11-1-2022

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ORIGINAL RESEARCH

Length of Anticoagulation in Provoked Venous Thromboembolism: A Multicenter Study of How Real-World Practice Mirrors Guideline Recommendations

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BACKGROUND: For more than a decade, guidelines have recommended a limited 3 months of anticoagulation for the treatment of provoked venous thromboembolism (VTE). How closely real-world practice follows guideline recommendations is not well described.

METHODS AND RESULTS: In our multicenter, retrospective cohort study, we evaluated trends in anticoagulation duration for patients enrolled in the MAQI[2] (Michigan Anticoagulation Quality Improvement Initiative) registry who were receiving anticoagulation for a provoked VTE. The MAQI[2] registry comprises 6 centers in Michigan that manage patients' long-term anticoagulation. We identified 474 patients on warfarin and 302 patients on direct oral anticoagulants who were receiving anticoagulation for a primary indication of provoked VTE between 2008 and 2020. Using a predefined threshold of 120 days (3 months plus a buffer period), predictors of extended anticoagulant use were identified using multivariable logistic regression. Most patients received >120 days of anticoagulation, regardless of which medication was used. The median (25th–75th percentile) length of treatment for patients taking warfarin was 142 (91–234) days and for direct oral anticoagulants was 180 (101–360) days. Recurrent VTE (odds ratio [OR], 2.75 [95% CI, 1.67–4.53]), history of myocardial infarction (OR, 3.92 [95% CI, 1.32–11.7]), and direct oral anticoagulant rather than warfarin use (OR, 2.22 [95% CI, 1.59–3.08]) were independently associated with prolonged anticoagulation.

CONCLUSIONS: In our cohort of patients with provoked VTE, most patients received anticoagulation for longer than the guideline-recommended 3 months. This demonstrates a potential opportunity to improve care delivery and reduce anticoagulant-associated bleeding risk.

Key Words: anticoagulation ■ direct oral anticoagulant ■ venous thromboembolism

Anticoagulation is the cornerstone of venous thromboembolism (VTE) management, aimed at preventing thrombus propagation, embolization, and recurrence, but balanced against risk of bleeding.[1] For patients with provoked VTE, referring to VTE after a transient trigger, the American College of Chest Physicians (ACCP) guidelines have recommended 3 months of anticoagulation since at least 2008.[2–5] In patients with provoked VTE and without any other indication for anticoagulation, the ACCP recommends discontinuing anticoagulation at this 3-month mark. Although these guidelines have been in place for over a decade, it is unclear if they are followed in real-world practice.

In the past decade, direct oral anticoagulants (DOACs) have shifted anticoagulation administration practices.[6] The favorable safety and efficacy profiles

CLINICAL PERSPECTIVE

What Is New?

- This study examines anticoagulation practices in a real-world population of patients with provoked venous thromboembolism, and finds that most patients do not receive the recommended 3 months of anticoagulation recommended by the American College of Chest Physicians.
- This study identifies 3 variables associated with prolonged anticoagulation: direct oral anticoagulant use, history of prior venous thromboembolism, and history of myocardial infarction.
- This study highlights a group of patients who are at risk for prolonged anticoagulation and might benefit from early identification and intervention.

What Are the Clinical Implications?

- Future research is required to evaluate this relationship in the evolving anticoagulation landscape.
- Providers should be aware of the risk for these patients when prescribing and managing their anticoagulation.

Nonstandard Abbreviations and Acronyms

ACCP	American College of Chest Physicians
AMPLIFY-EXT	Apixaban After the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis With First-Line Therapy-Extended Treatment
ASH	American Society of Hematology
DOAC	direct oral anticoagulant
EINSTEIN CHOICE	Reduced-Dosed Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism
MAQI^2	Michigan Anticoagulation Quality Improvement Initiative

