The Effect of Antipsychotic Treatment on Recurrent Venous Thromboembolic Disease: A Cohort Study

Augusto Ferraris, MD[a,b,*]; Alejandro G. Szmulewicz, MD, MPH[b,c]; M. Lourdes Posadas-Martínez, MD, MSc, PhD[a]; Marina Alonso Serena, MD[a]; Fernando J. Vazquez, MD, PhD[a]; and Federico Angriman, MD, MPH[d]

ABSTRACT

Background: Venous thromboembolism (VTE) represents a major cause of morbidity and mortality worldwide. Antipsychotic treatment is associated with an increased risk of thromboembolic disease, an effect that seems to be constant across the spectrum of distinct agents. This study sought to delineate the effect of new antipsychotic use on the risk of recurrent thromboembolic events after a first episode of either deep venous thrombosis or pulmonary embolism.

Methods: This cohort study, conducted between January 2010 and June 2017, was based on a prospectively collected database of adult patients with VTE. The main exposure was the new onset of antipsychotic treatment after having a first episode of venous thromboembolic disease. The primary outcome was defined as recurrent VTE, either deep venous thrombosis or pulmonary embolism, during long-term follow-up. The composite of all-cause mortality and recurrent VTE served as the secondary outcome. An inverse probability weighted multivariable Cox proportional hazards model was fitted to adjust for measured confounding and competing risks.

Results: One thousand one hundred three patients were included in the present analysis, of whom 136 were identified as new users of antipsychotic agents. A total of 67% of patients were currently treated with full-dose anticoagulation at baseline. No association was found between the new use of antipsychotic agents and recurrent VTE during follow-up (adjusted hazard ratio (HR) = 1.08; 95% CI, 0.38–3.08). However, the use of these agents was associated with a 63% increased risk of recurrent VTE or all-cause mortality (adjusted HR = 1.63; 95% CI, 1.26–2.10).

Conclusions: The use of antipsychotic agents among patients with a first episode of VTE and full-dose anticoagulation was not associated with an increased risk of recurrent thromboembolic events. However, antipsychotic treatment was associated with a higher risk of both VTE and all-cause mortality. Further studies are warranted to confirm these findings.

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[a]Department of Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[b]Pharmacology Department, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina

[c]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

[d]Department of Critical Care Medicine, Sunnybrook Health Sciences Centre. Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario

**Corresponding author:* Augusto Ferraris, MD, Department of Internal Medicine, Hospital Italiano de Buenos Aires, Pharmacology Department, School of Medicine, University of Buenos Aires, Peron 4190 Ciudad Autonoma de Buenos Aires, Ciudad Autonoma de Buenos Aires C1199ABB Argentina (augusto.ferraris@hospitalitaliano.org.ar).

Venous thromboembolism (VTE) represents a major cause of morbidity and mortality worldwide.[1–3] Furthermore, recurrent VTE remains as a frequent complication during follow-up, is associated with poor outcomes, and may change overall treatment strategies and their duration.[4] In addition, the use of antipsychotic agents is associated with incident VTE,[5–15] an effect that appears constant across the spectrum of antipsychotic agents. The underpinnings of this effect are unknown[16] and might include a combination of changes in weight, sedation, and prolactin or a change in platelet function.[17–22]

Moreover, a recent cohort study[5] including adult patients with unprovoked VTE after they had finished a course of anticoagulation treatment showed an increased risk of recurrent events among users of antipsychotic agents. However, the effect of antipsychotic use on the risk of recurrent VTE has not been evaluated in the general population of patients with VTE (for example, those with known risk factors for VTE or still undergoing current anticoagulation treatment). Of specific importance is the subgroup of older adults, in whom the rate of adverse drug-related events remains high.[23–27] Thus, clarifying the safety of antipsychotic agents in patients with a previous VTE episode and still undergoing anticoagulation treatment remains warranted to improve patient-centered outcomes.

Hence, we designed a cohort study including adult patients with a first episode of VTE to evaluate the risk of recurrent thromboembolic disease associated with the new use of antipsychotic agents. Our overall goal is to improve the use of antipsychotics and help in the tailoring of prescription patterns based on the individual patient's comorbidity profile.

