Identifying the Risks of Anticoagulation in Patients with Substance Abuse

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BACKGROUND: Warfarin is effective in preventing thromboembolic events, but concerns exist regarding its use in patients with substance abuse.

OBJECTIVE: Identify which patients with substance abuse who receive warfarin are at risk for poor outcomes.

DESIGN: Retrospective cohort study. Diagnostic codes, lab values, and other factors were examined to identify risk of adverse outcomes.

PATIENTS: Veterans AffaiRs Study to Improve Anticoagulation (VARIA) database of 103,897 patients receiving warfarin across 100 sites.

MAIN MEASURES: Outcomes included percent time in therapeutic range (TTR), a measure of anticoagulation control, and major hemorrhagic events by ICD-9 codes.

RESULTS: Nonusers had a higher mean TTR (62 %) than those abusing alcohol (53 %), drugs (50 %), or both (44 %, $p<0.001$). Among alcohol abusers, an increasing ratio of the serum hepatic transaminases aspartate aminotransferase/alanine aminotransferase (AST:ALT) correlated with inferior anticoagulation control; normal AST:ALT $\leq$ 1.5 predicted relatively modest decline in TTR (54 %, $p<0.001$), while elevated ratios (AST:ALT 1.50–2.0 and > 2.0) predicted progressively poorer anticoagulation control (49 % and 44 %, $p<0.001$ compared to nonusers). Age-adjusted hazard ratio for major hemorrhage was 1.93 in drug and 1.37 in alcohol abuse ($p<0.001$ compared to nonusers), and remained significant after also controlling for anticoagulation control and other bleeding risk factors (1.69 $p<0.001$ and 1.22 $p=0.003$). Among alcohol abusers, elevated AST:ALT >2.0 corresponded to more than three times the hemorrhages (HR 3.02, $p<0.001$ compared to nonusers), while a normal ratio AST:ALT $\leq$ 1.5 predicted a rate similar to nonusers (HR 1.19, $p<0.05$).

CONCLUSIONS: Anticoagulation control is particularly poor in patients with substance abuse. Major hemorrhages are more common in both alcohol and drug users. Among alcohol abusers, the ratio of AST/ALT holds promise for identifying those at highest risk for adverse events.

INTRODUCTION

Substance abuse is extremely common, with a lifetime prevalence in the US population of 7.7 % for drug and 17.8 % for alcohol abuse.[1,2] Clinicians confront a dilemma when faced with the need for anticoagulation in patients with substance abuse disorders. They may choose not to prescribe anticoagulation, realizing that the patient will be at risk for thromboembolic events. Or clinicians may prescribe, without knowing the likelihood of successful anticoagulation control or risk of hemorrhagic events. Concerns of clinicians include pharmacologic interaction, comorbid conditions, falls, compliance, and implications of addiction and chaotic lifestyle.[3,4] Alcohol may be associated with increased antithrombotic effect of warfarin by protein-binding interactions and decreased metabolism through the cytochrome P450 system.[4] Furthermore, the newer direct thrombin inhibitors and factor Xa inhibitors do not offer likely alternatives because trials of the agents excluded substance abusers.[5–8] Managing patients with substance abuse who require anticoagulation is an area lacking guiding evidence.

The severity of abuse has been historically difficult to measure, and studies have used a variety of quantitative and qualitative data to address this issue. The DSM-IV uses criteria (such as failure to fulfill obligations, legal problems,

tolerance, withdrawal) to define abuse and dependence,[9] but clinicians may not record such distinctions, making subtleties of diagnoses less helpful. Attempts to use laboratory values to identify the severity of alcohol abuse are limited; a recent study found no utility of gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase/alanine aminotransferase, (AST:ALT) ratio, mean corpuscular volume (MCV) of erythrocytes, or apolipoproteins to predict unhealthy drinking.[10]

Therefore, this study addresses the following three questions: First, what clinically useful indicators, such as specific substance abuse diagnosis and common laboratory values, exist among patients with substance abuse to predict poor control with anticoagulation pharmacotherapy? Second, do these clinical indicators also predict rates of major hemorrhagic events? Finally, assuming patients with substance abuse have more major hemorrhagic events, does controlling for anticoagulation control eliminate the difference? We expected to find higher rates of major hemorrhage in patients with substance abuse diagnoses than others, and that more severe substance abuse would be associated with even higher rates. Answering these questions will help clinicians predict which patients with substance abuse disorders may safely receive warfarin and in which patients it is best avoided.

