Outcomes of Anticoagulation Therapy in Patients with Mental Health Conditions

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BACKGROUND: Patients with mental health conditions (MHCs) experience poor anticoagulation control when using warfarin, but we have limited knowledge of the association between specific mental illness and warfarin treatment outcomes.

OBJECTIVE: To examine the relationship between the severity of MHCs and outcomes of anticoagulation therapy.

DESIGN: Retrospective cohort analysis.

PARTICIPANTS: We studied 103,897 patients on warfarin for 6 or more months cared for by the Veterans Health Administration during fiscal years 2007–2008. We identified 28,216 patients with MHCs using ICD-9 codes: anxiety disorders, bipolar disorder, depression, post-traumatic stress disorder, schizophrenia, and other psychotic disorders.

MAIN MEASURES: Outcomes included anticoagulation control, as measured by percent time in the therapeutic range (TTR), as well as major hemorrhage. Predictors included different categories of MHC, Global Assessment of Functioning (GAF) scores, and psychiatric hospitalizations.

KEY RESULTS: Patients with bipolar disorder, depression, and other psychotic disorders experienced TTR decreases of 2.63 %, 2.26 %, and 2.92 %, respectively (p <0.001), after controlling for covariates. Patients with psychotic disorders other than schizophrenia experienced increased hemorrhage after controlling for covariates [hazard ratio (HR) 1.24, p=0.03]. Having any MHC was associated with a slightly increased hazard for hemorrhage (HR 1.19, p<0.001) after controlling for covariates.

CONCLUSION: Patients with specific MHCs (bipolar disorder, depression, and other psychotic disorders) experienced slightly worse anticoagulation control. Patients with any MHC had a slightly increased hazard for major hemorrhage, but the magnitude of this difference is unlikely to be clinically significant. Overall, our results suggest that appropriately selected patients with MHCs can safely receive therapy with warfarin.

KEY WORDS: anticoagulation; mental health; veterans; warfarin therapy; psychiatric conditions.
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INTRODUCTION

Mental illness affects one in four Americans[1] and is associated with worse health outcomes. Among patients with various medical illnesses, those with mental health conditions (MHCs) encounter greater barriers to care, receive less intense management, undergo fewer interventions, and experience worse outcomes.[2–7] Factors contributing to some of these observations include non-adherence, fragmentation of care, stigma, and biases.[8–10]

Warfarin is a widely used anticoagulant, but its utility can only be optimized with regular evaluation and dose adjustment, which promote improved anticoagulation control.[11] Percent time in the therapeutic range (TTR) provides a summary measure of overall anticoagulation control, with lower TTR being associated with more adverse outcomes, such as stroke, venous thromboembolism, and major hemorrhage.[11–15] Among patients with atrial fibrillation, those with MHCs are known to be less likely to be started on warfarin therapy,[16] and are more likely to have poorly controlled therapy[17] and to experience adverse events such as hemorrhage and stroke.[18]

However, important questions regarding MHC and warfarin therapy remain unanswered. We do not know which MHCs are most strongly associated with low TTR and adverse events, and whether MHC-specific risk factors,

such as a history of psychiatric hospitalization or the Global Assessment of Functioning (GAF) score, can help to identify an especially vulnerable subgroup of patients.

We sought to examine the association of specific MHCs with anticoagulation control and major hemorrhage; to determine the portion of risk for hemorrhage attributable to poor anticoagulation control; and to examine the ability of additional MHC-specific severity indicators—GAF and psychiatric hospitalization—to more precisely determine risk for patients with MHCs receiving warfarin therapy. We hypothesized that different MHCs would affect anticoagulation control and bleeding non-uniformly and that psychiatric diagnoses, GAF scores, and psychiatric hospitalization history would be independent predictors of lower TTR and increased incidence of major hemorrhage.

METHODS

Study Population

We used data from the Veterans AffaiRs Study to Improve Anticoagulation (VARIA),[17,19] which included patients receiving warfarin therapy from the Veterans Health Administration (VHA) between October 1, 2006 and September 30, 2008. To eliminate the complexities uniquely associated with therapy initiation, we only included data from the 103,897 "experienced" warfarin users, who had been on warfarin for at least 6 months (Table 1). We excluded patients with valvular heart disease or mechanical heart valves because of their different INR goals. The study was approved by the Institutional Review Board of the Bedford Veterans Affairs (VA) Medical Center.

