RESEARCH ARTICLE

Anticoagulant Usage and Risk of Thromboembolic Events After Ischemic Stroke in Adults With Cancer

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Abstract

Background and Objectives

Ischemic stroke and cancer often coexist. The aim of this study was to determine the prevalence of cancer among patients with stroke, their antithrombotic treatment patterns, and the risk of subsequent thromboembolic events in a large population-based cohort.

Methods

This retrospective cohort study used data from Optum's deidentified Clinformatics Data Mart Database to assess the 6-month risk of recurrent thromboembolic and major bleeding events identified using validated International Classification of Diseases code algorithms, among adults with active cancer hospitalized with ischemic stroke between October 2020 and September 2021. In addition, we explored the risk of recurrent thromboembolic events stratified by anticoagulant exposure. Landmark analyses were undertaken with anticoagulant exposure status based on dispensations in the week after hospital discharge. Propensity score matching aimed to minimize selection bias between the groups. Hazard ratios (HRs) were estimated using Cox proportional hazard models with robust variance estimators to account for clustering within propensity score–matched pairs.

Results

Among 86,365 patients identified with ischemic stroke, 10.2% had active cancer (most common types: 34% genitourinary, 25% gastrointestinal, 23% hematologic). After applying eligibility criteria, 4,781 patients were included in the main analysis (median age 74 [interquartile range 68–81] years; 48% female). Anticoagulants were dispensed to 14.7% of patients. The incidence of thromboembolic event recurrence and major bleeding events was 38.4 (95% CI 35.4–41.6) and 20.9 (95% CI 18.8–23.4) per 100 person-years, respectively. After propensity score matching, the risk of thromboembolism recurrence was not statistically different between those with and without anticoagulant prescription (HR 1.21; 95% CI 0.91–1.61). Anticoagulant prescription was also not associated with a higher risk of major bleeding events (HR 1.13; 95% CI 0.78–1.63).

Discussion

In this large-scale study, approximately 10% of patients with ischemic stroke had active cancer and they faced a markedly elevated short-term risk of recurrent thromboembolism and major bleeding events. Anticoagulants were infrequently prescribed after discharge and did not differentially affect the rate of ischemic or bleeding outcomes compared with alternative treatment strategies, although confounding by indication is likely. Clinical trials are required to further assess optimal antithrombotic strategies in this high-risk population.

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Introduction

Approximately 10%–15% of hospitalized patients with ischemic stroke have a history of cancer.[1,2] Patients with cancer-associated stroke face a very high risk of recurrent thromboembolic

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Glossary

AF = atrial fibrillation; **CPT** = Current Procedural Terminology; **HR** = hazard ratio; **ICD-9** = International Classification of Diseases, Ninth Revision; **ICD-10** = International Classification of Diseases, 10th Revision; **IR** = incidence rate; **MI** = myocardial infarction; **VTE** = venous thromboembolism.

events[3,4]; the 1-year risk of recurrent stroke in patients with cancer is estimated to range from 14% to 29% and is approximately 3-fold higher than in patients without cancer.[3,5-7] Stroke in patients with cancer can arise from a variety of causes; however, in up to 50% of cases, no definitive etiology is identified after standard diagnostic evaluation, leading to an embolic stroke of undetermined source classification.[3,8,9] Up to 70% of these patients exhibit infarctions in multiple vascular territories, suggesting an underlying embolic source.[10] This observation, along with the established role of anticoagulation in cancer patients with venous thromboembolism (VTE), indicates a potential role for anticoagulants in secondary stroke prevention for these patients.[11,12] However, considering the heightened risk of bleeding with anticoagulation in patients with stroke ascribed to cancer-mediated hypercoagulability, current guidelines do not recommend anticoagulants for these patients unless a clear indication for anticoagulation, such as atrial fibrillation (AF), exists.[12-14] Consequently, the use of antithrombotic therapy in these patients varies widely among health care providers.[10]

There are limited population-based data on the prevalence, risk of thromboembolic events, and treatment in cancer-associated stroke patients. Many previous studies were based on cohorts from large cancer centers or were single-center studies and may have had limited generalizability. The aim of this study was to determine the incidence of recurrent thromboembolic events after discharge from hospitalization with ischemic stroke in a large national sample of the US population with active cancer. We further aimed to compare outcomes between those with and without an anticoagulant prescription after discharge based on current practice.