of DOACs have raised the possibility of providing a longer duration of anticoagulation for VTE. The 2013 AMPLIFY-EXT (Apixaban After the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis With First-Line Therapy-Extended Treatment) study evaluated the use of apixaban, and the 2017 EINSTEIN CHOICE (Reduced-Dosed Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism) study evaluated the use of rivaroxaban for extended duration of anticoagulation in patients with provoked and unprovoked VTE. Both studies found a reduced risk of recurrent VTE in the group taking DOACs compared with the control group, without substantial increase in bleeding episodes.[7,8] The low bleeding rates reported in studies of patients receiving anticoagulation beyond the 3- to 6-month window may influence how clinicians think about the risk–benefit of anticoagulation at the 3-month mark. Although fewer than 10% of patients in the AMPLIFY-EXT had a provoked VTE, clinicians may apply the study findings to their patients with a provoked VTE, despite the updated ACCP guidelines released in August 2021 that continue to recommend only 3 months of anticoagulation for patients with provoked VTE, regardless of which anticoagulation agent is prescribed.[5]

The primary aim of this study was to measure anticoagulation duration in an unselected, real-world population of patients and compare current clinical practice to long-standing guideline recommendations for patients with provoked VTE. The secondary aims were to compare duration of anticoagulation between patients taking warfarin and DOACs, and to identify variables that predict anticoagulant duration in patients with provoked VTE taking warfarin compared with DOACs.

METHODS

The data from this study are available from the corresponding author upon reasonable request.

Study Population

This is a multicenter, retrospective cohort study. Patients were identified from the MAQI^2 (Michigan Anticoagulation Quality Improvement Initiative) registry. The MAQI^2 registry draws from 6 hospital and group practices in Michigan offering long-term management of patients with chronic anticoagulation.[9] MAQI^2 is funded by Blue Cross Blue Shield of Michigan/Blue Care Network. The goal of this collaborative registry is to improve patient outcomes by identifying patterns and participate in quality improvement related to anticoagulation care delivery. MAQI^2 data collection is performed by trained data abstractors using predefined electronic data forms with random audits. MAQI^2 has been approved by the institutional review board at the coordinating center (University of Michigan) and each participating center, with a waiver of informed consent for all sites.

Patients included were those initiating warfarin or DOAC therapy for a provoked VTE, defined as a deep

vein thrombosis (DVT), pulmonary embolism, or both after transient risk factors: surgery, casting/immobilization, childbirth, or oral contraceptive use. Patients with an anticoagulant indication other than VTE and those with upper extremity DVT were excluded, given the differences in prevalence, cause, and typical clinical course.[10] Sites were included if they had at least 10 patients being followed in the MAQI[2] registry to minimize variation in anticoagulation practices arising from centers with a low volume of patients requiring chronic anticoagulation management.

Study Outcomes

Patient characteristics and comorbidities including age, sex, race, insurance status, type of VTE, history of prior VTE, history of cancer, concurrent antiplatelet use, bleeding within 30 days of VTE, and transient provoking factors for the VTE were obtained via manual chart review. The date of anticoagulation initiation and discontinuation was identified from clinic notes. Duration of treatment was categorized as <80, 80 to 120, or >120 days. Appropriate length of treatment was defined as 80 to 120 days to account for variable clinic visit scheduling. Patients were grouped based on whether the patient was prescribed warfarin or DOACs. Anticoagulation duration was evaluated over the entire study period (2008–2020) and compared between 2008 and 2014 and between 2015 and 2020, because DOACs were introduced to the MAQI[2] registry in 2015.

Statistical Analysis

Statistical methods were used to compare the group of patients taking warfarin compared with DOACs. Baseline characteristics were compared using the t test, Fisher exact test, and χ^2 test, as appropriate. Treatment length was analyzed using a median 2-sample test and compared with the treatment guidelines for both groups. Prevalence of prolonged treatment for patients with their first VTE and for recurrent VTE were analyzed using the χ^2 test. Multivariable logistic regression, adjusted for all variables (age, sex, DOAC versus warfarin usage, chronic liver disease, history of myocardial infarction, history of VTE, history of stroke or transient ischemic attack, history of gastrointestinal bleeding, history of bleeding within 30 days of VTE, history of cancer, history of CHF, and not taking antiplatelets), was used to analyze characteristics that were associated with >120 days anticoagulation and calculate odds ratio (OR) and 95% CI. Using Kaplan-Meier time-to-event analysis, survival curves depicting the number of patients on anticoagulation versus time were created for patients treated with warfarin and DOAC. Patients were followed until discontinuation of anticoagulation, death, or the end of the study period (December 2020). A P value of <0.05 was set as the threshold for statistical significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