Table 1. Characteristics of Experienced Warfarin Users with and Without Mental Health Conditions During Fiscal Years 2007–2008 in the Veterans Health Administration (*N*=103,897)

Variables	With any mental health condition *N*=28,216 (%)	No mental health conditions *N*=75,681 (%)
Female gender	881 (3.1)	1,095 (1.4)
Age group		
20–54	3,395 (12.0)	3,957 (5.2)
55–59	5,327 (18.9)	6,156 (8.1)
60–64	4,493 (15.9)	8,174 (10.8)
65–69	2,756 (9.8)	8,885 (11.7)
70–74	3,416 (12.1)	13,546 (17.9)
75+	8,829 (31.3)	34,963 (46.2)
Race/ethnicity		
Non-Hispanic white	23,666 (83.9)	64,815 (85.6)
Non-Hispanic black	2,827 (10.0)	6,745 (8.9)
Others	1,723 (6.1)	4,121 (5.4)
Primary indication for warfarin*		
Atrial fibrillation	15,801 (56.0)	50,955 (67.3)
Venous thromboembolism	9,990 (35.4)	18,360 (24.3)
All others combined	2,425 (8.6)	6,366 (8.4)
Time since warfarin inception		
≥6 months before study inception	19,815 (70.2)	57,343 (75.8)
6 months before study: First year of study	7,111 (25.2)	15,541 (20.5)
Second year of study	1,290 (4.6)	2,797 (3.7)
Comorbid conditions		
Alcohol abuse	4,818 (17.1)	4,765 (6.3)
Cancer (newly diagnosed)	2,039 (7.2)	4,994 (6.6)
Chronic kidney disease	4,102 (14.5)	10,479 (13.8)
Chronic liver disease	466 (1.7)	762 (1.0)
Chronic lung disease	10,134 (35.9)	20,177 (26.7)
Dementia	2,615 (9.3)	2,876 (3.8)
Diabetes	11,926 (42.3)	29,581 (39.1)
Epilepsy	1,313 (4.7)	1,590 (2.1)
Heart failure	9,768 (34.6)	23,959 (31.7)
Hypertension	20,948 (74.2)	54,916 (72.6)
Stroke	6,147 (21.8)	14,229 (18.8)
Substance abuse (non-alcohol)	2,766 (9.8)	1,398 (1.8)
Mean no. (SD) of non-warfarin medications	11.3 (4.9)	8.1 (4.2)

$p < 0.001$ for all comparisons (t-test and chi-square)
**Patients with valvular heart disease or mechanical heart valves were excluded*

Categories of Mental Health Disorders

We identified six categories of MHC: anxiety disorders, bipolar disorder, major depressive disorder, post-traumatic stress disorder (PTSD), schizophrenia, and other psychotic disorders. Online Appendix 1 lists the International Classification of Disease, 9th Revision (ICD-9) codes that comprise each category. We also compared the proportions of patients with MHCs in our cohort to historical norms based on the 1999 Veterans' Large Health Survey[20] (Online Appendix 5).

Independent Variable: GAF Score

GAF is a component of comprehensive psychiatric assessment and is scored on a scale of 0 to 100 based on a patient's overall psychological, occupational, and social function and symptom severity.[21] A lower score suggests worse function or symptoms. A directive from the VHA in 1999 recommended that mental health patients be rated a GAF at time of discharge from psychiatric hospitalization and at least once every 90 days during active outpatient treatment.[22] While some studies have found an association between GAF and patient outcomes,[22,23] other studies have casted doubt on the utility of the GAF score for predicting clinical outcomes and allocating resources.[24,25]

Because GAF is scored based on the lowest level of function or worst symptom, typically over the previous week[21,26,27], we examined all GAF scores for patients with MHCs and selected the lowest GAF during the 2-year study period. Analysis using mean GAF scores had similar results (Online Appendix 3, Table 5). We also partitioned GAF into four groups based on severity descriptors[21]. GAF scores of 0–30, 31–50, 51–70, and 71–100 correspond to severe impairment with hallucination and suicidal symptoms, major impairments and serious symptoms, mild to moderate symptoms, and transient or no impairment or symptoms, respectively.

We assigned the 12,471 patients without documented GAF a "missing GAF" indicator and contrasted the characteristics of these patients with those with GAF (Online Appendix 2). We also imputed for missing GAF using multiple imputation (SAS PROC MI and PROC MI ANALYZE) and compared the results obtained using the category of "missing" GAF with the results obtained after imputing missing GAF scores.