Methods

Study Design

For this retrospective cohort study, Optum's deidentified Clinformatics Data Mart Database (Clinformatics) was used to estimate the incidence of recurrent thromboembolic events in patients with cancer after discharge from a hospitalization with ischemic stroke. Clinformatics is derived from a database of administrative health claims, including inpatient and outpatient hospital visits, primary and secondary care ambulatory visits, and outpatient pharmacies, for members of large commercial and Medicare Advantage health plans covering all US states. This database does not include patients covered by Medicaid or without insurance coverage. These administrative claims are submitted by providers and pharmacies and are verified, adjudicated, and deidentified before inclusion. We examined the association between early anticoagulant exposures—defined a priori as dispensation within the first 7 days after hospital discharge—and outcomes of interest using landmark analysis. In landmark analysis, a specific time point during the follow-up period (7 days in this study) is set a priori as the landmark time, which restricts the evaluation only to those individuals who survived, were outcome free, and were not lost to follow-up until the landmark time point.[15,16] The purpose of this approach was to avoid erroneous attribution of events during hospitalization to the postdischarge period as a consequence of delayed administrative coding.

Study Population

We included patients with active cancer, aged 18 years or older, hospitalized with an acute ischemic stroke between October 2020 and September 2021 who were continuously enrolled in health insurance benefits (based on the individual-level enrollment start and end dates) from 3 months before the index stroke to 7 days after hospital discharge following the index stroke. If the discharge date was not available, it was assumed to be the same day as the index stroke. Individuals were excluded if the discharge date was more than 1 month after the index stroke. We removed patients with relevant indications and contraindications to anticoagulation, specifically a documented history of AF before the index stroke or a history of intracerebral hemorrhage or subarachnoid hemorrhage recorded in the year before the index stroke or a diagnosis of traumatic brain injury at the time of stroke hospitalization based on diagnostic codes from the ICD-10 (eTable 1).

Among patients hospitalized with an acute ischemic stroke, we identified the subset of patients with an active cancer diagnosis using ICD codes and Current Procedural Terminology (CPT) codes. A validated coding algorithm based on diagnostic codes from the ICD-9 was used to identify patients hospitalized for ischemic stroke (positive predictive value = 91%). Diagnostic codes for the algorithm were converted to the equivalent ICD-10 codes through Centers for Medicare and Medicaid Services General Equivalence Mapping for both forward and reverse mapping.[17] Active cancer status was defined using a previously established algorithm based on diagnosis and procedure claims in the year before the index ischemic stroke.[18] Previously, it was shown that Medicare claims data can identify incident cancer with high specificity (>98%).[19] We included any cancer (except cutaneous basal cell and squamous cell carcinoma) identified with at least one of the following criteria: (1) at least 1 ICD-10 diagnosis code for cancer in any diagnosis position, with the place of service

specified as an inpatient or outpatient emergency department setting; (2) at least 1 ICD-10 diagnosis or procedure code for chemotherapy or radiotherapy in any diagnosis position, with no restrictions on place of service; or (3) at least 2 ICD-10 diagnosis codes for cancer in any diagnosis position, with outpatient places of service, associated with CPT physician evaluation and management codes 30–365 days apart. The ICD and CPT codes used for cancer detection, chemotherapy, and radiotherapy ascertainment are presented in eTables 2 and 3.

Anticoagulant Therapy

The primary exposure of interest was prescription of an anticoagulant soon after the index stroke. Dispensed anticoagulants were identified based on generic names and included direct oral anticoagulants, low-molecular-weight heparins, and vitamin K antagonists (eTable 4). We included all anticoagulants dispensed in the 3 months before the index stroke or within 7 days after hospital discharge. We included those with anticoagulant dispensations within 3 months before the index stroke, assuming they would have restarted their residual anticoagulant supply (which is often dispensed in 3-month aliquots) after hospital discharge. Information on inpatient drug dispensations was not available with these data. Of note, we could not explicitly provide information on antiplatelet therapy using claims-based data because there are no prescription data on aspirin, the most commonly used antiplatelet agent.

