DANISH MEDICAL JOURNAL

Original Article

Extended anticoagulation after venous thromboembolism

Rasmus Laursen, Hanne M. Søndergaard, Pia Børding & Dorthe Svenstrup

Department of Cardiology, Regional Hospital Viborg, Denmark

Dan Med J 2024;71(10):A01240063. doi: 10.61409/A01240063

ABSTRACT

INTRODUCTION. Venous thromboembolism (VTE) carries a high risk of recurrence, and this risk is strongly related to the nature of the index event. Thus, extended anticoagulation treatment is recommended for patients with a high recurrence risk and should be considered for patients with an intermediate risk. This study aimed to provide insight into the clinical practice of extended anticoagulation for VTE patients

METHODS. This was a retrospective study of VTE patients covering the period from January 2020 through June 2021. We categorised patients by their estimated risk of recurrence as low (< 3% per year), intermediate (3-8% per year) or high (> 8% per year). The decision to stop or extend anticoagulation was made in a multidisciplinary VTE clinic.

RESULTS. A total of 343 patients were included; 315 patients were eligible for analysis. The majority of patients (58.7%) had an intermediate recurrence risk. In total 80.3% received extended treatment. The use was highest (97.9%) among patients with a high recurrence risk, whereas 82.7% with an intermediate risk and 15.2% with a low risk received extended therapy. Non-vitamin K antagonist oral anticoagulants were preferred for extended therapy (82.2%), whereas 5.1% received warfarin and 12.6% low molecular weight heparin.

CONCLUSIONS. In this real-world clinic, the majority of VTE patients switched to extended treatment after initial standard anticoagulation. The role of patient and physician preference as determinants driving this decision should be investigated further.

FUNDING. This study received an unrestricted grant from Bayer, which had no involvement in the study design, data collection, analysis, or manuscript preparation.

TRIAL REGISTRATION. Not relevant.

Venous thromboembolism (VTE), clinically presenting as deep venous thrombosis (DVT) or pulmonary embolism (PE), is a frequent and serious medical condition associated with substantial morbidity and mortality [1]. Anticoagulation is the mainstay of VTE treatment and is recommended for at least three months in all patients with VTE as initial treatment [2].

The risk of recurrent VTE after discontinuation of treatment is related to the features of the index event. Thus, VTE patients with minor or non-existing risk factors for VTE have a higher recurrence risk than patients with major transient or reversible risk factors after discontinuation of anticoagulation treatment [3]. Consequently, the European Guidelines 2019 recommend discontinuing treatment after three months only for patients with VTE secondary to a major transient or reversible risk factor and an estimated low (< 3% per year) recurrence risk. Extension beyond the acute phase is recommended for patients with a high (> 8% per year) recurrence risk,

most commonly active cancer or previous VTE episodes, and it should be considered for patients with an intermediate (3-8% per year) risk [2].

Treatment options in Denmark consist of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin. NOACs have been shown to have similar risk reduction for recurrent VTE, but a lower risk of major bleeding complications [4]. Hence, NOACs are now recommended as first-line therapy by national and international guidelines for treating and preventing VTE [2].

The duration of treatment for venous thrombosis is decided by weighing the risks of recurrence against the risks of bleeding. In daily practice, shared decision-making and considering patients' preferences are essential when deciding whether to stop or continue anticoagulation.
Studies investigating physicians' considerations when choosing treatment durations found that the most important reasons for extended anticoagulation were patient preference, active malignancy, low estimated bleeding risk, history of VTE and haemodynamic instability during previous VTE [5]. The most prominent reasons for short-term anticoagulation treatment are frequent falls and previous bleeding on anticoagulation [5].

This study aimed to gain insight from a specialised multidisciplinary VTE clinic regarding the use of extended anticoagulation for VTE patients, hence contributing to enlightening the transition from guideline to clinical practice.

Methods

In this retrospective longitudinal study, we included all adult in- and outpatients (age ≥ 18 years) with a new diagnosis of VTE at Viborg Regional Hospital in Denmark from January 2020 through June 2021. Data were systematically collected from electronic medical records.

