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ORIGINAL ARTICLE

Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA)

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Summary. *Background:* In patients receiving oral anticoagulation, improved control can reduce adverse outcomes such as stroke and major hemorrhage. However, little is known about patient-level predictors of anticoagulation control. *Objectives:* To identify patient-level predictors of oral anticoagulation control in the outpatient setting. *Patients/Methods:* We studied 124 619 patients who received oral anticoagulation from the Veterans Health Administration from October 2006 to September 2008. The outcome was anticoagulation control, summarized using percentage of time in therapeutic International Normalized Ratio range (TTR). Data were divided into inception (first 6 months of therapy; 39 447 patients) and experienced (any time thereafter; 104 505 patients). Patient-level predictors of TTR were examined by multivariable regression. *Results:* Mean TTRs were 48% for inception management and 61% for experienced management. During inception, important predictors of TTR included hospitalizations (the expected TTR was 7.3% lower for those with two or more hospitalizations than for the non-hospitalized), receipt of more medications (16 or more medications predicted a 4.3% lower than for patients with 0–7 medications), alcohol abuse (− 4.6%), cancer (− 3.1%), and bipolar disorder (− 2.9%). During the experienced period, important predictors of TTR included hospitalizations (four or more hospitalizations predicted 9.4% lower TTR), more medications (16 or more medications predicted 5.1% lower TTR), alcohol abuse (− 5.4%), female sex (− 2.9%), cancer (− 2.7%), dementia (− 2.6%), non-alcohol substance abuse (− 2.4%), and chronic liver disease (− 2.3%). *Conclusions:* Some patients receiving oral anticoagulation therapy are more challenging to maintain within the therapeutic range than others. Our findings can be used to identify patients who require closer attention or innovative management strategies to maximize benefit and minimize harm from oral anticoagulation therapy.

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Background

Warfarin is received by millions of patients in the USA for the treatment and prevention of thromboembolic diseases [1]. Although it is highly effective, warfarin has a narrow therapeutic window, and undergoes numerous interactions with drugs, diet, and comorbid conditions [1]. The potential consequences of deviating from the therapeutic range are serious: insufficiently anticoagulated patients remain at risk for thromboembolic events [2], and over-anticoagulated patients are at risk for major hemorrhage, particularly intracranial hemorrhage [3].

Despite the importance of good control for patients receiving warfarin, little is known about patient-level predictors of percentage time in therapeutic International Normalized Ratio (INR) range (TTR) [4], a measure of anticoagulation control over time. White *et al*. [5] identified several patient-level factors that predicted poor control (TTR < 60%): non-white race, paroxysmal as opposed to continuous atrial fibrillation, and being new to warfarin ('inception'). Our group [6] found additional factors that predict poor control: non-standard target INR range (i.e. other than 2.0–3.0), and female sex. These studies examined a relatively narrow range of patient-level factors, and lacked the power to examine uncommon predictors or factors with real, but modest, effects on TTR.

Here, we used data from almost 125 000 patients receiving oral anticoagulation from the Veterans Health Administration

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[Veterans AffaiRs Study to Improve Anticoagulation (VARIA)], to explore a more comprehensive range of patient characteristics as potential predictors of anticoagulation control. Our findings could help clinicians and healthcare systems to identify patients who require extra attention or innovative management strategies to achieve acceptable levels of anticoagulation control.

Methods

Data

The VARIA database included all patients deemed to be receiving oral anticoagulation therapy (OAT) from the Veterans Health Administration (VA) between 1 October 2006 and 30 September 2008. The VA, the largest integrated health system in the USA, delivered care to 5.6 million patients in 2009, representing 1.8% of the US population [7]. Patients become eligible to receive VA care by serving in the military for two or more years; eligibility is for life. Many patients receive all of their care in the VA system, although some also visit non-VA healthcare facilities for a portion of their care. The VA collects comprehensive data regarding the care delivered within the VA system, including demographics, dates of service, pharmacy, and laboratory data. Laboratory data, including INR values, are first entered into local clinical databases (uploaded from the laboratory analyzer), and then these local databases are periodically uploaded to the national VA Corporate Data Warehouse, the source for our data. The study was approved by the Institutional Review Board of the Bedford VA Medical Center.

Each VA site consists of a central hospital along with its on-site outpatient clinics and several outlying satellite clinics. By policy, all VA anticoagulation care is delivered in dedicated anticoagulation clinics (ACCs) [8]. However, VA ACCs differ in organization, management, and performance. We address these between-site differences in a separate article.

We included INR tests within the VA when patients were 'on warfarin': that is, when a patient was either (i) 'in possession' of warfarin or (ii) having INR tests every 42 days. A similar approach was used to define time 'on warfarin' in a previous study [9]. We defined the period of warfarin possession as the duration of the most recent VA prescription for warfarin, plus 30 days. Because patients may be instructed to take half-doses of warfarin, we recognize that going more than 30 days beyond the end of a prescription does not necessarily indicate that warfarin therapy has stopped. We therefore also allowed a consistent pattern of INR measurements (i.e. every 42 days or less) to indicate that a patient was still being managed. Patients with chronic liver disease only qualified though receipt of warfarin; frequent INR tests for such a patient might have been performed to monitor liver function. We excluded INR tests performed while the patient was hospitalized within the VA system. Patients who are hospitalized may receive temporary parenteral anticoagulation (e.g. with heparin) or no anticoagulation, so low INR values are likely to be intentional.