METHODS

Data Source

We conducted a retrospective cohort study based on the prospective institutional registry of venous thromboembolic disease (Registro Institucional de Enfermedad Tromboembólica [RIET; Institutional Registry of Thromboembolic

Clinical Points

- The effect of antipsychotic treatment on recurrent venous thromboembolism remains unknown.
- New antipsychotic use among patients with a first episode of venous thromboembolism while they are undergoing current anticoagulation treatment is not associated with recurrent thromboembolic events during long-term follow-up.

Disease], NCT01372514) in a tertiary teaching hospital in Buenos Aires, Argentina. The local Ethics Review Board approved our study protocol (protocol reference number: 3552), and the latter was conducted in accordance to the amended Declaration of Helsinki.

The registry contains comprehensive information regarding demographic, clinical, laboratory, and pharmacologic data with long term follow-up. It includes information based on an extensive baseline evaluation of common risk factors for VTE. The database has a system of double-check entrance of data and undergoes periodic data validation assessments. Furthermore, information regarding drug exposure was complemented using the institutional pharmacy electronic records, which include extensive information concerning pharmacy dispensing events in both the ambulatory and in-hospital settings. Data were extracted performing a search using the Anatomic Therapeutic Chemical (ATC) Classification System[28] as the method to identify each individual drug.

Study Population

We included adult patients (older than 17 years) with a confirmed diagnosis of VTE between January 2010 and June 2017. Study subjects were considered to have a baseline diagnosis of VTE if they had deep venous thrombosis (DVT, confirmed by either leg Doppler ultrasound [Toshiba XARIO 200; Toshiba Medical Systems; Japan] or lower limb angiography [Artis Q; Siemens; Germany]) or a confirmed diagnosis of pulmonary embolism (PE, made by computed tomographic pulmonary angiography [CTPA; Aquilion 64-slice scanner and Toshiba Aquilion ONE 320-slice scanner; Toshiba Medical Systems; Japan]). We defined the index date as the documented date of the first episode of VTE in the institutional registry. Patients were excluded if they had a documented antipsychotic prescription before index date and if the recurrent event was recorded in the first 3 days of follow-up, as this very likely reflected the same disease and not a new episode. Study subjects were followed from the index date until the occurrence of the main outcome or disenrollment from the hospital's health plan.

Main Covariates Considered

We captured baseline information including age, sex, alcohol use, tobacco status, hypertension, known risk factors for VTE (recent surgery, travel or immobilization, known prothrombotic status, cancer diagnosis, heart failure, chronic kidney disease, stroke, sedentarism, and oral contraceptive drug use), and the type of treatment initiated from the institutional registry. In addition, data regarding lipid-lowering drugs, antiplatelet agents, antidepressants, and hypnotics were extracted from the pharmacy registry.

Main Exposure

Patients were considered new users of antipsychotics if they had at least 1 documented dispensing event in the institutional pharmacy's registry after the index date. Patients with no exposure to antipsychotic medication were used as the comparator group. To account for immortal time bias,[29] we modeled our exposure as a time-varying covariate, considering patients as nonexposed until the first documented antipsychotic agent prescription date after the index date and as ever-exposed until the end of follow-up or censoring in an intent to reproduce an intention-to-treat approach. As previously noted, we excluded past users (eg, those that had a dispensing date of an antipsychotic agent preceding the index date) from the present analysis.

Outcome Measures

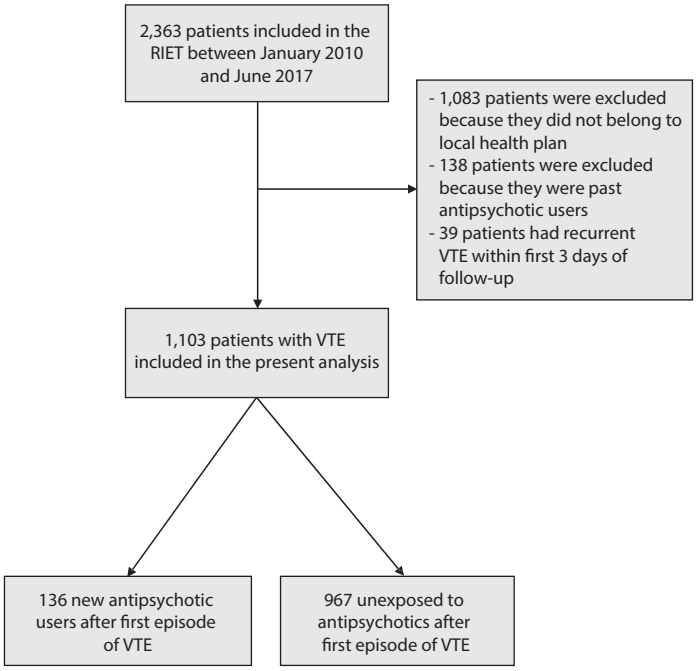
Our main outcome was the composite of either DVT or PE during follow-up. DVT was defined as a new occlusion in a different territory confirmed by Doppler ultrasound and registries in the RIET. New PE was defined by CTPA. The composite of recurrent VTE or all-cause mortality served as a secondary outcome. The latter was defined as the time to the first VTE event—an episode of either DVT or PE—or death after the index date. We chose this composite outcome as a measure to assess for competing risks, especially in the face of the association with all-cause mortality that all antipsychotic agents present.