All patients with PE were categorised as "pulmonary embolism", regardless of any concomitant DVT. Patients were excluded from the study if they had thrombosis in other sites, such as upper extremity DVT or another indication for long-term oral anticoagulant treatment, typically atrial fibrillation.

Patients were followed in a structured, multidisciplinary VTE clinic focused on patient involvement, education and adequate anticoagulation and compliance. The clinic is staffed by nurses and cardiologists with special education in anticoagulation and VTE.

Anticoagulation with a NOAC was recommended over warfarin for VTE treatment, and apixaban and rivaroxaban were preferred over dabigatran and edoxaban to avoid an initial phase of parenteral anticoagulation. For patients with VTE and malignancy, either low molecular weight (LMW) heparin or a NOAC was used, provided there were no contraindications to the chosen agent. For extended treatment, the same type of anticoagulant used for initial treatment was usually used. Low-dose rivaroxaban was defined as 10 mg once daily and apixaban as 2.5 mg twice daily.

For patients nearing completion of the initial phase of anticoagulant treatment, we assessed the risk of recurrence and whether anticoagulation should be discontinued, consistent with the guidelines of the European Society of Cardiology [2]. We obtained details regarding the VTE event and risk factors to assess risk. The patients were categorised according to the estimated risk of recurrence as the following:

Low (< 3% per year)

Intermediate (3-8% per year)

High (> 8% per year).

The decision to stop or extend treatment after the initial phase of anticoagulation was made with the patients involved in the risk–benefit analysis through shared decision-making and consideration of patient preference. Furthermore, the risk of bleeding was also taken into account.

Trial registration: not relevant.

Results

A total of 343 patients with VTE were seen in the study period. Two patients were excluded due to upper extremity DVT, and 18 patients due to atrial fibrillation. Eight patients died during the follow-up period, leaving a total of 315 patients for analysis. None of these patients were lost to follow-up.

Patient characteristics are presented in **Table 1**. Overall, 52.4% were male and the median age was 68 years. The thrombotic event was isolated DVT without confirmed PE in 168 (53.3%) cases and PE with or without DVT in 147 (46.7%) cases.

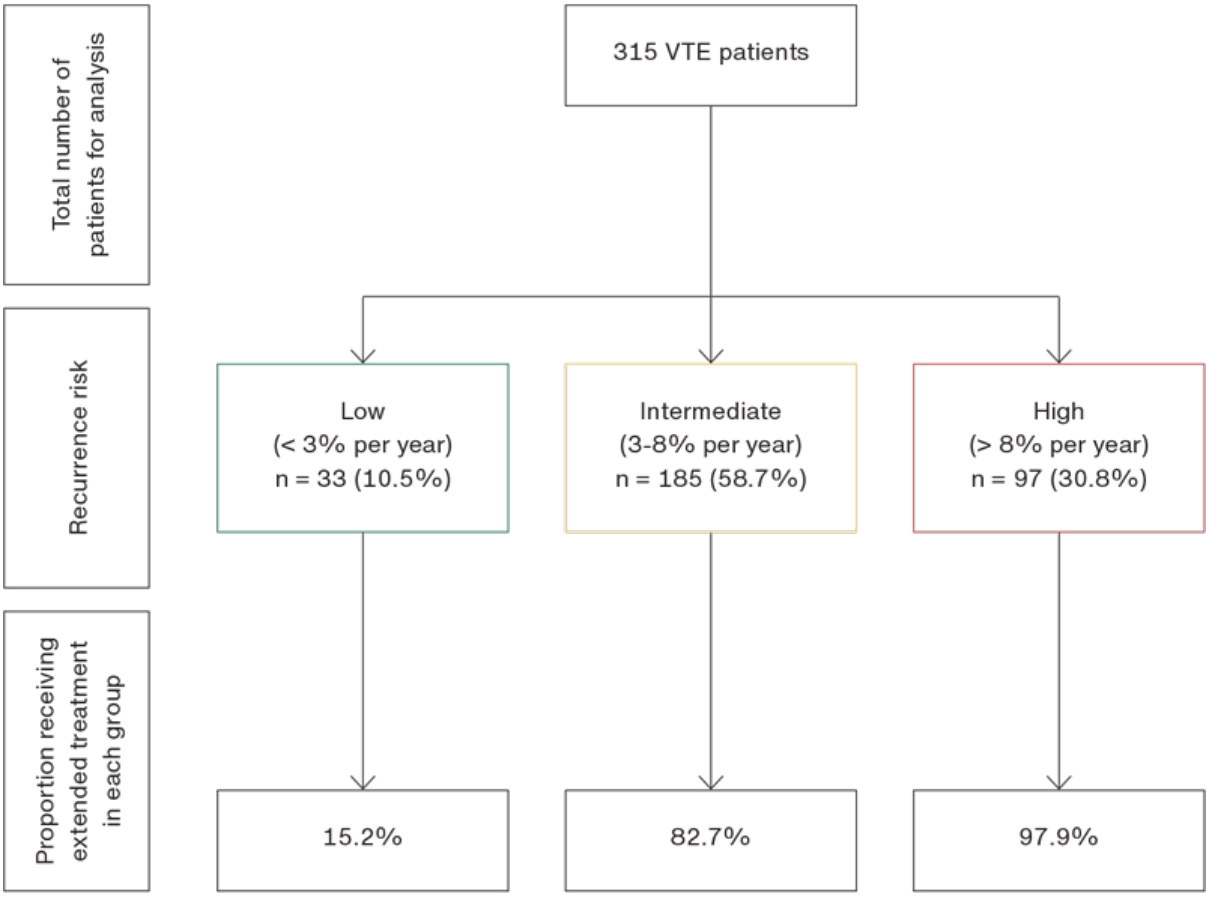
TABLE 1 Patient characteristics (N = 315).