METHODS

Database

The Veterans AffaiRs Study to Improve Anticoagulation (VARIA) database included 103,897 patients receiving oral anticoagulation with warfarin from 100 sites of care in the Veterans Health Administration (VA) between October 2006 and September 2008.[11] Patients were considered to be receiving warfarin and thus included only when they were in possession of warfarin as dispensed by a VA pharmacy, or when they had international normalized ratio (INR) values recorded within the VA at least every 6 weeks, as this value is used by clinicians to adjust warfarin dosing. Values obtained during hospitalizations were excluded to minimize effect of acute illness, reversal for procedures, or alternative forms of anticoagulation. For this study, patients were excluded during their first 6 months on warfarin; thus, this is a database of experienced warfarin users. Patients with valvular heart disease as the primary indication for anticoagulation pharmacotherapy were excluded due to varying goal INR ranges. This study was approved by the institutional review board (IRB) of the Bedford VA Medical Center.

Definition of Substance Abuse

Patients were defined as having substance abuse disorders if at least one of the ICD-9 codes for substance abuse was recorded in VA inpatient or outpatient data during 10/1/06–9/30/08 (Online Appendix A).

Independent Variables: Risk Predictors

The independent clinical variables were the specific alcohol-related and drug-related diagnosis. We combined drug-related diagnoses, as preliminary analyses revealed little difference in anticoagulation control among specific drug-related ICD-9 codes (Online Appendix A). Though ICD-9 codes for cannabis abuse were part of the original definition of substance abuse,[11] we eliminated these from further analyses, as cannabis use had little effect on either time in therapeutic range (TTR) or hemorrhagic events (Online Appendix B). Likewise, the specific ICD-9 code used to describe alcohol abuse offered little additional predictive value, so we combined all such codes into a single category. We also examined the ability of the AUDIT-C, an annual alcohol screening tool collected on many VA patients,[12] to identify patients with alcohol abuse. AUDIT-C scores did not predict anticoagulation control or hemorrhage, either in patients with ICD-9 codes for alcohol abuse or those without. Therefore, we did not retain these data (Online Appendix C). For both drug and alcohol abuse, the specific ICD-9 code, frequency of coding, inpatient vs outpatient coding had little relationship to TTR and therefore were combined into categories of drug abuse only, alcohol abuse only, or both (data not shown).

Additionally, we examined the following putative markers as predictors of TTR and major hemorrhage among patients with substance abuse. Independent variables included the worst recorded and mean outpatient serum albumin, and bilirubin, ALT, AST, and ratio of AST:ALT (when both values obtained on the same day). These labs are readily available and often used by clinicians, despite the poor sensitivity and specificity of these labs to identify and evaluate the extent of substance abuse.[10] Albumin is often low in patients with poor nutritional status as well as liver disease. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are transaminases associated with metabolic processes of liver parenchymal cells and are often elevated in alcohol abuse, and a ratio of AST:ALT > 2.0 is suggestive of alcohol abuse.[13]

Dependent Variable: Anticoagulation Control

The percentage of time within therapeutic range (TTR) was calculated for each patient with Rosendaal's method, which uses linear interpolation to assign an INR value to each day between two successive observed INR values.[14] We then calculated the percentage of time during which the

interpolated INR values lie between 2 and 3 (between 0 % and 100 %).[14]

Dependent Variable: Major Hemorrhagic Events

The algorithm for identifying major hemorrhage was based in part on the definition of the International Society of Thrombosis and Haemostasis (ISTH).[15] ICD-9 codes were used to identify candidate events that occurred while the patients were undergoing anticoagulation using both VA and Medicare data.[16] Events were retained if they occurred while a patient was receiving warfarin, as described above, and fulfilled at least one of four conditions: 1) Associated with death within 30 days; 2) Associated with blood transfusion; 3) Associated with bleeding into a critical anatomic site; or 4) Cited as the main reason for a hospitalization.[16] Approximately 16 % of candidate events were retained as "major hemorrhages" by this definition, although this percentage was much higher for events likely to be severe (e.g. diverticula of colon, 46 %). Patients were censored after the first bleeding event; therefore, all analyses were time to first hemorrhagic event. For analyses of major hemorrhage, patients with Medicare Advantage were excluded due to concern for missing data, as these patients do not generate itemized bills to Medicare for each service rendered.