Dependent variable: TTR

We calculated TTR (between 0% and 100%) using Rosendaal's method [4], which uses linear interpolation to assign an INR value to each day between two successive observed INR values. Gaps of 56 days or more between INR values are not interpolated. After interpolation, the percentage of time during which the interpolated INR values lie between 2 and 3 is calculated [4]. Previous studies have linked TTR and clinical outcomes such as stroke, venous thromboembolism (VTE), and major hemorrhage [5,10], thus validating this intermediate outcome measure for use as a surrogate endpoint for OAT [11].

Independent variable: primary indication for OAT

Patients receiving OAT for different indications may vary in duration of therapy, INR target range, health status, and other factors. We developed an algorithm to assign a primary indication for therapy to patients with more than one of these conditions. A list of the ICD-9 codes used to define these conditions is given in Appendix S1. When present, valvular heart disease (VHD) was considered to be the primary indication; if VHD was absent, VTE was the primary indication; if both VHD and VTE were absent, atrial fibrillation (AF) was the primary indication. If VHD, VTE and AF were absent, a group called 'other indications' (including cardiomyopathy, left ventricular thrombus, and left ventricular aneurysm) encompassed all other therapeutic indications [1].

Independent variables: demographics

We collected patient demographics, including sex, age, race/ethnicity, and zip code of residence. Race/ethnicity was classified as non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Native American, and Missing (11%). We did not attempt to impute race, because of concern that it was not missing by chance [12]. The patient's zip code of residence was linked to US Census data [13] to obtain the percentage of people living below the federal poverty line in each geographic area, which was used as a proxy measure for socio-economic status [14]. We also used the patient's zip code of residence to obtain the straight-line driving distance between the centroid representation of the zip code and the nearest VA healthcare facility.

Independent variable: warfarin experience

We have previously observed that anticoagulation control differs markedly between the first 6 months of therapy ('inception') and the period thereafter ('experienced') [6]. We therefore examined predictors of TTR separately for each period. We defined each patient's date of warfarin initiation, looking back as far as 1 October 2001. Initiation was defined as the first INR value greater than 1.2 or the first outpatient warfarin fill, whichever came first. It would be extremely unusual for a patient to record an INR value above 1.2 unless

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he or she had taken warfarin. We then stratified the sample into inception time (the first 6 months of warfarin therapy for each patient) and experienced time (any time thereafter). A single patient might contribute only to the inception dataset (if he or she had less than 6 months of therapy), only to the experienced dataset (if he or she began warfarin more than 6 months prior to the inception of our study), or to both. Having controlled for inception data through stratification, we also considered duration of warfarin experience as a potential indicator within the experienced dataset.

Independent variables: clinical variables

We used ICD-9 codes to define comorbid conditions as detailed in Appendix S2. Previous studies have demonstrated that ICD-9 codes can be used successfully to identify comorbid conditions within VA databases [15,16]. Conditions were examined because they were expected to affect anticoagulation control. Examples include conditions already shown to worsen anticoagulation control (e.g. cancer) [17], conditions treated with medications that interact with warfarin (e.g. epilepsy and bipolar disorder), conditions associated with chaotic lifestyle or poor adherence (e.g. dementia and substance abuse), and conditions that directly interfere with hepatic function (e.g. alcohol abuse and chronic liver disease). To further characterize each patient's illness burden, we also counted the number of times each patient was hospitalized within the VA system during the inception period (zero, one, or two or more) and during the experienced period (zero, one, two, three, or four or more), as well as the total number of distinct classes of non-warfarin medications received chronically (for at least 30 days) during the study period (0–7, 8–11, 12–15, and ≥ 16).

Assembling the final database

Figure 1 describes our database construction. First, we required at least two interpolable between-test intervals of 56 days or fewer for study entry, to ensure that our population consisted of 'VA users', or patients who use the VA for most or all of their care. We excluded patients whose primary indication for warfarin was VHD, since their target INR range might be 2.5–3.5 rather than 2–3. We also excluded patients who only recorded INR values 1.2 and lower, reasoning that their INR tests were unlikely to be related to warfarin management. Finally, we required at least two interpolable between-test intervals of 56 days or fewer for study entry, to ensure that our population consisted of 'VA users', or patients who use the VA for most or all of their care.

There are 128 sites of care in the VA system. We excluded 28 of these sites from our study and also excluded several months of data from an additional 14 sites, because our data-checking procedures revealed possible problems with data completeness at those sites. The problem with data completeness relates to the laboratory data only. Whereas accurate data are collected about which laboratory tests are performed (because something akin to a billing code is generated), the data regarding laboratory results must be checked carefully. Specifically, the name given to each laboratory test by the local facility is not uniform throughout the system, and these names may change unexpectedly. After this happens, there may be a period of