Patient Characteristics and Total Study Rate of Extended Anticoagulation

We identified a total of 776 patients from 4 clinical sites who met inclusion criteria and began anticoagulation therapy between 2008 and 2020 (Table 1). Four hundred eighty-two (62.1%) patients received anticoagulation for >120 days (Table 2). Of the 776 patients, 474 patients were on warfarin, and 302 patients were on DOACs, the majority of which were apixaban (153, 50.7%) or rivaroxaban (147, 48.7%). Age, race, and insurance status were similar between the warfarin- and DOAC-treated groups, with the exception that there was a higher proportion of patients with Medicaid taking DOACs compared with warfarin. A larger percentage of patients treated with DOACs were women compared with patients treated with warfarin (70.2% versus 55.5%, $P<0.001$). DVT was the primary indication for anticoagulation in 363 (76.6%) patients on warfarin and 172 (57.0%) patients on DOACs ($P<0.001$). Pulmonary embolism, with or without concurrent DVT, was the primary indication in 111 (23.4%) patients on warfarin and 130 (43.1%) patients on DOACs. Of the patients on DOACs, 16 (5.3%) were transitioned to a reduced DOAC dose at a point after initiating anticoagulation, 12 of which (4.0%) were after 3 months of anticoagulation (Table 1). About comorbidities, 88 (18.6%) patients on warfarin and 15 (5.6%) patients on DOACs had a history of prior VTE ($P<0.001$), and 25 (5.3%) patients on warfarin and 36 (11.9%) patients on DOACs had bleeding within 30 days of VTE ($P<0.001$). Other comorbidities were not statistically different between groups (Table 1). Surgery was the provoking condition in 394 (83.1%) patients on warfarin and 208 (68.9%) patients on DOACs ($P<0.001$), and oral contraceptives were the provoking conditions in 44 (9.3%) patients on warfarin and 59 (19.5%) patients on DOACs ($P<0.001$). Casting/lower extremity immobilization and childbirth were not statistically different between groups.

Anticoagulation Duration Based on Anticoagulant Agent Subgroup

The median (25th–75th percentile) length of treatment with warfarin and DOACs was 142 (91–234) days and 180 (101–360) days, respectively ($P<0.001$) (Table 2). There were 112 (23.6%) patients on warfarin and 71 (23.5%) on DOACs who received 80 to 120 days of treatment ($P=0.97$). Two hundred sixty-seven

Table 1. Patient Characteristics

Characteristic	Warfarin, N=474	DOAC, N=302	P value
Age, y, mean±SD	58.4±16.8	57.7±16.9	0.58
Women, n (%)	263 (55.5)	212 (70.2)	<0.001
Race			
White, n (%)	337 (71.1)	221 (73.2)	0.18
Black, n (%)	82 (17.3)	58 (19.2)	
Other, n (%)	55 (11.6)	23 (7.6)	
Insurance			
Medicare, n (%)	178 (37.6)	97 (32.1)	0.12
Medicaid, n (%)	17 (3.6)	29 (9.6)	<0.001
Private insurance, n (%)	271 (57.2)	185 (61.3)	0.26
Other, n (%)	8 (1.7)	8 (2.7)	0.36
Indication			
DVT only, n (%)	363 (76.6)	172 (57.0)	<0.001
PE with or without DVT, n (%)	111 (23.4)	130 (43.1)	<0.001
Change to reduced dose at any time, n (%)	…	16 (5.3)	…
Change to reduced dose after 3 mo, n (%)	…	12 (4.0)	…
Recurrent VTE, n (%)	88 (18.6)	17 (5.6)	<0.001
History of cancer, n (%)	95 (20.0)	61 (20.2)	0.96
History of chronic heart failure	31 (6.5)	12 (4.0)	0.13
History of stroke/TIA	33 (7.0)	17 (5.6)	0.46
History of gastrointestinal bleed	26 (5.5)	16 (5.3)	0.91
History of myocardial infarction	17 (3.6)	14 (4.6)	0.47
Chronic liver disease	14 (3.0)	11 (3.6)	0.60
History of renal disease, n (%)	46 (9.7)	23 (7.6)	0.32
NSAID use, n (%)	32 (6.8)	12 (4)	0.10
Concurrent antiplatelet, n (%)	141 (29.8)	66 (21.9)	0.015
Recent bleeding, within 30 d of VTE, n (%)	25 (5.3)	36 (11.9)	<0.001
Provoking conditions, n (%)			
Surgery	394 (83.1)	208 (68.9)	<0.001
Casting/immobilization	99 (20.9)	83 (27.5)	0.034
Childbirth	8 (1.7)	4 (1.3)	0.69
Oral contraceptives	44 (9.3)	59 (19.5)	<0.001