Statistical Analysis

Quantitative variables are presented as means and standard deviations or as medians and interquartile ranges in the case of skewed data. Categorical variables are presented using proportions. Differences in baseline covariates between new users of antipsychotic agents and never users were tested using Fisher exact test for categorical variables and either the Student *t* test or the Wilcoxon rank sum test for continuous variables as appropriate.

To adjust for measured confounding, we fitted a multivariable Cox proportional hazards model for both the primary and secondary outcomes. For the purposeful selection of covariates, we used clinical subject knowledge to decide which variables to include in the model, and, specifically, we used a directed acyclic graph (DAG) to select them (Supplementary Figure 1). We modeled our main exposure as a time-varying covariate, and we tested the linearity assumptions for all continuous predictors considered using either higher-order polynomials or restricted cubic splines. We tested the proportional hazards assumption using log-log plots and Schoenfeld residuals. Finally, we constructed adjusted cumulative hazards curves to graphically depict the recurrence-free survival experience of both new users and never users of antipsychotic agents.

Figure 1. Flowchart of Study Patients



Abbreviations: RIET = Registro Institucional de Enfermedad Tromboembólica (Institutional Registry of Thromboembolic Disease), VTE = venous thromboembolism.

Since all-cause mortality may act as a competing risk of recurrent VTE, for the primary outcome analysis we performed inverse probability weighting of a multivariable Cox proportional hazards regression model to account for the aforementioned censoring. For the latter, we built a logistic model of death including all potential measured predictors to create a pseudopopulation in which there were no deaths. Continuous variables were modeled flexibly to account for potential nonlineal relationships.

Sensitivity Analysis

Finally, we also conducted several sensitivity analyses. First, we compared the risk of occurrence of recurrent VTE in patients with a diagnosis of dementia. The basis of this analysis relies on the increased susceptibility of the elderly and specifically patients with dementia to adverse events with psychotropic drugs. Furthermore, we also restricted our analysis by including only patients with a cancer diagnosis. This is a population of interest since patients with malignancy are at a particularly high risk of poor clinical outcomes and antipsychotic agents are increasingly being proposed for their use in the management of a variety of cancer-related clinical conditions, eg, nausea and vomiting.[30] Moreover, we compared our inverse probability weighting approach for censoring both with a naive analysis (not considering all-cause mortality as a competing risk) and with the one using a combined outcome approach.

In addition, to account for potential unmeasured confounding by indication, we included as a secondary analysis a comparison group of past users. The latter would be expected to be more similar in their characteristics to new users than never users. Furthermore, we also restricted our analysis to include patients that started antipsychotic treatment (or remained nonexposed) after 1 year of follow-up to decrease the risk of differential underlying risk owing to distinct timing from the first VTE event. Finally, to test the overall robustness of our findings we calculated the "E value" as a measure of the quantity of unmeasured confounding that would change our estimated causal effects (Supplementary Figure 2).[31] We used a threshold of $P < .05$ to declare statistical significance, and all presented tests are 2-sided. All analyses were performed using STATA v.14.2 (StataCorp LP, College Station, Texas).

RESULTS

Between January 2010 and July 2017, 2,363 patients were included in the RIET with a diagnosis of VTE. In all, 1,260 patients were excluded for the following reasons: 1,083 did not belong to the local institutional health plan and hence did not have enough pharmacy claims data (see Supplementary Table 1), 138 were identified as previous antipsychotic users, and 39 had a new VTE event occur in the first 3 days after the index date, most likely reflecting the same episode and not a new one (see Figure 1). Hence, 1,103 patients were included in the present analysis, of whom 136 patients were identified as new users of antipsychotic agents (see Figure 1). Risperidone and quetiapine accounted for the majority of prescriptions.