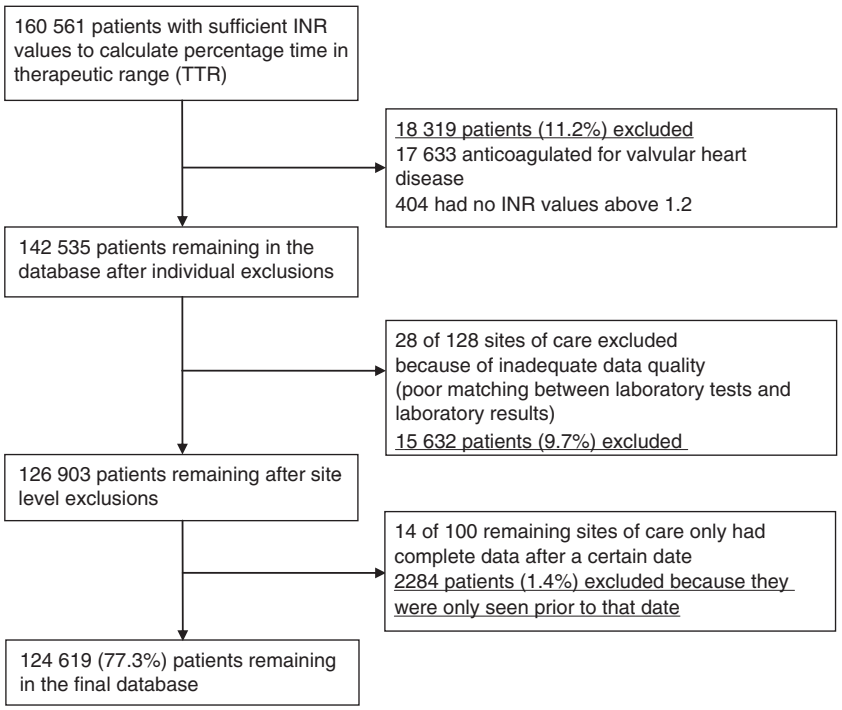

Fig. 1. Enrollment flowchart. INR, International Normalized Ratio.

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several months when the local laboratory results are not captured by the national database, until the name change is noted. We identified which sites had this issue by dividing the data into 3-month periods; problematic sites had few or no INR results in certain periods, whereas the number of INR tests performed remained constant over time. In contrast, there were 86 sites that had complete data for the entire 2-year study period, and 14 sites that began to have complete data during the period and continued to have it through to the end. Thus, 28 sites were excluded because of incomplete data, and 14 sites were partially included.

Statistical analyses

We calculated TTR for each patient; for patients with both inception and experienced data, we calculated TTR separately for each period. We also analyzed the inception and experienced data separately, in each case first examining the effect of each variable upon TTR individually and then in a fully adjusted multivariable model. We used linear regression for our adjusted models, employing a mixed model (SAS PROC MIXED) with exchangeable correlation structure to account for the correlation of patient outcomes by site of care. We performed all analyses with SAS version 9.1 (SAS Corporation, Cary, NC, USA).

Creation of a clinical prediction tool

When considering the initiation of warfarin therapy, clinicians may find it useful to know which patients could be difficult to control in the future. We therefore developed a clinical prediction tool to help predict a patient's future TTR at the time of initiation of therapy. The predicted TTR during the experienced period may be especially helpful, so the prediction tool provides separate estimates for the first 6 months of therapy (inception) and the 18 months after that (experienced). The models underlying the tool were generally based on our main results, but we re-derived the models using only data that would be available to clinicians at the time of initiation.

To enable our model to predict TTR during the inception period, we located all patients in our database who were new to warfarin and remained on it for a full 6 months thereafter (n = 25 788). To enable our model to predict TTR during the experienced period, we located all patients who were managed in the experienced period for at least 18 months (n = 86 731). We assessed all the predictor variables at baseline, that is, during the year prior to the patient's first INR value in our model. We divided each of these datasets into a larger (60%) derivation set and a smaller (40%) validation set. We derived and validated a somewhat simplified model to predict the mean TTR over the first 6 months (inception) and the succeeding 18 months (experienced). The model was simplified as follows: race was removed (because of our concern that keeping race in the model might perpetuate racial disparities in care), poverty and distance were removed (their effects were small, and clinicians might not be able to assess them easily), and the list of comorbid conditions was abbreviated to those that had statistically significant effects in at least one time period. In addition, only hospitalizations that occurred during the year prior to warfarin initiation were considered as a predictor of TTR. On the basis of the parameters of this simplified model, we then created a clinical prediction tool in the form of a spreadsheet.

Results

Enrollment and baseline characteristics

After exclusion of individual patients and sites of care with missing data, there were 124 619 patients who received anticoagulation from 100 sites of care. There were 163 144 total patient-years of observation in the database. TTR could not be calculated during 34 963 of these 163 144 patient-years (21.4% of all patient-time), because of hospitalizations or gaps in therapy.

Details of the study sample are given in Table 1 (inception) and Table 2 (experienced management). The following results are for patient characteristics during the inception period; experienced period results were similar. The sample was overwhelmingly male. The age distribution reflects the fact that the indications for anticoagulation are most common in the elderly. A considerable number of minority patients were enrolled (e.g. 11.3% non-Hispanic Black). Most patients were anticoagulated for AF (55%), with the remainder being anticoagulated for VTE (35%) or other indications (10%). Patients had a considerable burden of comorbid illness. For example, 80% had hypertension, 37% had diabetes, 26% had heart failure, and 10% received a new diagnosis of cancer during the study. Mental health and substance abuse conditions were also common: 24% had major depression, 14% abused alcohol, and 7% abused some other substance. Medication and hospitalization data also reflect high levels of comorbid illness: 61% received at least eight non-warfarin chronic medications, and 22% were hospitalized at least once during the 6-month inception period.