Data were obtained using a *t* test for means and Fischer exact test and χ² test for percentages. Other race includes patient races other than Black or White as well as patients with multiple races selected or no race data available. DOAC indicates direct oral anticoagulant; DVT, deep vein thrombosis; NSAID, nonsteroidal anti-inflammatory drug; PE, pulmonary embolism; TIA, transient ischemic attack; and VTE, venous thromboembolism.

(56.3%) patients on warfarin and 215 (71.2%) patients on DOACs received >120 days of anticoagulation (*P*<0.001) (Figure 1). There were 95 (20.4%) patients on warfarin and 16 (5.3%) patients on DOACs who received <80 days of anticoagulation (*P*<0.001). When considering anticoagulation patterns before DOACs were introduced in 2015, the median (interquartile range) length of treatment was 137 (92–220) days. Of these, there were 32 patients (25.6%) who received 80 to 120 days of treatment (*P*=0.36), 132 patients (53.7%) who received >120 days of treatment (*P*=0.001), and 51 patients (20.7%) who received <80 days of treatment (*P*<0.001) (Table 3).

Predictors of Prolonged Anticoagulation Based on Anticoagulant Agent Subgroup

Independent predictors of prolonged anticoagulation included recurrent VTE (OR, 2.71 [95% CI, 1.64–4.47]), history of myocardial infarction (OR, 3.96 [95% CI, 1.32–11.9]), and DOAC rather than warfarin use (OR, 2.21 [95% CI, 1.59–3.08]) (Figure 2). No variables were independently associated with a statistically significant decrease in prolonged anticoagulation.

DISCUSSION

In this multicenter study, most patients received longer than the recommended 3-month anticoagulation for provoked VTE, regardless of which agent was used. Patients on DOACs were more likely than those on warfarin to have treatment >120 days. Patients on warfarin were more likely than those on DOACs to receive <80 days of treatment. Independent predictors of prolonged anticoagulation therapy included recurrent VTE, history of myocardial infarction, and DOAC rather than warfarin use.

VTE management has changed markedly over the past decade. A 2010 metanalysis found the case-fatality rate of recurrent VTE was equal to the case-fatality rate of major bleeding events during the first 3 months of anticoagulation in patients with VTE.[11] Older data found that after the first 3 months, a higher proportion of patients died from bleeding than VTE, although subsequent research has found the 3-month case-fatality rate of major bleeding to be lower in patients receiving DOACs.[11,12] Therefore, patients with a relatively lower risk of recurrence after the initial 3-month period (ie, those with reversible provoking risk factors) were generally recommended to stop anticoagulation therapy after the initial 3-month course. Newer trials of extended therapy with DOACs describe a decreased risk of VTE without increased bleeding risk even beyond the initial 3-month period.[7,8] These new trials could explain why the majority (215, 71.2%) of patients in our study received longer than guideline-recommended therapy, or why 12 (4.0%) were changed to a reduced dose at 3 months but continued anticoagulation. However, the shift in the efficacy-risk balance was not immediately endorsed by the 2016 ACCP guidelines