Covariates: Risk Factors for Bleeding

Additionally in the bleeding analysis, we controlled for other factors that have been validated as part of the HAS-BLED score for predicting hemorrhagic events in patients undergoing anticoagulation for atrial fibrillation.[17] HAS-BLED incorporates predictors of bleeding risk, including hypertension, chronic liver disease, chronic kidney disease, substance abuse, age, labile INR control, history of stroke, history of bleeding, and use of antiplatelet medications.[17] For the study, hypertension, liver disease, and history of stroke were obtained using ICD-9 codes. Age was also included, and chronic kidney disease was defined as having an eGFR below 40 by MDRD equation.[18] We included TTR as a covariate for this analysis to capture labile INR control. History of bleeding and use of antiplatelet agents were not available, but we controlled for the remainder of the HAS-BLED variables and sought to better define the predictors surrounding substance abuse.

Statistical Analyses

We examined the ability of laboratory values to predict TTR, in addition to the substance abuse diagnosis itself.

The laboratory values were examined first individually, and then in combination. Similarly, the ability of these laboratory values to predict major hemorrhage was also examined. To determine the proportion of hemorrhagic risk attributable to poor anticoagulation control as compared to substance abuse itself, we controlled for age in all analyses and additionally TTR and HAS-BLED risk factors in some analysis. We modeled age and TTR as categories rather than continuous variables. For bivariate tests we used ANOVA or chi-square, as appropriate; and for multivariate analyses, linear regression (for the TTR) or Cox Proportional Hazards Model (for major hemorrhage). All analyses were performed using SAS, version 9.1.

RESULTS

Characteristics of Patients with Substance Abuse

Of the 103,897 patients receiving warfarin, 6,781 (6.5 %) had a substance abuse disorder as defined by a diagnosis of any drug-related or alcohol-related ICD-9 codes (Appendix A). The baseline characteristics of the patients with and without alcohol or drug abuse are summarized in Table 1. ICD-9 codes were used to identify comorbid conditions and indications for anticoagulation. Patients with a substance abuse disorder were younger than those without (62.0 vs. 71.2 years, $p < 0.001$). Non-Hispanic Blacks were more likely to use drugs than non-Hispanic Whites. Patients using drugs, but not those abusing only alcohol, were less likely to be receiving warfarin for atrial fibrillation. Liver disease was much more common in patients with alcohol abuse as compared to those without (9.2 % vs. 0.7 %, $p < 0.001$). Remarkably, though the substance abusers were much younger than the general population, they had slightly higher rates of chronic obstructive pulmonary disease (COPD), epilepsy, and congestive heart failure (CHF). Not surprisingly, patients with substance abuse had much higher rates of mental health disorders.

Anticoagulation Control Among Patients with Substance Abuse

Patients with any substance abuse had a mean TTR that was lower compared to patients without substance abuse, as shown in Table 2. Specifically, as compared to patients without substance abuse (mean TTR of 62 %), those with alcohol abuse alone had an average TTR of 53 %, drug abuse alone 50 %, and combination of both 44 % ($p < 0.001$).

We examined the relationship of potential clinical indicators of poor outcomes in patients with substance abuse, with a goal of finding a marker for more severe decrements in TTR and hemorrhagic risk. Several factors had some ability to predict TTR, including levels of bilirubin, AST,

Table 1. Baseline Characteristics of Patients with and without Alcohol and Drug Abuse, Among Patients Receiving More than 6 Months of Oral Anticoagulation Therapy from the VA. Number and (%) Given. Total *n*=103,897