Predictors of TTR: inception period

We observed inception (first 6 months of therapy) for 39 447 patients (Table 1). Mean TTR during inception was 48%. In the adjusted analysis, younger age predicted worse control; patients under age 55 years had TTR 3.9% lower than the reference category (age ≥ 75 years). Most racial minorities had lower TTR during inception, although these relationships were attenuated after multivariable adjustment. Poverty in the zip code of residence predicted worse control, with residents of the poorest areas having TTR 2.7% lower than the wealthiest. Driving distance to the nearest VA had a small negative influence upon inception-period TTR, but only when the distance was 20 miles or greater (− 1.3%). Most comorbid conditions reduced inception-period TTR. Among the physical illnesses that had the strongest adverse effects during inception

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Table 1 Patient characteristics and effects on percentage time in therapeutic International Normalized Ratio range during the inception period, that is, the first 6 months of warfarin therapy (n = 39 447)

Variable	Number (%)	Unadjusted effect (95% CI)	Adjusted effect (95% CI)
Intercept			52.4
Female sex	1046 (2.7)	−0.6 (−1.3 to 0.1)	+0.6 (−1.0 to 2.2)
Age group (years)			
20–54	4993 (12.7)	−6.0 (−6.4 to −5.6)**	−3.9 (−4.9 to −2.9)**
55–59	6404 (16.2)	−3.3 (−3.6 to −2.9)**	−1.7 (−2.5 to −0.8)**
60–64	6599 (16.7)	−1.7 (−2.0 to −1.3)**	−0.8 (−1.6 to 0.1)
65–69	4335 (11.0)	−1.2 (−1.6 to −0.8)**	−0.6 (−1.6 to 0.3)
70–74	5404 (13.7)	−0.7 (−1.1 to −0.4)**	−0.3 (−1.2 to 0.5)
≥ 75	11 712 (29.7)	–	–
Race/ethnicity			
Non-Hispanic White	29 137 (73.9)	–	–
Non-Hispanic Black	4459 (11.3)	−5.6 (−5.9 to −5.2)**	−2.9 (−3.8 to −2.0)**
Hispanic	1149 (2.9)	−4.2 (−4.9 to −3.5)**	−2.7 (−4.3 to −1.1)*
Asian	134 (0.3)	−1.1 (−3.1 to 0.9)**	−1.7 (−6.2 to 2.7)
Native American	148 (0.4)	+2.8 (0.9 to 4.7)**	+3.8 (−0.4 to 8.0)
Other/unknown	4420 (11.2)	+3.1 (2.7 to 3.5)**	+2.0 (1.2 to 2.9)**
Percentage poverty in zip code of residence (quintile)			
Wealthiest (0–5.9)	7697 (19.5)	–	–
Wealthy (5.9–9.0)	7865 (19.9)	−1.1 (−1.5 to −0.7)**	−0.5 (−1.3 to 0.3)
Moderate (9.0–12.6)	7753 (19.7)	−1.7 (−2.1 to −1.4)**	−0.9 (−1.8 to −0.1)*
Poor (12.6–17.8)	7724 (19.6)	−2.8 (−3.2 to −2.4)**	−1.5 (−2.3 to −0.6)*
Poorest (17.8–100)	8408 (21.3)	−5.3 (−5.7 to −5.0)**	−2.7 (−3.6 to −1.9)**
Driving distance from nearest VA facility in miles (quintile)			
Nearest (0–3.1)	8022 (20.3)	–	–
Near (3.1–6.0)	8167 (20.7)	+0.5 (0.2 to 0.9)**	+0.2 (−0.6 to 1.0)
Moderate (6.0–10.5)	8110 (20.6)	+1.5 (1.2 to 1.9)**	+0.4 (−0.4 to 1.2)
Far (10.5–20.3)	7811 (19.8)	+1.3 (0.9 to 1.6)**	+0.1 (−0.8 to 0.9)
Furthest (>20.3)	7337 (18.6)	−0.5 (−0.9 to −0.1)**	−1.3 (−2.1 to −0.4)*
Primary indication for warfarin†			
Atrial fibrillation	21 584 (54.7)	–	–
Venous thromboembolism	13 951 (35.4)	−0.8 (−1.1 to −0.6)**	+1.4 (0.8 to 2.0)**
All others combined	3912 (9.9)	−1.9 (−2.3 to −1.5)**	−1.1 (−2.0 to −0.2)*
Physical comorbid conditions			
Cancer (newly diagnosed)	3945 (10.0)	−3.5 (−3.9 to −3.1)**	−3.1 (−3.9 to −2.2)**
Chronic kidney disease	5233 (13.3)	−2.8 (−3.2 to −2.5)**	−0.9 (−1.7 to −0.1)*
Chronic liver disease	565 (1.4)	−5.7 (−6.6 to −4.7)**	−0.8 (−3.0 to 1.4)
Chronic lung disease	11 018 (27.9)	−2.3 (−2.6 to −2.0)**	−0.1 (−0.8 to 0.5)
Coronary artery disease	16 654 (42.2)	−0.7 (−0.9 to −0.4)**	−0.1 (−0.7 to 0.5)
Diabetes	14 433 (36.6)	−2.0 (−2.2 to −1.7)**	−1.3 (−1.9 to −0.7)**
Epilepsy	1091 (2.8)	−3.6 (−4.3 to −2.9)**	−1.0 (−2.6 to 0.5)
Heart failure	10 139 (25.7)	−2.6 (−2.9 to −2.4)**	−0.3 (−1.0 to 0.3)
Hyperlipidemia	26 983 (68.4)	+2.1 (1.8 to 2.3)**	+2.5 (1.9 to 3.1)**
Hypertension	31 368 (79.5)	−0.4 (−0.7 to −0.1)*	+0.5 (−0.2 to 1.2)
Pain disorders	28 281 (71.7)	−2.3 (−2.6 to −2.1)**	−0.3 (−0.9 to 0.3)
Peripheral arterial disease	6390 (16.2)	−1.7 (−2.0 to −1.3)**	−0.6 (−1.3 to 0.1)
Mental comorbid conditions			
Alcohol abuse	5345 (13.5)	−7.4 (−7.7 to −7.0)**	−4.6 (−5.4 to −3.7)**
Anxiety	4369 (11.1)	−1.9 (−2.3 to −1.6)**	+0.8 (−0.1 to 1.7)
Bipolar disorder	1279 (3.2)	−6.8 (−7.5 to −6.2)**	−2.9 (−4.5 to −1.4)**
Dementia	1726 (4.4)	−2.1 (−2.7 to −1.6)**	−1.6 (−2.9 to −0.3)*
Major depression	9389 (23.8)	−3.4 (−3.6 to −3.1)**	−0.6 (−1.3 to 0.1)
PTSD	3718 (9.4)	−3.1 (−3.5 to −2.7)**	+0.3 (−0.7 to 1.2)
Schizophrenia	701 (1.8)	−5.9 (−6.8 to −5.0)**	−0.7 (−2.7 to 1.3)
Substance abuse (non-alcohol)	2677 (6.8)	−8.7 (−9.2 to −8.2)**	−2.4 (−3.5 to −1.2)**
Number of non-warfarin medications			
0–7	15 416 (39.1)	–	–
8–11	12 231 (31.0)	−2.5 (−2.8 to −2.3)**	−1.7 (−2.4 to −1.0)**
12–15	7266 (18.4)	−5.4 (−5.7 to −5.0)**	−3.4 (−4.2 to −2.5)**
≥ 16	4534 (11.5)	−7.6 (−8.0 to −7.2)**	−4.3 (−5.4 to −3.3)**
Number of hospitalizations during inception period			
None	30 675 (77.8)	–	–
1	5860 (14.9)	−4.9 (−5.2 to −4.6)**	−3.1 (−3.9 to −2.4)**
≥ 2	2912 (7.4)	−10.1 (−10.6, −9.7)**	−7.3 (−8.3, −6.2)**

