal function, treatment adherence, active malignancy or comorbidity in general. 20/142 (14%) always continues the initial anticoagulant.
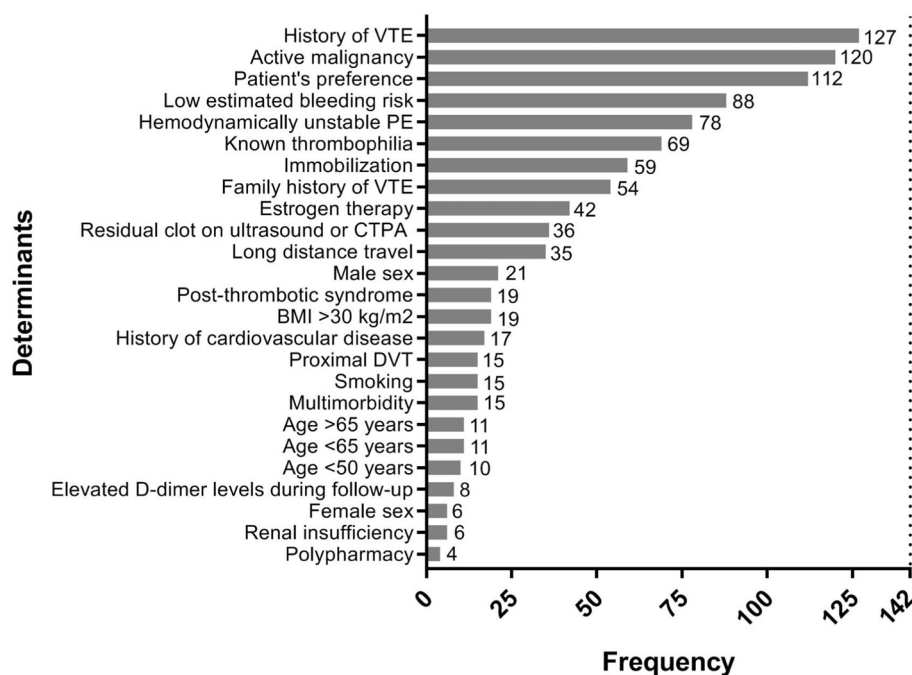

Fig. 1. Rationale for prescribing extended treatment in patients with unprovoked VTE.
Abbreviations: BMI body mass index; CTPA computed tomographic pulmonary angiography; DVT deep vein thrombosis; PE pulmonary embolism; VTE venous thromboembolism.
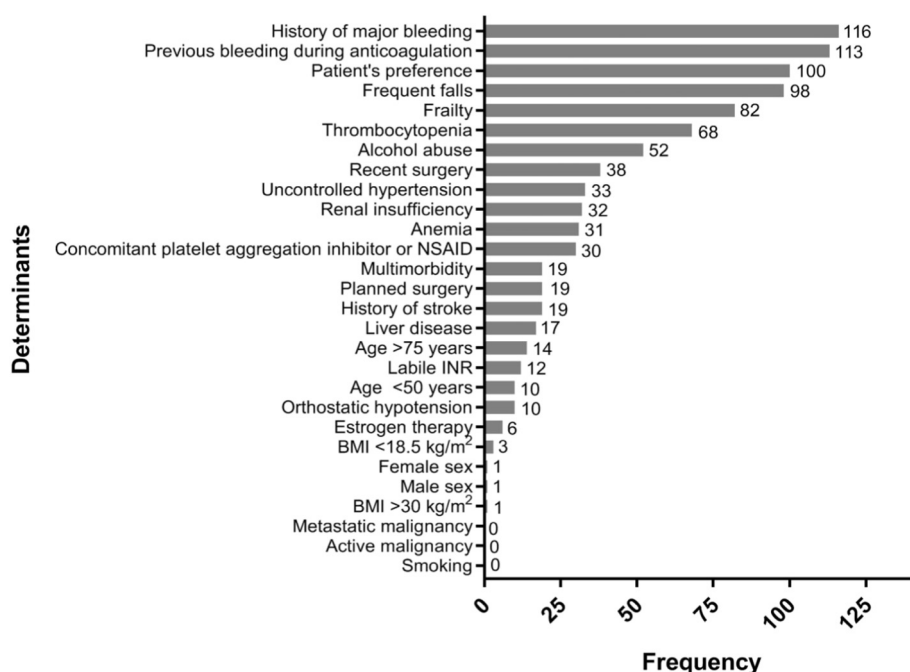
Fig. 2. Rationale for prescribing short-term treatment in patients with unprovoked VTE.
Abbreviations: BMI body mass index; INR International Normalized Ratio; NSAID non-steroidal anti-inflammatory drugs.
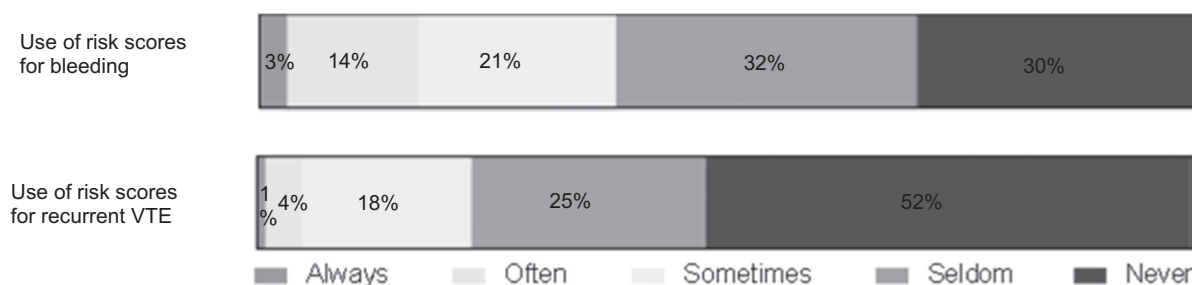
3.3. Use of tools