Variable	No drugs or alcohol (reference)	Alcohol only	Drugs only	Both drugs and alcohol
Total, N and column %	97,116 (93.5)	4,988 (4.8)	842 (0.8)	951 (0.9)
Sex				
Female	1,882 (1.9)	51 (1.0)	29 (3.4)	14 (1.5)
Male	95,234 (98.1)	4,937 (99)	813 (96.6)	937 (98.5)
Age (mean)	71.3	63.8	59.2	54.9
Race/ethnicity				
Non-Hispanic White	83,260 (85.7)	4,163 (83.5)	509 (60.5)	549 (57.7)
Non-Hispanic Black	8,465 (8.7)	497 (10.0)	268 (31.8)	342 (36.0)
Hispanic	3,013 (3.1)	160 (3.2)	31 (3.7)	25 (2.6)
Asian	378 (0.4)	7 (0.1)	4 (0.5)	3 (0.3)
Native American	411 (0.4)	24 (0.5)	9 (1.1)	5 (0.5)
Other/unknown	1,589 (1.6)	137 (2.7)	21 (2.5)	27 (2.8)
Primary indication for warfarin[*]				
Atrial fibrillation	63,109 (65.0)	2,930 (58.7)	344 (40.9)	373 (39.2)
Venous thromboembolism	25,701 (26.5)	1,710 (34.3)	427 (50.7)	512 (53.8)
All others combined	8,306 (8.6)	348 (7.0)	71 (8.4)	66 (6.9)
Physical comorbid conditions				
Cancer (newly diagnosed)	6,480 (6.7)	420 (8.4)	75 (8.9)	58 (6.1)
Chronic kidney disease (GFR < 40)	13,804 (14.2)	526 (10.5)	154 (18.3)	97 (10.2)
Chronic liver disease	689 (0.7)	461 (9.2)	17 (2.0)	61 (6.4)
Chronic lung disease	27,721 (28.5)	1,894 (38.0)	353 (41.9)	343 (36.1)
Coronary artery disease	49,695 (51.2)	2,083 (41.8)	397 (47.1)	368 (38.7)
Diabetes	39,297 (40.5)	1,592 (31.9)	323 (38.4)	295 (31.0)†
Epilepsy	2,577 (2.7)	213 (4.3)	51 (6.1)	62 (6.5)
Heart failure	31,279 (32.2)	1,804 (36.2)	333 (39.5)	311 (32.7)
Mental comorbid conditions				
Bipolar disorder	1,771 (1.8)	304 (6.1)	92 (10.9)	192 (20.2)
Dementia	5,181 (5.3)	235 (4.7)	53 (6.3)	22 (2.3)
Major depression	19,302 (19.9)	1,989 (39.9)	449 (53.3)	638 (67.1)

*Patients with valvular disease were excluded due to varying goal ranges of INR.

ALT, and albumin (data not shown). However, the most striking finding was among alcohol abusers with increasing ratios of AST:ALT. Those with AST:ALT ratios greater than 2.0 had exceptionally poor TTR (44 %), while alcohol abusers with a normal ratio of ≤ 1.5 had only a modestly decreased TTR (54 %) compared to nonusers. Increasing ratios from 1.0 to 3.0 displayed a near linear decrease in TTR; this continuous predictor and continuous outcome is depicted by a cubic smoothing spline in Fig. 1.

Hemorrhagic Events among Patients with Substance Abuse

Patients with any sort of substance abuse had increased incidence of major hemorrhage (Table 3). We observed 142,348 patient years among 84,492 patients, with a total of 4,525 major hemorrhagic events. Age-adjusted hazard ratios (HR) for major hemorrhage were 1.93 ($p<0.001$) in patients with drug abuse and 1.37 ($p<0.001$) with alcohol. Among patients abusing alcohol, an increasing AST:ALT ratio was associated with more hemorrhagic events. We modeled the AST:ALT ratio as a time-varying covariate, allowing AST:ALT to vary as often as every 30 days. An AST:ALT ratio of > 2.0 had an age adjusted hazard ratio of 3.02 compared to nonusers ($p<0.001$), while those with a normal ratio had a HR of 1.19 compared to nonusers ($p<0.05$). Controlling for anticoagulation control and other bleeding

risk factors, in addition to age, attenuated these effects somewhat, but the increase in hemorrhagic events among patients with an abnormal AST:ALT ratio remained present and statistically significant (Table 3).

DISCUSSION

Using data from the VA, we looked for predictors of anticoagulation control and major hemorrhagic events among substance-abusing patients receiving warfarin. Patients with substance abuse disorders had poorer

Table 2. Anticoagulation Control (Percent Time in Therapeutic Range, or TTR) in Subcategories of Substance Abuse Among Patients Receiving Anticoagulation Therapy from the VA

| Variable	Number of patients	Mean % TTR (95 % CI)
No alcohol or drugs (reference)	97,116	62.3 (62.1–62.4)
Alcohol only	4,988	53.0 (52.4–53.6)*
Drugs only	842	50.2 (48.6–51.7)*
Both alcohol and drugs	951	44.0 (42.5–45.5)*
Alcohol Status and AST:ALT ratio		
No Alcohol (reference)	97,958	62.2 (62.0–62.3)
Alcohol and AST:ALT ≤ 1.5	3,708	54.2 (53.5–54.9)*
Alcohol and AST:ALT > 1.5–2.0	1,298	49.4 (48.2–50.6)*
Alcohol and AST:ALT > 2.0	933	44.1 (42.6–45.5)*