CI, confidence interval; PTSD, post-traumatic stress disorder; VA, Veterans Health Administration. All β-coefficients are in units of percentage time in therapeutic International Normalized Ratio range. All P-values account for the correlation of outcomes by site of care. Adjusted effects are adjusted for all the other variables in the table.

*$P < 0.05$.

**$P < 0.001$.

†Patients whose main indication for anticoagulation was valvular heart disease or prosthetic heart valve were excluded from this study.

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Table 2 Patient characteristics and effects on percentage time in therapeutic International Normalized Ratio range during the experienced period, that is, any time after the first 6 months of warfarin therapy (n = 104 505)

Variable	Number (%)	Unadjusted effect (95 CI)	Adjusted effect (95% CI)
Intercept			63.2
Female sex	1984 (1.9)	−5.5 (−5.9 to −5.0)**	−2.9 (−3.9 to −2.0)**
Age group (years)			
20–54	7430 (7.1)	−9.2 (−9.5 to −9.0)**	−4.7 (−5.3 to −4.1)**
55–59	11 590 (11.1)	−4.8 (−5.0 to −4.6)**	−1.2 (−1.7 to −0.7)**
60–64	12 783 (12.2)	−2.5 (−2.6 to −2.3)**	+0.1 (−0.3 to 0.5)
65–69	11 705 (11.2)	−0.1 (−0.3 to 0.1)	+1.0 (0.6 to 1.5)**
70–74	17 046 (16.3)	+0.5 (0.3 to 0.7)**	+1.1 (0.7 to 1.4)**
≥ 75	43 951 (42.1)	–	–
Race/ethnicity			
Non-Hispanic White	80 728 (77.2)	–	–
Non-Hispanic Black	8853 (8.5)	−6.5 (−6.7 to −6.3)**	−2.6 (−3.1 to −2.1)**
Hispanic	2977 (2.8)	−2.0 (−2.3 to −1.6)**	−0.6 (−1.4 to 0.2)
Asian	302 (0.3)	−0.3 (−1.4 to 0.8)	−0.5 (−2.9 to 1.9)
Native American	279 (0.3)	−4.3 (−5.5 to −3.2)**	−2.4 (−4.9 to 0.1)
Other/unknown	11 366 (10.9)	+2.4 (2.3 to 2.6)**	+0.3 (−0.2 to 0.7)
Percentage poverty (quintiles)			
Wealthiest (0.0–5.9)	21 193 (20.3)	–	–
Wealthy (5.9–9.0)	20 933 (20.0)	−0.5 (−0.7 to −0.3)**	+0.1 (−0.3 to 0.5)
Moderate (9.0–12.6)	20 987 (20.1)	−1.4 (−1.6 to −1.2)**	−0.5 (−0.9 to −0.1)*
Poor (12.6–17.8)	20 910 (20.0)	−2.0 (−2.2 to −1.8)**	−0.8 (−1.3 to −0.4)**
Poorest (17.8–100.0)	20 482 (19.6)	−4.0 (−4.2 to −3.8)**	−1.5 (−2.0 to −1.1)**
Driving distance to nearest VA in miles (quintiles)			
Nearest (3.1 or closer)	21 119 (20.2)	–	–
Near (3.1–6.0)	20 985 (20.1)	+0.4 (0.2 to 0.6)**	+0.1 (−0.3 to 0.5)
Moderate (6.0–10.5)	21 094 (20.2)	+0.5 (0.3 to 0.7)**	−0.4 (−0.8 to 0.0)
Far (10.5–20.3)	21 024 (20.1)	+1.0 (0.8 to 1.2)**	+0.0 (−0.4 to 0.4)
Furthest (20.3 or farther)	20 283 (19.4)	+0.5 (0.3 to 0.7)**	+0.0 (−0.4 to 0.4)
Date of warfarin inception			
≥6 months before study inception	78 142 (74.8)	–	–
6 months before the study, first year of the study	8885 (8.5)	−4.5 (−4.7 to −4.4)**	−3.6 (−3.9 to −3.3)**
Second year of the study	3658 (3.5)	−6.0 (−6.3 to −5.6)**	−5.8 (−6.5 to −5.1)**
Primary indication for warfarin[†]			