Table 2. Length of Treatment for Provoked VTE From 2008 to 2020

Treatment length	Warfarin, N=474	DOAC, N=302	*P* value
Length of treatment, d, median (25th–75th percentile)	142 (91–234)	180 (101–360)	0.001
Guideline appropriate length of treatment, ≥80 to ≤120 d, n (%)	112 (23.6)	71 (23.5)	0.97
Treatment >120 d, n (%)	267 (56.3)	215 (71.2)	<0.001
Treatment <80 d, n (%)	95 (20.4)	16 (5.3)	<0.001

Data were obtained using a median 2-sample test for length of treatment and χ2 test for the rest. DOAC indicates direct oral anticoagulant; and IQR, interquartile range.

or the 2021 update, which continue to recommend a short 3-month course of anticoagulation for patients with reversible provoking risk factors without dose reduction.[2] In contrast, the 2020 American Society of Hematology (ASH) guidelines suggest at least 3 to 6 months of anticoagulation after VTE, rather than recommending prompt discontinuation of anticoagulation at 3 months.[13] Our study demonstrates that between 2008 and 2020 (before publication of the most recent ASH guidelines), most patients received more than the 3 months of anticoagulation therapy recommended by numerous ACCP guidelines. Future studies will be required to determine how patients are impacted by ever-increasing data and the new ASH guidelines. Patients might be at risk for further prolonged anticoagulation, but it could also be that real-world practice will be unchanged, and the guidelines are catching up to what

is being done in the clinical setting. Additionally, our study population is limited to 4 sites in Michigan, so it could also be that national anticoagulation patterns differ. Further study is required to make more definitive conclusions about anticoagulation practices on a larger scale.

The appropriate anticoagulation duration for patients with recurrent provoked VTE is less well defined. The ACCP guidelines make no specific distinction between a single episode of provoked VTE and several episodes of provoked VTE.[2–4] Unprovoked patients are classified as isolated or recurrent and then stratified by bleeding risk, with those of high bleeding risk receiving 3 months of anticoagulation and those of low and moderate bleeding risk receiving extended anticoagulation.[2–4] The ASH guidelines stratify patients by whether the patient's prior VTE was in the setting of a
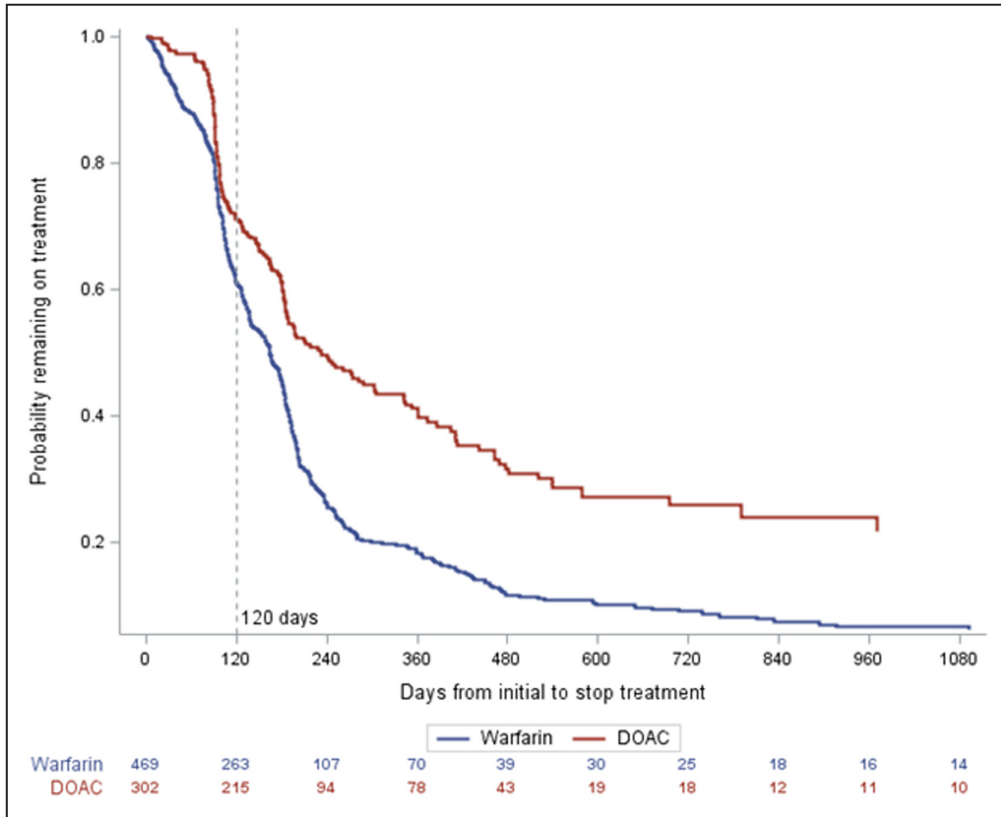