Table 1. Baseline Clinical and Demographic Characteristics of Included Patients According to Antipsychotic Exposure Status[a]

Baseline Covariate	Full Cohort (N = 1,103)	Antipsychotic Never Users (n = 967)	Antipsychotic New Users (n = 136)	*P* Value[b]
Age, mean (SD), y	74.3 (13.4)	73.6 (13.5)	78.8 (11.2)	< .01
Female	64.0	63.8	65.2	.85
Charlson score,[c] median (IQR)	2.0 (0.0–3.0)	2.0 (0.0–3.0)	2.0 (1.0–3.0)	.70
VTE-related variables				
Full-dose anticoagulation	66.6	66.9	64.0	.50
Wells score,[d] median (IQR)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	.77
Comorbidities				
Hypertension	62.4	61.2	70.6	.03
COPD	11.5	11.1	14.7	.25
Heart failure	9.4	9.1	11.7	.35
Dementia	9.1	6.4	27.9	< .01
Malignancy	30.7	32.0	22.1	.02
Stroke	17.5	16.3	25.8	.01
Metabolic syndrome	9.7	9.6	10.3	.76
Known VTE risk factors				
Recent travel	10.2	11.1	3.7	< .01
Sedentarism	54.4	52.6	66.9	< .01
Contraceptive use	0.5	0.6	0.0	1.00
Recent surgery	26.3	26.7	23.5	.47
Other pharmacologic treatments				
Benzodiazepines	26.3	23.8	43.4	< .01
Antidepressants	18.4	14.2	48.5	< .01
Cholinesterase inhibitors	4.0	2.3	16.2	< .01
Statins	25.6	25.0	29.4	.29
Antiplatelet agents	4.54	3.7	9.6	< .01

[a]Values shown as percentages unless otherwise noted.
[b]Proportions are compared with the Fisher exact test, means with the *t* test with unequal variances, and medians with the Wilcoxon rank sum test.
[c]Score on the Charlson Comorbidity Index.[32]
[d]Score on the Wells' Criteria for Pulmonary Embolism.[33]
Abbreviations: COPD = chronic obstructive pulmonary disease, IQR = interquartile range, VTE = venous thromboembolism.

The distribution of concomitant medication use and the baseline demographic and clinical characteristics are summarized in Table 1. Mean (SD) age at baseline was 74.3 (13.4) years, and 64.0% of patients were women. Malignancy was present in nearly one-third of study subjects, and almost 1 of every 10 patients had a history of dementia. Previous stroke, heart failure, and metabolic syndrome were the main vascular comorbidities at baseline. Of note, 67% of patients were currently treated with full-dose anticoagulation at baseline.

Differences between exposed and nonexposed groups were evident. Compared to the nonexposed group, new users of antipsychotic agents were older on average and more likely to have a diagnosis of dementia. In addition, the prevalence of stroke, sedentarism, and the use of psychotropic or antiplatelet agents at baseline was higher in the antipsychotic user group. Recent travel was more frequent among never users of antipsychotic agents.

Outcome Analysis

Overall, the incidence rate of recurrent VTE was 6.5 per 100,000 person-days for both new antipsychotic users and nonusers. Roughly half of the total population faced the composite outcome of all-cause death or new VTE during long-term follow-up. Specifically, the incidence rate for the secondary composite outcome was 5.5 and 5.1 cases per 10,000 person-days for the new users and never users of antipsychotic agents, respectively (see Table 2). Figure 2 shows the recurrence-free survival curve for both antipsychotic new users and never users.

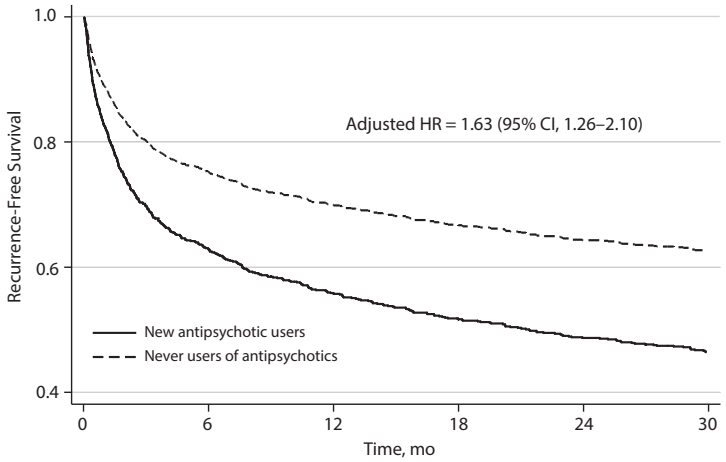
Table 2. Recurrent VTE and All-Cause Mortality for New Users and Never Users of Antipsychotics