Atrial fibrillation	67 077 (64.2)	–	–
Venous thromboembolism	28 585 (27.4)	−3.8 (−4.0 to −3.7)**	−1.2 (−1.5 to −0.9)**
All others combined	8843 (8.5)	−1.5 (−1.7 to −1.3)**	−1.5 (−1.9 to −1.0)**
Physical comorbid conditions			
Cancer (newly diagnosed)	7100 (6.8)	−4.8 (−5.0 to −4.5)**	−2.7 (−3.2 to −2.2)**
Chronic kidney disease	14 806 (14.2)	−4.4 (−4.6 to −4.3)**	−1.6 (−2.0 to −1.2)**
Chronic liver disease	1253 (1.2)	−8.3 (−8.8 to −7.7)**	−2.3 (−3.5 to −1.1)**
Chronic lung disease	30 687 (29.4)	−3.8 (−3.9 to −3.7)**	−0.7 (−1.0 to −0.4)**
Coronary artery disease	53 114 (50.8)	−1.4 (−1.5 to −1.2)**	−0.6 (−0.9 to −0.3)**
Diabetes	41 863 (40.1)	−2.1 (−2.2 to −2.0)**	−1.0 (−1.3 to −0.7)**
Epilepsy	2926 (2.8)	−5.1 (−5.4 to −4.7)**	−1.6 (−2.4 to −0.8)**
Heart failure	34 229 (32.8)	−3.6 (−3.7 to −3.5)**	−1.0 (−1.3 to −0.7)**
Hyperlipidemia	78 754 (75.4)	+2.1 (2.0 to 2.2)**	+2.0 (1.7 to 2.3)**
Hypertension	87 776 (84.0)	+0.0 (−0.2 to 0.1)	+1.0 (0.7 to 1.4)**
Pain disorders	76 159 (72.9)	−3.4 (−3.5 to −3.3)**	−0.3 (−0.6 to 0.0)
Peripheral arterial disease	20 746 (19.9)	−2.3 (−2.5 to −2.2)**	−0.5 (−0.8 to −0.1)*
Mental comorbid conditions			
Alcohol abuse	9729 (9.3)	−9.4 (−9.6 to −9.2)**	−5.4 (−5.9 to −4.9)**
Anxiety	10 253 (9.8)	−4.3 (−4.5 to −4.1)**	−0.2 (−0.6 to 0.3)
Bipolar disorder	2386 (2.3)	−8.4 (−8.8 to −8.0)**	−1.8 (−2.7 to −1.0)**
Dementia	5517 (5.3)	−4.2 (−4.4 to −3.9)**	−2.6 (−3.2 to −2.0)**
Major depression	22 583 (21.6)	−5.9 (−6.1 to −5.8)**	−2.0 (−2.3 to −1.6)**
PTSD	8066 (7.7)	−5.0 (−5.2 to −4.7)**	+0.4 (−0.2 to 0.9)
Schizophrenia	1263 (1.2)	−6.7 (−7.2 to −6.1)**	+0.8 (−0.4 to 2.0)
Substance abuse (non-alcohol)	4233 (4.1)	−11.8 (−12.1 to −11.5)**	−2.4 (−3.2 −1.7)**
Number of non-warfarin medications			
0–7	43 380 (41.5)	–	–
8–11	33 393 (32.0)	−3.6 (−3.7 to −3.4)**	−1.8 (−2.1 to −1.5)**
12–15	17 915 (17.1)	−7.3 (−7.4 to −7.1)**	−3.2 (−3.6 to −2.8)**

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Table 2 (Continued)

Variable	Number (%)	Unadjusted effect (95 CI)	Adjusted effect (95% CI)
≥ 16	9817 (9.4)	−11.7 (−11.9 to −11.5)**	−5.1 (−5.6 to −4.5)**
Number of hospitalizations during experienced period			
None	77 107 (73.8)	–	–
1	13 858 (13.3)	−6.2 (−6.4 to −6.0)**	−3.7 (−4.1 to −3.3)**
2	6261 (6.0)	−8.5 (−8.8 to −8.3)**	−5.1 (−5.7 to −4.5)**
3	3066 (2.9)	−10.6 (−11.0 to −10.3)**	−6.5 (−7.3 to −5.7)**
≥ 4	4213 (4.0)	−14.9 (−15.2 to −14.6)**	−9.4 (−10.1 to −8.7)**

CI, confidence interval; PTSD, post-traumatic stress disorder; VA, Veterans Health Administration. All β-coefficients are in units of percentage time in therapeutic International Normalized Ratio range. All P-values account for the correlation of outcomes by site of care. Adjusted effects are adjusted for all the other variables in the table.