Figure 1. Length of anticoagulation duration by anticoagulant medication.
DOAC indicates direct oral anticoagulant.

Table 3. Length of Treatment in Provoked VTE Comparing 2008 to 2014 and 2015 to 2020

Treatment length	Warfarin before 2015, N=246	Warfarin after 2015 and DOAC, N=530	P value
Length of treatment, d, median (25th–75th percentile)	137 (92–220)	180 (96–272)	0.001
Guideline-appropriate length of treatment, ≥80 to ≤120 d, n (%)	63 (25.6)	120 (22.6)	0.36
Treatment >120 d, n (%)	132 (53.7)	350 (66)	0.001
Treatment <80 d, n (%)	51 (20.7)	60 (11.3)	<0.001

Data were obtained using a median 2-sample test for length of treatment and χ^2 test for the rest. DOAC indicates direct oral anticoagulant; and IQR, interquartile range.

transient risk factor, recommending 3 to 6 months in duration of anticoagulation if the prior VTE was provoked by a transient risk factor and indefinite anticoagulation if the prior VTE was without a transient risk factor.[13] In our study, 105 patients had recurrent VTE. The lack of specific guidance from the ACCP guidelines about recurrent provoked VTE could encourage providers to manage all patients with recurrent VTE by the unprovoked recurrent VTE guidelines. Alternatively, prolonged anticoagulation could reflect clinician-perceived increased risk of thrombosis, despite the ACCP guidelines recommending the same duration