Age, median (IQR), yrs	68 (57-76)
Female sex, n (%)	150 (47.6)
Weight, median (IQR), kg	82 (71-95)
BMI, median (IQR), kg/m²	27 (25-31)
Haemoglobin concentration, median (IQR), mmol/l	8.2 (7.5-9.0)
Creatinine concentration, median (IQR), µmol/l	72 (62-85)
eGFR, median (IQR), ml/min.	86 (72-90)
VTE location, n (%)	
Distal DVT	40 (12.7)
Proximal DVT	128 (40.6)
PE	147 (46.7)

DVT = deep venous thrombosis; eGFR = estimated glomerular filtration rate; IQR = interquartile range; PE = pulmonary embolism; VTE = venous thromboembolism.

Figure 1 presents the categorisation of patients by recurrence risk and the proportion of patients receiving extended treatment in each category. Most patients (58.7%) had an intermediate recurrence risk, whereas 30.8% of the patients had a high risk and 10.5% had a low risk of recurrence.

FIGURE 1 Proportion of patients receiving extended treatment according to recurrence risk.



VTE = venous thromboembolism.

A total of 253 patients (80.3%) received extended treatment; the use of extended anticoagulation treatment was highest (97.9%) among patients with a high recurrence risk, whereas 82.7% of the patients with an intermediate risk and 15.2% of those with a low risk received extended anticoagulation.

NOACs were preferred for extended treatment in 208 (82.2%) patients, while 32 (12.6%) patients received LMW heparin and 13 (5.1%) warfarin.

Among the patients given extended treatment with a NOAC, 190 (91.3%) patients received a low dose, whereas 18 (8.76%) patients were given the full dose.

Discussion

In this real-world clinical setting with VTE patients handled in a structured, multidisciplinary clinic, most patients received extended VTE prophylaxis after the initial period with standard anticoagulation.

International guidelines recommend a short anticoagulation treatment period in patients with an estimated low recurrence risk (< 3% per year). All other patients should be considered for long-term anticoagulation, and hence this study indicates that guidelines have been highly adopted into practice.

Thus, in clinical practice, an important decision must be made after standard anticoagulation treatment to either

discontinue anticoagulation or to continue treatment indefinitely. Patients should be involved in this risk-benefit analysis of extended anticoagulation through shared decision-making, and patient preference is among the key factors considered when deciding on extended treatment.