As shown in Fig. 3, risk scores for bleeding [3,11,12] and recurrent VTE [13–15] are infrequently used by participants. Of note, the majority (62%) of participants never or seldom use a bleeding score, while this percentage is even higher for a recurrent VTE score (77%). A significant proportion of participants agrees that bleeding risk scores (40%) as well as recurrent VTE risk scores (25%) are difficult to translate into clinical practice (Fig. 4). The majority of participants state that they need a score combining both risk of bleeding and risk of recurrence (73%) or a tool to assess individual risks (62%).

Fig. 5 shows that the majority of participants always involve patients in the decision-making process. However, f20% does not always discuss risks and benefits of treatment options. 91% always or often asks for patient's preferences. A Dutch information leaflet called "De Consultkaart: trombose of longembolie", originally intended to inform patients, is seldom to never used by 80%, while only very few (11%) use it regularly [16]. More than half of the participants have a need for explanatory tools.

4. Discussion

This survey reveals that the majority of 142 participants prescribe extended treatment in patients with unprovoked VTE and that there is a wide variety of determinants driving this decision. Patient's preference and a low estimated risk of bleeding are among the most important reasons to prescribe extended treatment.

Our results are in line with the recommendation of guidelines to prescribe extended treatment to all patients without a high risk of bleeding [3–5]. According to the ACCP risk score, half of the patients with VTE have a low to moderate risk of bleeding [3–5,7,17]. Since 62% of participants state that they seldom use a risk score for bleeding, it is unsure how this risk of bleeding is estimated. Also, it is intriguing that the decision to prescribe indefinite treatment is largely driven by the absence of contraindications rather than the risk of recurrent VTE [3–5]. Another explanation for the 73% of participants prescribing extended treatment in general may be that the majority of participants are more concerned about recurrent VTE than consequences of bleeding or for quality of life., After the initial 3 months of anticoagulation, case fatality rate of bleeding is > 3 times as high as that of recurrent VTE and from our results it cannot be deduced if and how this is weighted [18]. Moreover, patient's preference is among key determinants to

Abbreviations: VTE venous thromboembolism

Fig. 3. Present use of risk scores and information leaflet.
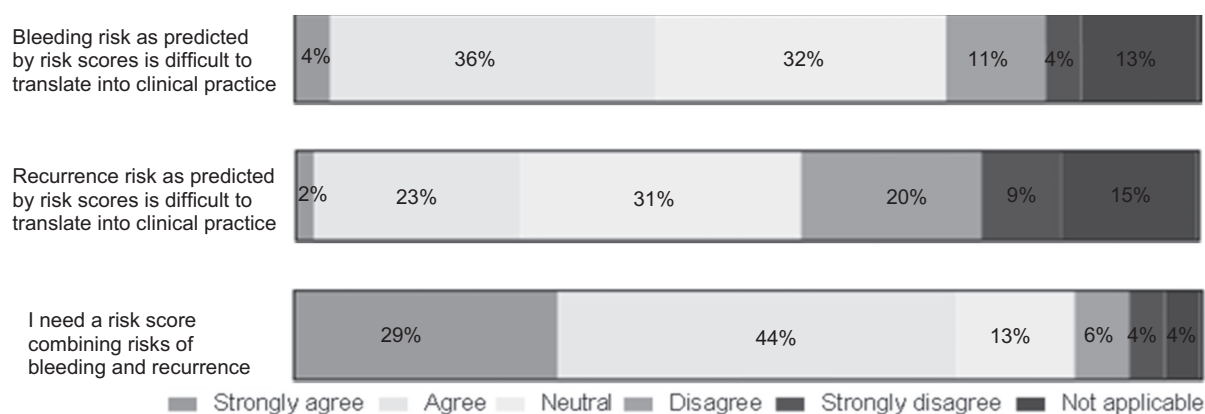Abbreviations: VTE venous thromboembolism.