of anticoagulation if the second VTE is provoked. Regardless, most of the patients in our study did not have recurrent VTE; however, most patients in our study received prolonged anticoagulation. It could also reflect gray areas such as a residual swollen leg, evidence of chronic DVT on ultrasound, and persistently positive D-dimer after 3 months of anticoagulation. The guidelines are unclear about the optimal management of such challenging clinical scenarios. Additional randomized controlled trials are needed to determine appropriate anticoagulation practices in these patient populations. Future research will also be needed to
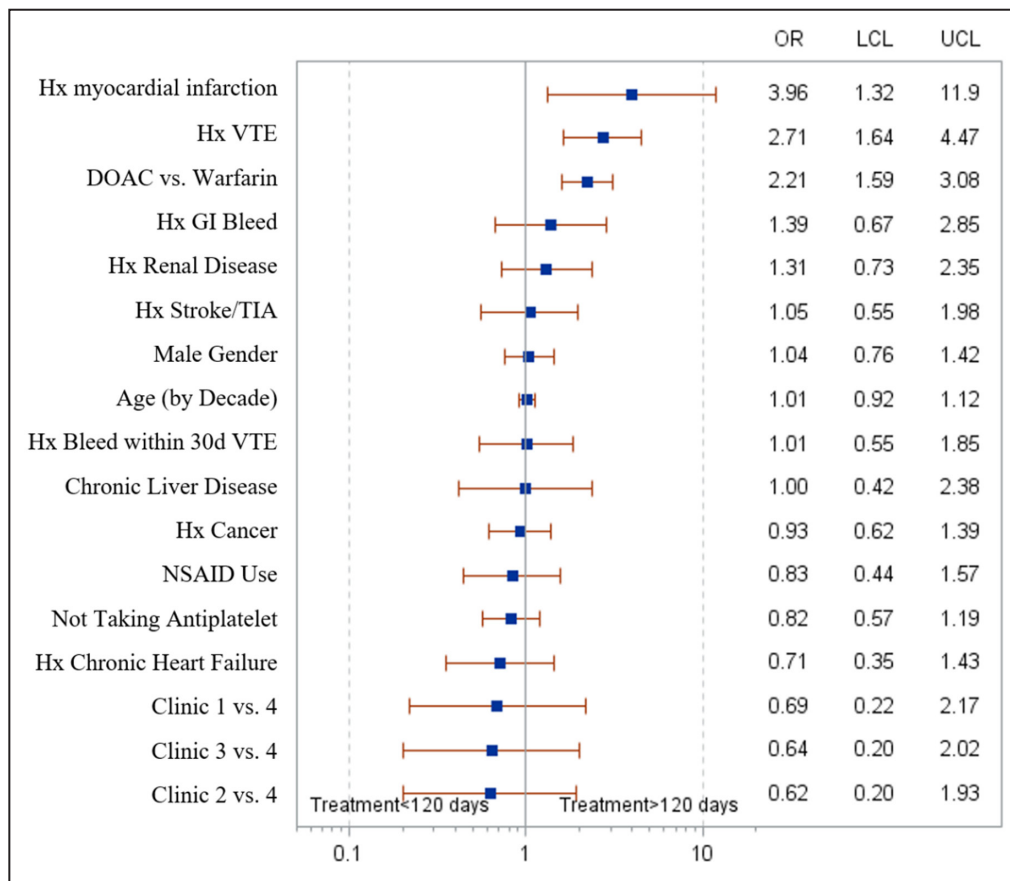

Figure 2. Predictors of anticoagulation for >120 days, odds ratio, and 95% CI.
DOAC indicates direct oral anticoagulant; GI, gastrointestinal; Hx, history of; LCL, lower 95% confidence limit; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; TIA, transient ischemic attack; UCL, upper 95% confidence limit; and VTE, venous thromboembolism.

evaluate anticoagulation in patients with recurrent VTE, particularly given the differing metrics used to guide the ACCP and ASH recommendations.

Another fundamental change in VTE management relates to the availability of multiple oral anticoagulant medications. For decades, warfarin was the only available oral anticoagulant.[14] The introduction of DOACs in 2010 led to many studies defining the appropriate use of these attractive warfarin alternatives. Across numerous clinical trials, DOACs were repeatedly found to be safe and effective in treating VTE in a broad spectrum of patients, including those with provoked VTE.[14,15] In particular, the EINSTEIN CHOICE study included 1970 patients with provoking VTE risk factors and still demonstrated benefit with 1 year of rivaroxaban therapy.[7] The risk–benefit profile of other DOACs have not been evaluated specifically within the context of provoked VTE. The abundance of DOAC research with generally positive findings may lead clinicians to overprescribe extended anticoagulation in patients in which it has not been thoroughly evaluated. In our study, patients taking DOACs were more likely to receive anticoagulation for longer than the 3 months recommended by ACCP guidelines than those taking warfarin. Additionally, when analyzing the average length of treatment before and after DOAC introduction, the average length of treatment after DOAC introduction was longer than for the entire period that included before and after DOAC, and the percentage of patients who received >120 days anticoagulation also increased from the cumulative percentages. These prolonged anticoagulation patterns may put patients at risk of bleeding, especially if they continue using DOACs indefinitely. Additional data about the safety of long-term anticoagulation with different DOACs for patients with provoked VTE could be useful to evaluate this risk.