Independent Variable: Psychiatry Hospitalization

We used a linked VA-Medicare data set to identify psychiatric hospitalization events. We examined inpatient codes during fiscal years 2002–2008 and considered a hospitalization to be psychiatric when its primary discharge diagnosis was on the list we had used to define MHCs.

Other Independent Variables

Other independent variables included age, gender, race, indications for anticoagulation, date of warfarin inception, comorbidities, alcohol abuse, non-alcohol substance abuse, and the number of non-warfarin medications and hospitalizations. Comorbidities included cancer, chronic kidney disease, chronic liver disease, chronic lung disease, dementia, diabetes, epilepsy, heart failure, hypertension, and stroke. In our Cox regression model, we adjusted for known risk factors for bleeding based on the HAS-BLED bleeding risk assessment model for patients on warfarin for atrial fibrillation.[28] Based on data availability, we created a HAS-BLED-derived factor set, which included age, hypertension, abnormal liver function, chronic kidney disease, labile INR, and alcohol abuse. We were unable to control for two variables that are part of the HAS-BLED score, namely prior bleeding and non-steroidal anti-inflammatory drugs, because of the inability to identify these variables with confidence in our data set.

Dependent Variable: Anticoagulation Control

We used Rosendaal's method[29] to calculate the percent time in the therapeutic range (TTR) for each patient. We assigned an international normalized ratio (INR) value to each day between successively recorded INR values using linear interpolation and computed TTR based on the fraction of time (0–100 %) during which these interpolated values fell between 2 and 3, which is the target INR range for most indications for warfarin therapy. In the multivariate model for major hemorrhage, we defined TTR to be a six-level categorical variable based on the following ranges: 0–30 %, 31–40 %, 41–50 %, 51–60 %, 61–70 %, and 71–100 %.

Dependent Variable: Major hemorrhage

We identified episodes of major hemorrhage based on an algorithm that we adapted from the definition of the International Society of Thrombosis and Haemostasis (ISTH) for use with our automated VA-Medicare data set.[30] Those patients with Medicare Part C were excluded from analyses of hemorrhage because of a high likelihood of incomplete event ascertainment, as Medicare Part C does not generate itemized bills for episodes of care. We aggregated the ICD-9 codes for hemorrhage and determined an event to be a "major hemorrhage" based one of four criteria: bleeding associated with death within 30 days, life-threatening bleeding into a critical anatomic site, bleeding accompanied by a blood transfusion, or bleeding as the primary reason for hospital admission.

Analyses

We conducted bivariate analyses to compare the clinical and demographic characteristics of patients with and without MHCs and to compare TTR for patients with different MHCs, GAF scores, and psychiatric hospitalization history.

We created four nested linear regression models to determine the association between MHCs and TTR. In model 1, we included only MHCs, and in model 2, we adjusted for gender, age, and race. In model 3, we adjusted additionally for comorbid conditions, and in model 4, we added an additional covariate including date of warfarin inception, primary indication for warfarin, and the number of non-warfarin medications and hospitalizations.

We also created four Cox proportional hazards regression models to determine the effect of different MHCs and other independent variables after adjusting for known predictors of bleeding. We censored patients after the first major hemorrhage event, and TTR was included in the model as a six-level categorical variable. Those patients with Medicare Part C were excluded from analysis because of incomplete event ascetainment[30]. In model 1, we analyzed the effect of any MHC on major hemorrhage, and in model 2, we analyzed the effect of individual MHCs on major hemorrhage. Both models included the entire study population. Models 3 and 4 included only patients with MHCs to determine the additional effect of GAF, hospitalization, and specific MHCs. In model 3, those missing GAF scores in the database were included in the analysis as a separate category. In model 4, those without GAF were included in the model based on GAF values derived from the imputation algorithm using SAS PROC MI and PROC MI ANALYZE.

In addition, we performed a propensity score match between patients with and without MHCs to generate a set of matched "controls" without MHCs whose data looked like the MHC patients in other respects, including demographics, comorbid conditions, and anticoagulation control.

We then computed the hazard ratio of major hemorrhage between patients with MHCs and their propensity-matched controls. We performed all statistical analyses using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Among 103,897 experienced warfarin users, 28,216 (27.2 %) had at least one of the MHCs examined in our study. Patients with MHCs were more likely to be female, of non-white race, and have venous thromboembolism as the primary indication for warfarin (Table 1). Although they were younger, patients with MHCs had more comorbidities and substance abuse issues than those without MHCs, including chronic lung disease (35.9 % vs. 26.7 %, $p<0.001$), alcohol abuse (17.1 % vs. 6.3 %, $p<0.001$), and non-alcohol substance abuse (9.8 % vs. 1.8 %, $p<0.001$).