*$P < 0.05$.

**$P < 0.001$.

†Patients whose main indication for anticoagulation was valvular heart disease or prosthetic heart valve were excluded from this study.

were cancer (− 3.1%), diabetes (− 1.3%), and chronic kidney disease (− 0.9%). In general, mental illnesses exerted a stronger effect than physical illnesses, especially alcohol abuse (− 4.6%), bipolar disorder (− 2.9%), substance abuse (− 2.4%), and dementia (− 1.6%). There were several conditions that had paradoxical effects (associated with improved control), most notably hyperlipidemia (+ 2.5%). The number of chronic non-warfarin medications was inversely related to inception TTR: those receiving the most medications had TTR 4.3% lower than those receiving the least. Although inpatient INR values were excluded from calculations of TTR, hospitalizations were still associated with lower TTR, with those hospitalized two or more times having TTR 7.3% lower than those not hospitalized.

Predictors of TTR: experienced period

We observed post-inception ('experienced period') therapy for 104 505 patients (Table 2). Mean TTR during the experienced period was 61%. In the adjusted analysis, women had lower TTR (− 2.9%), an effect not seen during inception. Similar to what was found for the inception period, age less than 55 years predicted lower TTR (− 4.7%), and Black patients had lower TTR (− 2.6%) than Whites. Area poverty predicted lower TTR, but the effect size in the experienced period (1.5% lower in the poorest areas) was smaller than it had been during inception. In contrast to what was found for the inception period, driving distance was unrelated to TTR. Even during the experienced period, further experience with warfarin was associated with improved control: TTR was highest among patients who began warfarin at least 6 months before the study began.

As in the inception period, most comorbid conditions predicted lower TTR. Medical conditions with the strongest adverse effects included cancer (− 2.7%), chronic liver disease (− 2.3%), epilepsy (− 1.6%), chronic kidney disease (− 1.6%), diabetes (− 1.0%), and heart failure (− 1.0%). Mental health conditions had stronger effects, particularly alcohol abuse (− 5.4%), dementia (− 2.6%), substance abuse (− 2.4%), major depression (− 2.0%), and bipolar disorder (− 1.8%). As was seen during inception, several conditions were somewhat surprisingly associated with improved control, especially hyperlipidemia (+ 2.0%). Medications and hospitalizations were powerful predictors of control, even after adjustment for comorbid conditions. For example, patients hospitalized four or more times had TTR 9.4% lower than those not hospitalized.

Clinical prediction tool

We developed a tool to help clinicians to predict inception and experienced TTR for each patient on the basis of patient-level characteristics available at the time of initiation of therapy (Appendix S3). The tool is available as an online-only supplement to this article, and may be downloaded and used to predict TTR on the basis of patient characteristics known at the time of inception. The model parameters were generally quite similar to those presented in Tables 1 and 2. R^2 for inception TTR was 3.4% in the derivation set and 3.2% in the validation set. R^2 for experienced TTR was 6.5% in the derivation set and 6.8% in the validation set.

Discussion

Using data from the VA, we examined patient-level factors related to anticoagulation control with warfarin, measured asTTR. Our study demonstrates that some patients are more difficult to keep within the target INR range than others. We estimated the effects of multiple patient-level characteristics on TTR, clarifying the contributions of illness burden and clinical complexity to poorer anticoagulation control. Alcohol abuse, substance abuse, cancer and dementia were particularly strong predictors of poor control. The persistence of hospitalizations as a strong predictor of TTR, even after controlling for a broad range of comorbid conditions, bears mention. Because we did not consider inpatient INR values, this finding suggests that the period after a hospitalization is also characterized by poorly controlled anticoagulation. A hospitalization event entails numerous changes in diet, lifestyle, and health status, which can perturb the management of warfarin, as has been noted in earlier studies [18]. Patients who have been hospitalized require prompt and

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vigilant follow-up after discharge to prevent such derangements, which have now been seen in multiple studies spanning multiple settings.

Several conditions were associated with improved TTR, most notably hyperlipidemia. To explore this, we compared patients receiving HMG-CoA reductase inhibitors (statins) for hyperlipidemia to those receiving fibrates, hypothesizing that statins themselves may improve TTR; however, the groups did not differ. Another possibility is that the presence of a code for hyperlipidemia (an asymptomatic risk factor) is a proxy for a proactive patient–clinician health maintenance partnership. This is supported by the similar positive effect for hypertension.

We found that achieving good control with warfarin is harder during the inception period than during the experienced period (mean TTR 48% vs. 61%), and that predictors of TTR differ between the two periods. Our study also suggests that, even within the VA, a system that provides comprehensive coverage and access, disparities in anticoagulation control still exist, with poorer, more distant, female and minority patients all experiencing poorer control in one or both of our study cohorts. In a previous non-VA study, our group also found that women have lower TTR than men [6]. The reason for this finding is unclear, but it is apparently not limited to the VA, and should be investigated further. In addition, younger patients experienced worse TTR. Although we cannot be certain, it is possible that the demands of a full-time job may be difficult to reconcile with the frequent follow-up expected of anticoagulation patients. On the basis of this finding, the VA may wish to consider improving access to care for working patients receiving anticoagulation.