*p< 0.001, compared to the reference category
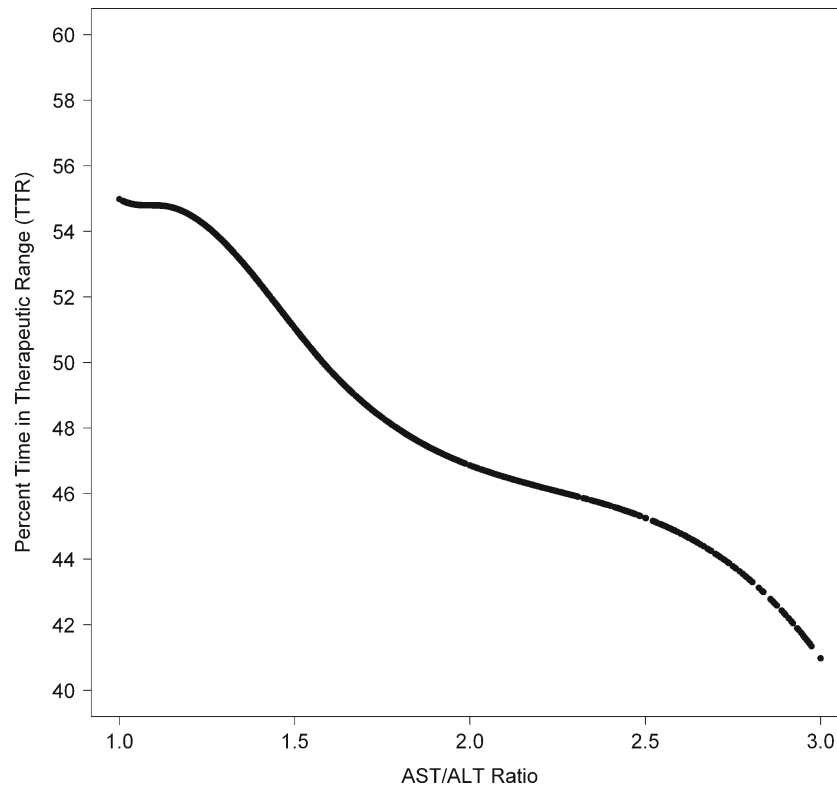
Figure 1. Among patients receiving oral anticoagulation pharmacotherapy from the VA with alcohol abuse, patient-level percent time in therapeutic range (TTR) vs. AST:ALT ratio, plotted using a cubic smoothing spline.[34]

anticoagulation control and elevated hazard of major hemorrhage. Additionally, in patients abusing alcohol, an elevated AST:ALT ratio identified patients with especially poor anticoagulation control and outcomes. This finding may have considerable clinical utility, by offering a simple, readily available indicator of a patient's likelihood to succeed on warfarin. While a ratio of AST:ALT of 2.0 is often used to identify alcohol pattern liver damage,[13] our study shows poorer outcomes increase substantially beginning at a ratio of 1.5. Another important finding is that while controlling for TTR somewhat attenuated the impact of substance abuse on rates of hemorrhage, it did not fully

explain the association between abuse and hemorrhage. This suggests that the excess bleeding risk is not entirely attributable to poor anticoagulation control; hence, improving anticoagulation control should not be the only clinical intervention in these patients.

This study is consistent with earlier findings that substance abuse is an important risk factor for major hemorrhage.[17] Risk of hemorrhage is a major concern for physicians contemplating prescribing warfarin. Drug and alcohol abuse have been incorporated into the HAS-BLED score,[17] a validated scoring system used to predict hemorrhagic events in patients undergoing anticoagulation for

Table 3. Time to Event Analysis of Any Major Hemorrhage in Patients with and without Alcohol and/or Drug Abuse Receiving Oral Anticoagulation in the VA Cohort. (*n*=4,525 Major Bleeding Events in 86,492 Patients)