Limitations

There are several limitations of our study. Data were collected from 2008 to 2020, and as previously discussed, treatment recommendations have changed substantially throughout this time. However, most guidelines from 2008 to 2020 recommended 3-month anticoagulation for provoked VTE, so our observation that most patients received prolonged anticoagulation remains. A second limitation of our study is that only a limited number of manually abstracted variables were available for evaluation. Therefore, as with all retrospective studies, unmeasured confounding is possible, and our findings are limited to that of association, not causation. A third limitation of our study is that it is possible patients developed additional indications for anticoagulation after initiating anticoagulation for their provoked VTE, such as a second, unprovoked VTE or atrial fibrillation. Our data abstractors are trained to screen for new anticoagulation indications and add these to patients' anticoagulation indication. It is unlikely but not impossible that an indication could have been mistakenly omitted if it developed after the patient began anticoagulation. A fourth limitation of our study is that all patients had insurance, and insurance could play a role in determining anticoagulation duration. Presumably, those who are under- or uninsured would be more likely to receive a shorter duration of anticoagulation to minimize unnecessary financial burden, so our findings about prolonged anticoagulation might only apply to those with insurance. A final limitation is that variables that could be clinically significant for individual patients might not be statistically significant in our data. Our primary aim was to evaluate general practices, not the anticoagulation choices made for individuals who might benefit from specifically altered anticoagulation regimens. We acknowledge this unavoidable limitation of statistical analysis.

CONCLUSIONS

Most patients in our real-world multicenter cohort study with provoked VTE received longer duration of anticoagulation therapy than recommended by ACCP guidelines. Patients taking DOACs with a history of recurrent VTE and a history of myocardial infarction were more likely to received longer treatment than what was guideline recommended. This study identifies a group of patients with provoked VTE who were more likely to receive prolonged anticoagulation and may be at increased risk of anticoagulant-related bleeding complications. Further study will be necessary to investigate how the duration of anticoagulation therapy changes with evolving guidelines and increasingly widespread DOAC use.

REFERENCES

1. Caprini JA. Risk assessment as a guide for the prevention of the many faces of venous thromboembolism. *Am J Surg*. 2010;199:S3–S10. doi: 10.1016/j.amjsurg.2009.10.006

2. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315–352. doi: 10.1016/j.chest.2015.11.026

3. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e419S–e496S. doi: 10.1378/chest.11-2301

4. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133:454S–545S. https://dx.doi.org/10.1378/chest.08-0658

5. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, Huisman MV, Kearon C, King CS, Knighton AJ, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest*. 2021;160:e545–e608. doi: 10.1016/j.chest.2021.07.055

6. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128:1300–1305.e2. doi: 10.1016/j.amjmed.2015.05.044

7. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376:1211–1222. doi: 10.1056/NEJMoa1700518

8. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368:699–708. doi: 10.1056/NEJMoa1207541

9. Barnes GD, Kaatz S, Golgotiu V, Gu X, Leidal A, Kobeissy A, Haymart B, Kline-Rogers E, Kozlowski J, Almany S, et al. Use of warfarin for venous thromboembolism prophylaxis following knee and hip arthroplasty: results of the Michigan Anticoagulation Quality Improvement Initiative (MAQI2). *J Thromb Thrombolysis*. 2013;35:10–14. doi: 10.1007/s11239-012-0766-y

10. Ageno W, Haas S, Weitz JI, Goldhaber SZ, Turpie AGG, Goto S, Angchaisuksiri P, Dalsgaard Nielsen J, Kayani G, Farjat AE, et al. Upper extremity DVT versus lower extremity DVT: perspectives from the GARFIELD-VTE registry. *Thromb Haemost*. 2019;119:1365–1372. doi: 10.1055/s-0039-1688828

11. Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med*. 2010;152:578–589. doi: 10.7326/0003-4819-152-9-201005040-00008

12. Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2015;13:2012–2020. doi: 10.1111/jth.13139

13. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4:4693–4738. doi: 10.1182/bloodadvances.2020001830

14. Allahwerdy F, Pan S, Feehan M, Jones AE, Munger MA, Witt DM. A descriptive study of antithrombotic medication patterns in adult patients with recent venous thromboembolism. *Pharm Pract (Granada)*. 2019;17:1539. doi: 10.18549/PharmPract.2019.3.1539

15. Van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124:1968–1975. doi: 10.1182/blood-2014-04-571232