Variable	Total Sample (N = 1,103)	Antipsychotic Never Users (n = 967)	Antipsychotic New Users (n = 137)
Follow-up time, median, d	1,530	1,825	1159
Recurrent VTE (either DVT or PE)			
Cumulative incidence, %	6.7	6.8	6.6
Incidence rate per 100,000 person-days	6.5	6.6	6.3
Combined primary outcome[a]			
Cumulative incidence, %	50.9	49.6	59.5
Incidence rate per 10,000 person-days	4.9	5.1	5.5

[a]All-cause mortality, DVT, or PE.
Abbreviations: DVT = deep venous thrombosis, PE = pulmonary embolism, VTE = venous thromboembolic disease.

We did not find an association between the new use of antipsychotic agents and recurrent VTE during follow-up (adjusted hazard ratio (HR) = 1.08; 95% CI, 0.38 to 3.08). However, the use of antipsychotic agents was associated with a 63% increased risk of recurrent VTE or all-cause

Figure 2. Effect[a] of New Antipsychotic Prescription on the Risk of the Composite Outcome[b] Among Patients With VTE



[a]Curves constructed after fitting a multivariable Cox proportional hazards model.
[b]Composite outcome defined as either VTE or all-cause mortality.
Abbreviations: HR = hazard ratio, VTE = venous thromboembolism.

Table 3. Estimated Causal Effect of New Antipsychotic Use After a First Episode of VTE on the Occurrence of a New VTE or the Composite Secondary Outcome[a]

Outcome Variable	Crude HR (95% CI)	*P* Value[b]	Adjusted HR (95% CI)	*P* Value[c]
Effect of new antipsychotic use on recurrent VTE during long-term follow-up[d]	1.22 (0.31–4.73)	.78	1.08 (0.38–3.08)	.89
Effect of new antipsychotic use on combined outcome during long-term follow-up	1.66 (1.30–2.12)	<.01	1.63 (1.26–2.10)	<.01

[a]Combined outcome is the composite of all-cause death, deep venous thrombosis, or pulmonary embolism during follow-up.
[b]Univariate Cox proportional hazards model with the exposure modeled as a time-varying covariate.
[c]Multivariable Cox proportional hazards model with the exposure as a time-varying covariate and a vector of potential confounders (see the directed acyclic graph in Supplementary Figure 1; confounders include age, sex, hypertension, chronic obstructive pulmonary disease, active malignancy, stroke, dementia, recent travel, benzodiazepines, and antiplatelet therapy).
[d]Model includes inverse probability weighting of a multivariable Cox proportional hazards regression so as to model censoring by death and create a pseudopopulation of patients without censoring. Robust standard errors were used for the CIs.
Abbreviations: HR = hazard ratio, VTE = venous thromboembolism.

mortality (adjusted HR = 1.63; 95% CI, 1.26 to 2.10) (see Table 3). In the subgroup analysis among patients with malignancy, new consumption of antipsychotic agents was also associated with an increased risk of occurrence of the secondary composite outcome (adjusted HR = 1.37; 95% CI, 1.09 to 1.72).

Sensitivity Analysis

Our findings were consistent across the a priori–defined subgroups of patients with active malignancy and dementia for the primary outcome (see Supplementary Table 2). Moreover, we did not find a significant effect of new antipsychotic use on the occurrence of a new VTE event during follow-up when restricted only to those patients who started treatment after 1 year or when compared to past users (see Supplementary Table 2). Finally, our alternative approaches to analyze competing risks are shown in Supplementary Table 3.

DISCUSSION

Our study shows that new antipsychotic use among patients with a first episode of VTE while they are undergoing current anticoagulation treatment is not associated with recurrent thromboembolic events during long-term follow-up. Further, the use of antipsychotics is associated with an increased risk of both all-cause mortality and VTE during long-term follow-up. To our knowledge,

this study is the first to evaluate the effect of antipsychotic agents on patients with a first episode of VTE and ongoing anticoagulation treatment.