Unadjusted Effect of Psychiatric Hospitalization

Table 2 shows that those with MHCs had worse anticoagulation control compared to those without MHCs (TTR 57.1 % vs. 63.2 %, $p<0.001$), and those with a psychiatric hospitalization history experienced even poorer anticoagulation control than MHC patients without such history (50.5 % vs. 57.6 %, $p<0.001$). The additional TTR reduction attributable to hospitalization ranged from 3.5 % for those with anxiety disorder to 7.1 % for those with bipolar disorder.

Table 2. The Association Between Mental Health and Anticoagulation Control Stratified by Psychiatric Hospitalization History Among Experienced Warfarin Users with Mental Health Conditions (*N*=28,216)

	Psychiatric hospitalization				Overall
	None		At least one		
	N	Mean TTR	*N*	Mean TTR	TTR
No mental health condition	75,681	63.2 %	–	–	63.2 %
Any mental health condition	26,562	57.6 %	1,654	50.5 %*	57.1 %‡
Diagnostic groups					
Anxiety disorders	8,044	57.8 %	73	54.4 %	57.8 %‡
Bipolar disorder	2,102	54.0 %	316	46.9 %*	53.1 %‡
Depression	18,795	56.8 %	780	50.0 %*	56.5 %‡
PTSD	7,219	57.1 %	329	51.5 %*	56.8 %‡
Schizophrenia	847	55.1 %	257	50.8 %†	54.1 %‡
Other psychotic disorders	1,909	54.3 %	86	48.2 %†	54.0 %‡

MHC: Mental health condition; PTSD: post-traumatic stress disorder
TTR: Percent time in the therapeutic range
**p< 0.05 and †p< 0.001 (t-test) compared to those without psychiatric hospitalization in the same category*
‡p< 0.001 (t-test) compared to those without mental health conditions

Unadjusted Effect of GAF

Lower GAF scores were associated with worse anticoagulation control (Table 3). Compared to those with GAF scores of 51–70, patients with lower GAF scores of 31–50 and 0–30 recorded lower TTR (54.3 % and 49.0 % vs. 57.3 %, $p<0.05$), while those with GAF scores above 70 recorded higher TTR (60.9 % vs. 57.3 %, $p<0.05$).

Multivariate Analysis of TTR

Table 4 includes the results of linear regression analysis of the association between specific MHCs and TTR. The results showed that those with bipolar disorder, depression, and other psychotic disorders had statistically significant decreased TTR in all four models. After adjusting for all available covariates, those with bipolar disorder had a 2.63 % decrease in TTR, while those with depression and other psychotic disorders had 2.26 % and 2.92 % decreases, respectively ($p<0.001$ for all 3 comparisons).

Hazard Rates of Major Hemorrhage

Table 5 includes four nested Cox regression models to predict major hemorrhage. Models 1 and 2 showed the effect of any MHC and of specific types of MHC among the entire study population. Compared to those without MHCs, patients with any MHC had an increased hazard for major hemorrhage after adjusting for known bleeding risk factors (i.e., HAS-BLED) (HR 1.19, $p<0.001$). In particular, patients with anxiety disorders, depression, and other psychotic disorders had slightly increased hazard for hemorrhage, compared to patients without MHCs (HR 1.13, $p=0.03$; HR 1.16, $p<0.001$; HR 1.25, $p=0.01$).

Models 3 and 4 included only those with MHCs. After adjusting for known predictors of bleeding, in model 3, higher GAF showed a trend toward decreased hemorrhage, but this trend was not statistically significant. After imputation of missing GAF scores (model 4), the GAF no longer showed any trend. In addition, psychiatric hospitalization was not associated with increased hemorrhage in

Table 3. The Effect of GAF Scores on Anticoagulation Control and Major Hemorrhage Among Experienced Warfarin Users with Mental Health Conditions (*N*=28,216)

GAF Score	*N*	Average TTR
Missing	14,588	58.3 %*
71–100	439	60.9 %*
51–70 (reference)	6,759	57.3 %
31–50	6,067	54.3 %*
0–30	363	49.0 %*