Previous studies have explored only a few possible predictors of TTR, including inception status, race, and sex [5,6]. Other studies have examined the effect of a single predictor in detail, including cancer [17], non-white race [19–21], health literacy [22], and the patient's understanding of the reason why warfarin was prescribed [23]. Although our study echoes some of these earlier findings, we examined a much more comprehensive set of predictors and adjusted for confounding, strengths not found in previous studies. In addition, the size and scope of our database allowed us to examine relatively uncommon predictors such as chronic liver disease and epilepsy.

The primary purpose of the models presented here is risk adjustment. Risk adjustment allows fair comparisons of outcomes between sites of care, despite the fact that some sites will have more challenging patient populations than others [24]. Thus, these models may be used to compare sites of care on risk-adjusted TTR, which could spur quality improvement and improve patient outcomes [11]. The results reported here will underpin a planned effort to improve anticoagulation control for VA patients receiving warfarin.

Our findings can also be used to identify patients who may require greater attention or innovative management strategies to achieve acceptable levels of anticoagulation control. The effect of each individual variable upon TTR in our study was relatively small, and no single risk factor that we studied establishes a patient as being too high-risk for anticoagulation therapy to be contemplated. In combination, however, the variables that we studied would indeed be useful for risk-stratifying patients receiving oral anticoagulation. To facilitate the use of this information to guide clinical practice, we have offered, with this article, a simplified version of our models in the form of a clinical prediction tool. This tool can help clinicians to predict a patient's eventual level of anticoagulation control before starting therapy. Such information could be helpful in determining which patients might require aggressive interventions to help them achieve an acceptable level of control, and which patients have such poor predicted control that they might not be suitable candidates for warfarin. Although warfarin is a superior therapy, aspirin is available as a second-line agent, at least for patients with AF [25], and its safety and effectiveness are unlikely to be compromised by patient characteristics in the same way.

In addition, it seems likely that novel oral anticoagulants may soon be approved for use, particularly dabigatran [26,27]. On the basis of studies of dabigatran and previous studies of other similar drugs, novel anticoagulants are likely to offer similar safety and effectiveness to warfarin, at a much higher cost [28], but might be a superior choice for patients with poor control on warfarin (although this has not yet been proven). Models such as the ones presented here could possibly be used prospectively to identify some patients who are likely to do well with warfarin and others who are unlikely to do well and might be candidates for the novel agents. Restricting the use of these agents to patients who are poor candidates for warfarin could markedly improve their cost-effectiveness.

Although our study is unprecedented in the amount and richness of the data collected to study anticoagulation, we do acknowledge some important limitations. First, there are some caveats regarding the clinical prediction tool. This tool is intended to predict TTR at the time of initiation; after a patient has received warfarin for several months, his or her past control will clearly be the best predictor of future control. In addition, a clinical prediction tool should not only be validated in the source population ('internal validation'), as ours was, but should also be validated again in a separate population ('external validation'). It is even more useful if the investigators can demonstrate the impact of the tool on patient outcomes as compared with usual practice [29,30]. Our rule has not yet been externally validated, and nor has its impact on clinical care been demonstrated. Clinicians should access this tool if they find it useful, but should be aware that it has not yet achieved these benchmarks for the highest-quality clinical prediction tools. In future research, we hope to accomplish these tasks to help this tool gain wider acceptance and increase its impact on clinical management.

Second, VA patients are mostly male and have a high burden of physical and mental health conditions. It is unclear how our results might have differed in a population of patients with more women and a lesser degree of comorbidity. Third, we studied an intermediate outcome of care (TTR) rather than definitive outcomes such as stroke or major hemorrhage.

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However, TTR has been convincingly linked to definitive outcomes [5,10], making higher TTR a good target for improving health outcomes [11]. Fourth, our administrative database did not contain information on some known determinants of anticoagulation control, such as adherence to therapy and dietary variation. Such data could only be collected through expensive procedures such as frequent questionnaires, which would greatly limit sample size. This would have precluded a study of such size and scope. In addition, the intended use of our models is to risk-adjust TTR, a task that must be accomplished with administrative data alone to be feasible. Fifth, our database did not contain information on care received outside the VA, and there is no comprehensive database of INR values obtained outside the VA system. This precluded a consideration of INR values obtained outside the VA. However, because we required at least two between-test intervals of 56 days or fewer for study entry, the great majority of the patients that we studied would have been 'VA users', who are likely to visit the VA for most, if not all, of their care.

Finally, although ICD-9 codes have been used in many previous studies to identify comorbid conditions, we acknowledge that this approach may lack sensitivity, particularly for some conditions that are stigmatized or difficult to recognize, such as alcohol abuse or dementia. We addressed this concern in part by requiring only one ICD-9 code for these conditions rather than two, a strategy that increased their frequency somewhat and thus presumably improved sensitivity (see Appendix S2 for details). Through this and other carefully considered decisions, we have tried to improve the performance of ICD-9 codes in identifying comorbid conditions as much as possible.

In conclusion, we have collected a database of patients receiving oral anticoagulation that is unprecedented in its size and scope. We used this database to identify the combined effect of multiple patient-level predictors of anticoagulation control. These data and models could enable the VA to measure and improve the quality of its oral anticoagulation care.

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Disclosure of Conflict of Interests

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Codes to define indications for oral anticoagulation therapy.
Appendix S2. Codes to define comorbid conditions.
Appendix S3. TTR calculator.

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