Fig. 4. Use of risk scores in clinical practice.

decide on extended treatment. Since patients are generally more concerned about recurrent VTE than bleeding, this may stimulate prescribing extended treatment [19].

We found a wide variation in choice of determinants, which likely reflects a large extent of between-practice variation as well as individual physician's preferences. Surprisingly, determinants included in existing risk scores for recurrent VTE were infrequently mentioned as reasons for extended treatment (age > 65 years, proximal DVT, obesity, body mass index, post-thrombotic syndrome and elevated D-dimer levels during follow-up) [13–15,20]. In addition, several frequently mentioned determinants for extended treatment are not supported by evidence nor guidelines, including hemodynamic instability during previous PE, known thrombophilia, immobilization, incomplete resolution of thrombi on ultrasound or CTPA and male sex [3–5]. Of note, estrogen therapy is frequently named as determinant for extended treatment. Because it is indeed associated with a higher risk of recurrent VTE, guidelines advise to discontinue estrogen therapy after cessation of anticoagulation [3–5,21,22]. However, prescribing extended treatment if there is a persistent wish for estrogen use is not part of the guidelines [3–5].

Regarding rationale for short-term treatment, all highly ranked determinants can easily be linked to guidelines and well-known risk scores [3–5,11,12]. This is even more evident in female participants. An explanation may be that female physicians are more likely to adhere to guidelines [23]. Interestingly, risk of frequent falls was deemed most important. While included in the ACCP risk score, it was left out of Dutch guidelines because a high risk of falls is associated with clinically relevant, non-major bleeding (CRNMB) only, and not with major bleeding [4–5,24]. However, CRNMB is associated with a decreased perception of quality of life and important healthcare costs and should therefore be taken into account [25,26].

The majority of participants never or seldom use risk scores for recurrent VTE and bleeding, while at the same time expressing a need for a risk score combining risks of recurrence and bleeding. This clearly illustrates an unmet need. In addition, adequate risk assessment is crucial in performing true SDM. Although the majority responded to always involve the patient in the decision on treatment duration, it would even be of more importance to know the perspective of the
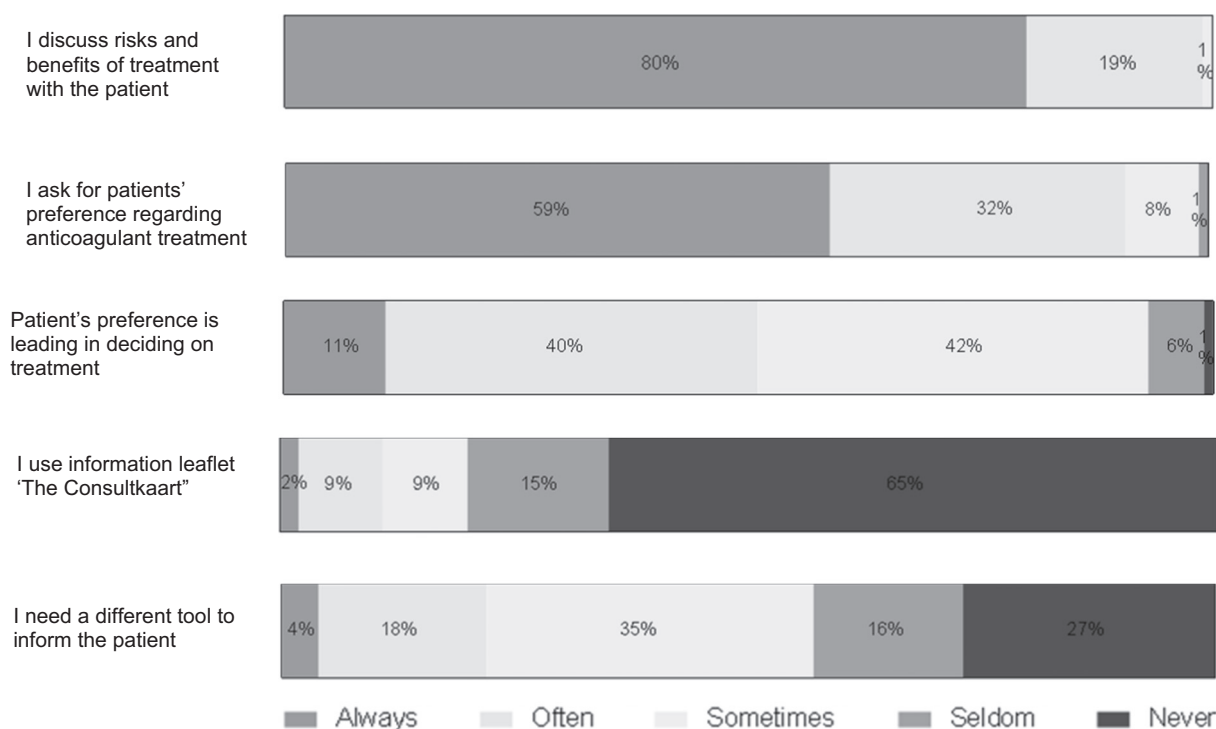