**p< 0.05 (ANOVA; Tukey's test) compared to the reference category (GAF 51–70)*
TTR: Percent time in therapeutic range

Table 4. Nested Linear Regression Models of the Association Between Mental Health Conditions and Percent Time in Therapeutic Range, a Measure of Anticoagulation Control (*N*=103,897)

	Model 1	Model 2	Model 3	Model 4
Intercept	63.06†	64.22†	66.35†	67.54†
Model R^2	0.0168	0.0306	0.0532	0.0756
Anxiety disorders	−1.31†	−1.18†	−0.86†	0.18
Bipolar disorder	−5.50†	−4.55†	−3.74†	−2.63†
Depression	−5.06†	−4.41†	−3.54†	−2.26†
PTSD	−2.22†	−1.12†	−0.68*	−0.01
Schizophrenia	−4.40†	−2.22†	−1.43*	−0.36
Other psychotic disorders	−5.59†	−5.77†	−4.51†	−2.92†

**p< 0.05 and †p< 0.001*
The coefficients associated with the other covariates are included in the Online Appendix 7
Model 1 adjusts for no other covariates
Model 2 adjusts for demographic information (gender, age, and race)
Model 3 adjusts for demographic information and comorbid conditions (hypertension, stroke, chronic liver disease, chronic kidney disease, alcohol abuse, and non-alcohol substance abuse)
Model 4 adjusts for demographic information, comorbid conditions, date of warfarin inception, indication for warfarin therapy, and the number of non-warfarin medications and hospitalizations

either model. However, patients with psychotic disorders other than schizophrenia had increased hemorrhage compared to patients with no MHC (model 3, HR 1.24, p=0.03) even after imputation for missing data (model 4, HR 1.24, p=0.03).

Propensity Score Match

We created a propensity score to predict which patients would have any MHC. Predictors included demographics, comorbid conditions, and anticoagulation control. We then matched 28,216 case patients (who had MHCs) with 28,216 control patients who did not have MHCs but who looked like the MHC patients in other respects. Pairs were matched within 5 % on the propensity score. Patients with MHCs (cases) were highly matched with those without MHCs (controls) for all available variables (Online Appendix 6). We repeated our main analysis regarding the hazard for major hemorrhage among this propensity-matched sample. There was no statistically significant difference between the groups, but if anything the patients with MHCs appeared to have a trend toward a reduced hazard for major hemorrhage compared to matched control patients (HR 0.94, 95 % CI: 0.87–1.01).

DISCUSSION

Our study examined outcomes of anticoagulation therapy among patients with and without MHCs, including anticoagulation control and major hemorrhage. In addition, our study is the first to examine putative severity indicators among patients with MHCs and their association with such outcomes. Our findings suggest that patients with MHCs had worse anticoagulation control as indicated by lower TTR, particularly among patients with bipolar disorder, depression, and other psychotic disorders. However, while patients with MHC did have a statistically significant increase in the hazard for major hemorrhage, the magnitude of this effect was small and likely not clinically significant. The propensity matched analysis also supports the contention that patients with and without MHCs did not differ significantly with regard to hemorrhage, especially after controlling for other patient factors. Also, other predictors including GAF and psychiatric hospitalization did not confer an increased bleeding risk among patients with MHCs.

Table 5. Hazard Ratios Based on Cox Regression Models to Predict Episodes of Major Hemorrhage

	All patients (*N*=86,492‡)		Only patients with MHCs (*N*=24,439§)	
	Model 1	Model 2	Model 3: without imputation	Model 4: with imputation
Any mental health condition	1.19 (1.11–1.27)†	–	–	–
GAF >50‖	–	–	0.86 (0.73–1.02)	1.00 (0.90–1.12)
GAF missing‖			1.01 (0.87–1.18)	
Psychiatric hospitalization	–	–	1.10 (0.86–1.41)	1.12 (0.88–1.43)
Anxiety disorders	–	1.13 (1.02–1.26)*	1.12 (0.99–1.27)	1.10 (0.98–1.25)
Bipolar disorder	–	1.10 (0.91–1.34)	1.11 (0.91–1.36)	1.09 (0.89–1.33)
Depression	–	1.16 (1.07–1.25)†	1.14 (0.99–1.30)	1.12 (0.98–1.27)
PTSD	–	1.01 (0.89–1.14)	1.00 (0.87–1.15)	0.98 (0.86–1.13)
Schizophrenia	–	0.84 (0.61–1.16)	0.82 (0.59–1.15)	0.81 (0.59–1.13)
Other psychotic disorders	–	1.25 (1.05–1.49)*	1.24 (1.02–1.50)*	1.24 (1.02–1.50)*