Our findings are in line with a recently reported cohort study[5] regarding antipsychotic use among patients with a first episode of unprovoked VTE. However, we assessed the risk in a more varied population of VTE patients. For example, our study subjects included patients with broader baseline characteristics, including patients with both provoked and unprovoked VTE, and a majority of them were currently receiving anticoagulation treatment. Furthermore, our combined outcome captures not only recurrent VTE but also its combination with all-cause mortality, which may prove to be a more relevant patient-centered outcome. The negative finding of our study needs to be contrasted to previous studies showing an increase in overall risk of VTE among new antipsychotic users mainly owing to the induction of metabolic abnormalities, drug-induced sedation, and hyperprolactinemia.[16] The fact that we did not find a specific effect on VTE alone might reflect different scenarios. First, our study might be underpowered to assess this outcome, mainly owing to the low overall cumulative incidence of recurrent VTE and the competing risk posed by all-cause mortality during follow-up. Second, our finding might reflect the absence of a distinct causal effect on this sample given that most patients were on active chronic anticoagulation treatment. Given that this null finding was still evident after censoring was taken into account, it is likely that the deleterious effect of antipsychotic agents on recurrent VTE is diminished among those patients that remain anticoagulated. Finally, given that the overall risk of new, recurrent VTE is highest at the beginning of follow-up, and since the exposure to an antipsychotic usually does not happen right after the VTE event, the time of antipsychotic nonexposure is associated with an inherent higher risk of recurrent VTE, rendering the risk of events higher among those that never received antipsychotics. Hence, it should be noted that our effect estimate may be at least partially explained by the timing of the exposure rather than the specific effect of antipsychotics on VTE events.

Our study presents with several limitations. First, since the exposure of antipsychotic agents was not randomized, both residual and unmeasured confounding might be present. However, we employed robust methods to account for measured confounding, and our results were similar across different methods. Further, our E-value estimation is moderately robust. Second, our retrospective design limits our analysis to already-collected and readily available data, which in turn might render residual confounding if the information on potential confounders is not complete. However, we had complete data on the most relevant necessary measured confounders to estimate a causal effect as depicted in our DAG. However, it should be noted nonetheless that the potential for unmeasured confounding remains. Third, our composite end point might be fully explained by all-cause mortality and hence might be considered of less importance than VTE alone. Fourth, and related to the previous point, our failure to report an effect of antipsychotic agents on recurrent VTE might be explained by low overall power rather than a lack of effect. Thus, additional studies are warranted to further explore this point among a broad population of patients with a first episode of VTE. Fifth, since we relied on pharmacy claims, patients allocated to the antipsychotic group might stop being compliant with treatment and, hence, some allocated follow-up time to the exposed group is in fact non-exposed time. This discrepancy would in turn yield estimates closer to the null. Finally, we acknowledge that a comparison between initiators of a drug and non-initiators inevitably entails challenging issues in making both populations comparable because people who initiate treatment are inherently different from people who do not initiate a treatment even if confounding by indication is properly addressed. Such factors may include, but are not limited to, access to health care facility, health-seeking behaviors, family support, timing of initiation of antipsychotic treatment, baseline underlying recurrence risk, and accuracy in the measurement of potential confounders and comorbidities. All of these are potential unmeasured variables that render this type of comparison cumbersome. However, we intended to address these by including a sensitivity analysis using a cohort of past users of antipsychotic medications as a comparison group, which yielded a similar point estimate as our main analysis, suggesting a small relevance of the aforementioned factors.

Conversely, our study presents with several strengths. First, it is the biggest study to date evaluating the effect of antipsychotic agents on recurrent VTE. Second, we included patients with a first episode of VTE and a variety of baseline characteristics, which may in turn enhance the generalizability of our results. Third, both our composite end point and our use of time-varying exposure adequately tackle competing risks and immortal time bias, respectively. Fourth, we report our causal effects based on robust methods to adjust for potential measured confounders, and our point estimates were similar across distinct methods.