Fig. 5. Shared decision-making.

patient on SDM and the communication of risks.

An Australian survey had important similarities with our study [27]. They aimed to identify the extent to which self-reported VTE treatment is consistent with guidelines and found significant variability. However, only 12% of physicians said to generally prescribe indefinite or lifelong treatment for unprovoked VTE, as opposed to 73% in the present study. This is a striking difference, especially as 77% of Australian participants stated to base clinical decisions on guidelines and 54% stated to be familiar with ACCP guidelines. Since the 2008 edition, indefinite treatment is recommended for unprovoked VTE in the ACCP guidelines [3,28]. Recently, Ten Cate and Prins assessed geographical differences in guideline adherence in secondary prevention of VTE by performing interviews with senior-level physicians [29]. In addition to international guidelines and local guidelines based thereon, area-specific features were of influence on actual VTE treatment, including, among others, financial aspects, comorbidities, genetic profile and access to health care [29]. Existing risk scores for bleeding or recurrent VTE were used by a minority of participants.

To our knowledge, this is the first study to survey considerations that physicians take into account when deciding for short-term or extended treatment in patients with unprovoked VTE. It assessed not only clinical practice, but also future needs to improve clinical decision-making. Our study population was sufficiently varied to represent an adequate cross-section of physicians treating patients with unprovoked VTE. As Dutch guidelines are largely based on international guidelines, our results are generalizable to other Western countries with similar healthcare financing systems.

However, it is important to acknowledge several limitations. First, as we invited all participants to forward the survey to colleagues and attracted participants by putting the link to the survey in newsletters, we were unable to calculate the response rate. This makes the extent of respondent bias difficult to ascertain. Second, as physicians with affinity with VTE will be more likely to participate, self-selection bias could have occurred. It is expected that heterogeneity in clinical management and considerations would be even more distinct when including those with less experience with VTE as well. In addition, results based on self-reporting are likely to be subject to social desirability bias and recall bias. To prevent self-reporting bias, it was explicitly stated that all data was anonymous and will not be used for purposes other than to assess clinical management on a group level. Finally, we did not specify some of the determinants, including thrombophilia, frailty, orthostatic hypotension and liver disease. This may dilute potential associations.

5. Conclusion

Most physicians follow the recommendations of guidelines to prescribe extended treatment in the absence of contraindications, taking into account the patient's preference. However, mentioned rationale is not always supported by evidence, especially regarding recurrence risk assessment. By identifying an unmet clinical need this survey provides direction for further research and education. A clinically useful decision tool combining recurrence risk and bleeding risk is clearly warranted. In addition, tools or training in SDM for physicians focusing on risk communication may be helpful to improve decision-making in clinical practice.

Addendum

M.A. de Winter, G.C.P. Remme, H.A.H. Kaasjager and M. Nijkeuter designed the study protocol and survey and distributed the survey. M.A. de Winter and G.C.P. Remme performed statistical analysis and drafted the manuscript. H.A.H. Kaasjager and M. Nijkeuter critically revised the manuscript. All authors were responsible for and approved of the final version of the manuscript.

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