GAF: Global Assessment of Functioning score; MHC: mental health condition
PTSD: Post-traumatic stress disorder; TTR: percent time in therapeutic range
**p< 0.05 and †p< 0.001*
Covariates for all models include age, TTR, hypertension, stroke, chronic liver disease, chronic kidney disease, alcohol abuse, and non-alcohol substance abuse. Online Appendix 4 includes the coefficients for all of the covariates not shown here
‡Excluded 17,405 patients with Medicare Part C without major hemorrhage data
§Excluded 3,777 patients with Medicare Part C without major hemorrhage data
‖Compared to reference group GAF≤50

In our database, 27 % of patients receiving warfarin from the VA carried a diagnosis for one or more MHCs. Compared to the 1999 Veteran's Large Health Survey[20] (Online Appendix 5), patients with depression, anxiety, and PTSD were not underrepresented in our study compared to the prevalence of these conditions among the overall population of VA patients. This similar prevalence suggests that our study's finding of no clinically significantly increased bleeding risk may be applicable to the general population of VA patients with depression, anxiety, and PTSD. However, patients with schizophrenia and bipolar disorder were under-represented in our database compared to their known prevalence in the VA population. This suggests that the patients with these conditions who were included in our study, because they received warfarin therapy, may have been more highly selected as likely ideal candidates for warfarin therapy.

Our observational study specifically examined the outcomes among patients whose clinicians thought that they were acceptable recipients of warfarin therapy beyond 6 months. We did not include patients needing anticoagulation who were never started on warfarin therapy, treated with warfarin for less than 6 months, and those who might have been judged to have unacceptably high risks for adverse outcomes by their clinicians. One area of additional examination would be to look at patients who were started on warfarin but were not continued on it for a full 6 months to see whether there is a difference in mental health attributes. Other areas of inquiry may include looking at additional barriers to care, such as health literacy and medication adherence, as possible contributors to differences in anticoagulation control.

Limitations

Our study has several limitations. While our database allowed us to study a large population of patients, we could not validate the completeness and accuracy of administrative data. Because our method of categorization differed from other studies[31], direct comparison of studies might be difficult. While our algorithm[30] for identifying major hemorrhage had face validity, it clearly could not be as precise as a chart review. Moreover, we lacked the data power to identify new thromboembolic events, which could have been contrasted with bleeding rates to better evaluate the overall risk and benefit of warfarin therapy.

Finally, our study included only those patients who were already considered to be appropriate for warfarin therapy, who actually received anticoagulation in the VA during our study period, and who remained on it successfully for at least 6 months. We did not specifically look for those who were taken off of warfarin during the study period to determine the impact of MHCs on the rate of warfarin discontinuation. Therefore, the study clearly was not reflective of what would have happened if all patients with MHCs and an indication for warfarin had received it.

CONCLUSIONS

Our study showed, among patients who had received warfarin for 6 or more months, that patients with MHCs did not have a meaningfully increased hazard for major hemorrhage as compared to those without MHCs, and could safely continue on warfarin therapy beyond 6 months. Subgroups of patients with MHCs experienced slightly worse anticoagulation control as indicated by lower TTR, but overall they did not experience clinically significant increases in major hemorrhage. We lacked data to determine whether they had experienced increased stroke or venous thromboembolic events. Those with other psychotic conditions showed a statistically significant increased risk of major hemorrhage, but this small increase might not translate into significance in clinical practice, and the result should be interpreted with the large size of our database in mind.

Our study therefore provides a reassuring message regarding warfarin therapy in patients with MHCs, in that most patients with MHCs do not experience clinically significant increased major hemorrhage, and suggests that most mental health conditions do not, by themselves, represent a contraindication to warfarin therapy. However, our study cannot be used to predict which patients with MHCs a priori will be good candidates for initiation of warfarin therapy as we limited the analysis to those who had already received treatment for 6 or more months. Additional studies should be done to determine the characteristics of patient with MHCs associated with early warfarin discontinuation to help identify additional risk factors for adverse outcomes.

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Conflict of Interest: *Dr. Hylek has served on advisory boards for Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Johnson and Johnson, Merck, and Pfizer. None of the other authors report any potential conflicts of interest.*

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