Variable	Number of patients	Number of events	Total patient-years of follow-up	Event per 100 patient-years	Hazard ratio adjusted for age only (95 % CI)	Hazard ratio adjusted for bleeding risk factors[*] (95 % CI)
No alcohol or drugs	80,337	4,206	132,560	3.2	–	–
Alcohol only	4,482	232	7,224	3.2	1.37 (1.20–1.57)**	1.23 (1.07–1.41)‡
Drugs only	777	48	1,219	3.9	1.93 (1.45–2.58)**	1.59 (1.19–2.12)‡
Both alcohol and drugs	896	39	1,442	2.7	1.61 (1.17–2.22)‡	1.27 (0.92–1.75)
No alcohol	81,114	4,254	133,780	3.2	–	–
Alcohol and AST:ALT ≤1.5[†]	3,382	125	5,549	2.3	1.19 (1.03–1.38)‡	1.08 (0.93–1.26)
Alcohol and AST:ALT >1.5–2.0[†]	1,153	76	1,835	4.1	1.88 (1.42–2.48)**	1.53 (1.15–2.03)‡
Alcohol and AST:ALT >2.0[†]	843	70	1,282	5.5	3.02 (2.13–4.28)**	2.31 (1.63–3.29)**

[*]*Controls for hypertension, renal disease, liver disease, age, sex, race, TTR, history of stroke by ICD-9 code.*
[†]*The AST:ALT ratio was analyzed as a time-varying covariate and was allowed to change as often as every 30 days, depending on when it was re-measured.*
‡*P<0.05*
**P<0.001*

atrial fibrillation. Many studies have shown that warfarin is underutilized and its risks are over-estimated by physicians.[19–22] In particular, warfarin is underutilized in patients with atrial fibrillation with co-morbid substance abuse,[23] but evidence to support this decision has been sparse.[24, 25] A recent systematic review found a statistically significant increase in hemorrhages in alcohol abusers in less than half of the studies and reported overall strength of the evidence as low.[25]

Poorer anticoagulation control in substance-abusing patients is concerning, since improved control is associated with fewer adverse events.[26–30] The reasons for poorer anticoagulation control among substance abusers are not fully understood, but likely involve pharmacology as well as compliance. While the specific interactions of warfarin and street drugs is not known, alcohol enhances the antithrombotic effect of warfarin through protein-binding interactions and decreased metabolism of warfarin through the cytochrome P450 system.[4] Notably, the poorer anticoagulation control in patients with substance abuse does not completely explain their increased rate of hemorrhagic events. Even after controlling for age and TTR, substance abusers had more hemorrhages, which may reflect a lifestyle of addiction, risky living environments, more frequent falls, underlying alcohol-related gastritis and varices leading to a propensity for bleed, or other factors. Therefore, clinicians might emphasize substance abuse intervention in addition to medically managing other modifiable bleeding risk factors.

In our study, patients with alcohol abuse and normal AST:ALT ratio had a similar risk of hemorrhagic events as nonusers. Physicians then may find that the benefits of oral anticoagulation likely outweigh the risks in such patients. Conversely, patients with an AST:ALT >1.5, and especially >2.0, had considerably poorer outcomes, both in terms of anticoagulation control and hemorrhagic events. While our study is not equipped to inform the entire risk-benefit calculation, it may assist the clinician to identify patients at risk for poor anticoagulation control and bleeding complications.

Some limitations should be noted. First, the study population of veterans was heavily male and may not reflect a general population of substance abusers. Second, the study cohort included only patients who had completed at least 6 months of warfarin, and may not apply to patients undergoing shorter courses or initiating therapy. This may select for patients who already demonstrated stability and those receiving warfarin for more serious indications. Third, our study does not consider patients with valvular heart disease due to variations in target therapeutic range. Fourth, we assessed major hemorrhagic events using automated data rather than chart review, although our algorithm is the result of careful development.[16] Fifth, while we show that controlling for anticoagulation control only partially impacts bleeding risk, we do not distinguish if the INR is supratherapeutic at the time of the bleeding event. Sixth, while we control for many known risk factors for hemorrhages while on warfarin, we are unable to account for previous hemorrhagic events or antiplatelet pharmacotherapy. Finally, we considered neither strokes nor recurrent venous thromboembolic events, as these outcomes are difficult to assess from automated data alone.[31–33] Future studies could collect more detailed information, particularly regarding the extent of substance abuse. Furthermore, comparing outcomes such as thromboembolic events in this population of both those who receive and do not receive warfarin therapy, would help clinicians balance the risks and benefits of therapy. While the present study provides helpful information regarding the risks of anticoagulation in patients with substance abuse, clearly the risks of foregoing such therapy must also be considered.

In conclusion, we examined a large database of VA patients receiving anticoagulation with warfarin for varied indications. Patients with substance abuse had notably poor anticoagulation control and elevated risk for major hemorrhage, even after controlling for covariates. Among patients with alcohol abuse, an elevated AST:ALT ratio holds promise for separating patients with elevated risk of hemorrhage from those whose risk may not differ meaningfully from the overall population.

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