In conclusion, new antipsychotic use among patients with a first episode of VTE while they are undergoing current anticoagulation treatment is not associated with recurrent thromboembolic events during long term follow-up. This finding can be explained by the absence of a detrimental effect, the ongoing protective effect of current anticoagulation, or the fact that the antipsychotic was typically started in a delayed fashion after the initial VTE, rendering the overall recurrence risk low. Further prospective studies should evaluate the effect of an antipsychotic when started close to the index VTE event and also among patients who have completed an anticoagulation course.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: The Effect of Antipsychotic Treatment on Recurrent Venous Thromboembolic Disease: A Cohort Study

Author(s): Augusto Ferraris, MD; Alejandro G. Szmulewicz, MD, MPH; M. Lourdes Posadas-Martínez MD, MSc, PhD; Marina Alonso Serena, MD; Fernando J. Vazquez MD, PhD; and Federico Angriman MD, MPH

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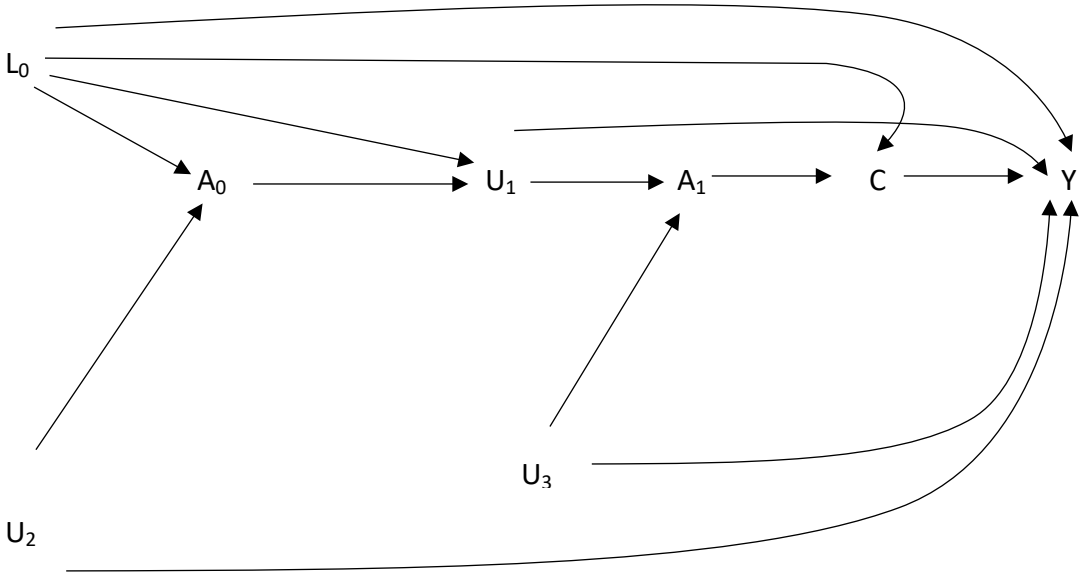
The effect of antipsychotic treatment on recurrent venous thromboembolic disease: a cohort study

Supplementary Figure 1. Directed acyclic graph (under the null)



Where:

L_0: Baseline covariates: metabolic syndrome, stroke, malignancy, dementia, chronic heart failure, chronic obstructive pulmonary disease, hypertension, statin treatment, anticholinesterase treatment, age, recent surgery, gender, benzodiazepine treatment, antidepressant treatment, anticoagulation treatment, antiplatelet treatment, sedentarism, recent travel

A_0: new AP agent use at baseline

U_1: unmeasured covariates at t=1

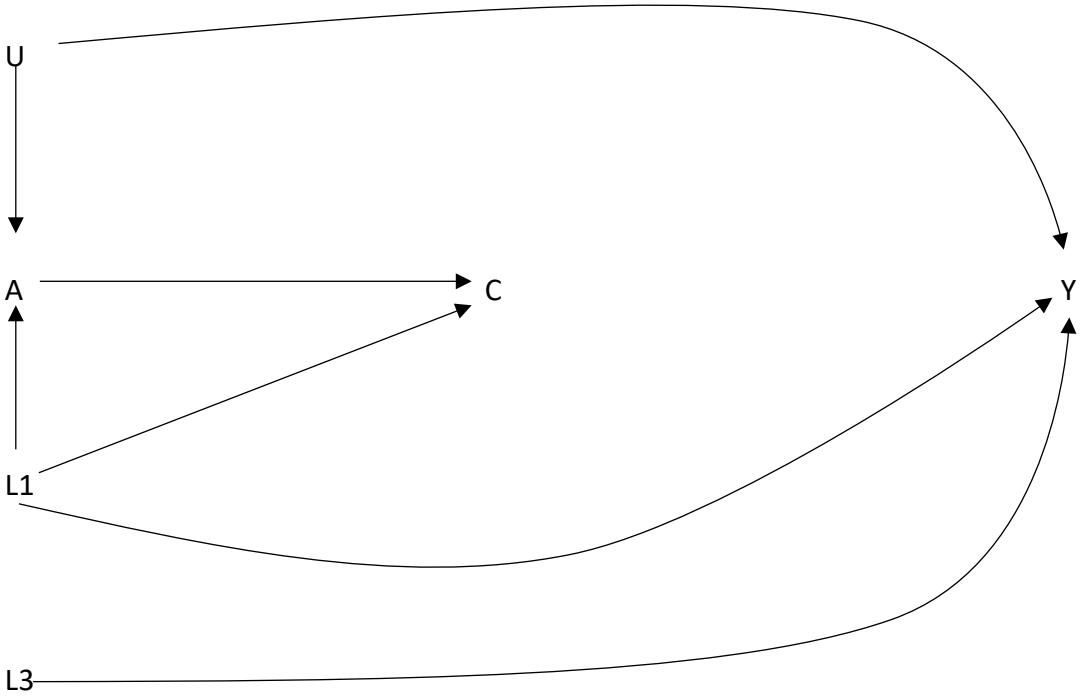
A_1: new AP agent use during follow-up (t=1)