For patients with first VTE secondary to a major transient or reversible risk factor, discontinuation of oral anticoagulation is recommended after three months. However, in this study, 15% (five) of the patients in the low-recurrence risk group received extended anticoagulation associated with a risk of bleeding. Extended treatment was decided in these patients because the index event was due to life-threatening PE – as recommended in Danish guidelines [6]. Hence, the vast majority of patients with a low recurrence risk were prevented from shared decision-making and treatment.

Almost two-thirds of the included patients were at intermediate recurrence risk for VTE. The clinical decision to discontinue or continue anticoagulation in this group is challenging and relies heavily on patient involvement through shared decision-making, hence individualising the decision.

An increase in the use of long-term anticoagulation during the past years seems ongoing in Denmark. A Danish study investigating the use of long-term anticoagulation from 2017-2018 in 6,030 patients with VTE showed that only 2.5% received extended treatment at that time [7].

Our study shows that a high proportion (80%) of the entire cohort received long-term anticoagulation treatment, with the highest proportion (almost 98%) being in the high-recurrence risk group. Hence, the element of individualised treatment plans can be questioned. The data do not disclose the specific reasons for deciding long-term treatment or whether the decision was driven by physician or patient preferences.

Evidence on the determinants driving patient preferences is scarce. An American study examining 519 self-reported concerns among VTE patients found that the patients were more concerned about recurring VTE than major bleeding [8]. Thus, long-term anticoagulation might be more compelling for the patients due to fear of recurrence.

Studies investigating the physician's perspective are not well elucidated in current literature. Further studies are needed to reveal if the high proportion of patients receiving extended treatment is due to patient fear of recurrent events or the physician's assessment that the risk of recurrent thromboembolism outweighs the risk of bleeding.

Limitations

Our study had some limitations. First, it is a single-centre retrospective study with a relatively small patient number and may be prone to bias. Second, the present study cohort included only Caucasians, and our findings cannot be generalised uncritically to other clinical settings or races.

Furthermore, the study data did not include more data regarding the decision process from both patient and physician perspectives.

Conclusions

The present study showed that extended anticoagulation is highly adapted, with most VTE patients being prescribed prophylaxis in a multidisciplinary VTE clinic. A high proportion of patients receiving extended treatment, particularly patients at intermediate risk of recurrence, was shown. Patient preference is believed to play a key role in decision-making; an important factor for medical adherence. More information regarding both patient and physician motives in choosing extended anticoagulation treatment is needed, along with multicentred studies to support these findings in a nationwide setting.

Correspondence *Rasmus Laursen*. E-mail: rblaursen@hotmail.dk

Accepted 28 June 2024

Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2024;71(10):A01240063

doi 10.61409/A01240063

REFERENCES

1. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(23 suppl 1):I4-I8. https://doi.org/10.1161/01.cir.0000078468.11849.66
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543-603. https://doi.org/10.1093/eurheartj/ehz405
3. Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ. 2019;366:l4363. https://doi.org/10.1136/bmj.l4363
4. Castellucci LA, Cameron C, Le Gal G, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ. 2013;347:f5133. https://doi.org/10.1136/bmj.f5133
5. de Winter MA, Remme GCP, Kaasjager K, et al.. Short-term versus extended anticoagulant treatment for unprovoked venous thromboembolism: a survey on guideline adherence and physicians' considerations. Thromb Res. 2019;183:49-55. https://doi.org/10.1016/j.thromres.2019.10.003
6. Bonde AN, Andersen A, Schultz J, et al. 12. Lungeemboli og dyb venetrombose. Dansk Cardiologisk Selskab, 2023. www.cardio.dk/lungeemboli (17 Apr 2024)
7. Albertsen IE, Jensen M, Abdelgawwad K, et al. Characteristics of patients receiving extended treatment after incident venous thromboembolism. Basic Clin Pharmacol Toxicol. 2021;129(4):332-42. https://doi.org/10.1111/bcpt.13637
8. Lutsey PL, Horvath KJ, Fullam L et al. Anticoagulant preferences and concerns among venous thromboembolism patients. Thromb Haemost. 2018;118(3):553-61. https://doi.org/10.1055/s-0038-1625985