U_2: unmeasured confounding at t=1

Y: new VTE during follow-up

C: censoring (mainly due to competing risks)

Supplementary Figure 2. Calculated E value for point estimate and confidence interval for secondary outcome analysis



Where the strength of U with A and Y, on the risk ratio scale should be: 2. 15 to fully explain the association found between new AP use and the secondary composite outcome.

As a measure of the robustness of our finding, we calculated the "E value". The latter, as defined by Vanderweele, is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome associations, conditional on the measured covariates. In our study, the E value is 2.15 representing a moderately strength of association between confounder and treatment or outcome to explain our findings relevant to the composite end-point during long term follow-up.

Supplementary Table 1. Comparison between patients enrolled - or not - in local health plan.

Baseline covariate	Enrolled in local health plan (N=1103)	No local health plan (N=1083)	p value[1]
Age - years, mean (SD)	74.3 (13.4)	60.6 (15.7)	< 0.01
Female sex - %	64.0	49.1	< 0.01
Charlson score - median (IQR)	2.0 (0.0-3.0)	2.0 (1.0-5.0)	< 0.01
Full dose anticoagulation - %	66.6	62.4	0.04
Wells score - median (IQR)	4.0 (3.0-6.0)	4.0 (3.0-6.0)	< 0.01
Hypertension - %	62.4	46.1	< 0.01
COPD - %	11.5	9.8	0.21
Heart failure - %	9.4	6.9	0.04
Dementia - %	9.1	1.4	< 0.01
Malignancy - %	30.7	41.2	< 0.01
Stroke - %	17.5	12.7	< 0.01
Metabolic syndrome - %	9.7	8.6	0.37
Recent travel - %	10.2	22.0	< 0.01
Sedentarism %	54.4	54.1	0.90
Contraceptive use - %	0.5	2.0	< 0.01
Recent surgery - %	26.3	33.9	< 0.01

Supplementary Table 2. Calculated effect of AP agents on different sensitivity analysis

Sensitivity analysis	Adjusted HR (95% CI)	p value
Patients with active malignancy		
New AP users	1.15 (0.34 - 3.90)	0.82
Patients with dementia		
New AP users	1.11 (0.06 - 20.45)	0.94
Comparison with past users		
New AP users	2.85 (0.23 - 35.8)	0.42
After one year of follow-up		
New AP users	1.63 (0.86 – 3.10)	0.14

Supplementary Table 3. Different strategies to account for competing risks

Analysis	Point estimate (95%CI)	Comment
Naïve (VTE as outcome)[1]	1.04 (0.44 – 2.44)	Not accounting for death as a competing risk
Combined outcome (VTE and death)[1]	1.63 (1.26 - 2.10)	Estimates the effect of AP on both death and recurrent VTE
Inverse probability weighting of a Cox model [2]	1.08 (0.38 – 3.08)	Estimates the effect of AP on VTE in a population without censoring

1. Multivariate Cox models including age, gender, hypertension, chronic obstructive pulmonary disease, active malignancy, stroke, dementia, recent travel, benzodiazepines, antiplatelet therapy.
2. Inverse probability weighting of a multivariate cox proportional hazards model.