Thromboembolic and Major Bleeding Events

Our primary outcome of interest was a composite of thromboembolic events, including recurrent ischemic stroke, VTE, and myocardial infarction (MI). Our secondary outcomes were (1) major bleeding events, defined as bleeding events leading to hospitalization, and (2) a composite of thromboembolic and major bleeding events. Events were identified using a series of validated ICD code algorithms (positive predictive value = 90%–95% for thromboembolic events and positive predictive value = 89%–99% for major bleeding events).[17,20-22] We used ICD-10 codes equivalent to the ICD-9 codes from the original algorithms using similar methods previously explained for ischemic stroke (eTables 5 and 6). Outcomes were recorded from 7 days after discharge until 6 months after discharge. We limited the follow-up window to 6 months to minimize censoring from health plan disenrollment and death as a potential competing event. Individuals were censored on occurrence of any of the primary or secondary outcomes or with the end of insurance eligibility or death. In accordance with the landmark analytic strategy, individuals were excluded from assessment if outcomes occurred between discharge from the hospitalization and post-discharge day 7.

Statistical Analyses

Propensity scores were estimated based on age; sex; race and ethnicity; geographic region; net worth; education level; and comorbidities at the time of index hospitalization including hypertension, complicated diabetes, MI, heart failure, prosthetic heart valve, stroke, transient ischemic attack, cerebrovascular malformations, paralysis, peripheral vascular disease, renal failure, liver disease, deep vein thrombosis/pulmonary embolism, coagulopathy, and major bleeding to account for differences between the 2 groups. Comorbidity covariates were ascertained using ICD-10 codes (eTable 7).[23] Propensity scores were applied using 1:1 nearest-neighbor matching on the logit of the propensity scores without replacement (i.e., greedy matching), with a caliper of 0.2. Covariate balance between the anticoagulant and no-anticoagulant groups was assessed using kernel density plot visualizations and standardized differences, with thresholds for relevant imbalances set at ≥0.10 or ≤−0.10.

For the matched and unmatched cohorts, we estimated the incidence rate (IR) per 100 person-years for each outcome during the 6-month period after ischemic stroke hospitalization. Kaplan-Meier statistics were used to calculate the cumulative incidence of the outcomes between those prescribed and those not prescribed anticoagulants.[24] To estimate the risk of each outcome in those with an anticoagulant prescription (vs those without), hazard ratios (HRs) were calculated using Cox proportional hazard models in the matched cohort. For these analyses, HRs were estimated using robust variance estimators to account for clustering within matched pairs.

In secondary analyses, we examined the IRs and HRs for recurrent ischemic stroke, VTE, and MI in patients who were prescribed vs not prescribed an anticoagulant in both matched and unmatched cohorts. Furthermore, we investigated the potential effects of specific anticoagulant medications on the risk of combined thromboembolic and major bleeding events. In subgroup analyses, we examined the associations between anticoagulant prescription and combined thromboembolic and major bleeding events according to broad cancer types (i.e., gastrointestinal, respiratory/thoracic, and gynecologic). Nonoverlapping 95% CIs were interpreted as significant between-group differences.

In sensitivity analyses, we calculated HRs associated with anticoagulant prescription for the unmatched cohort after adjustment for age; sex; race and ethnicity; geographic division; net worth; education level; and baseline comorbidities including hypertension, complicated diabetes, MI, heart failure, prosthetic heart valve, stroke, transient ischemic attack, peripheral vascular disease, renal failure, liver disease, deep vein thrombosis/pulmonary embolism, coagulopathy, and major bleeding. The proportionality assumption was assessed by the Score test using Schoenfeld residuals, log-log plots of event-free survival, and inclusion of a continuous time-varying variable. Statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, TX). A p value of <0.05 was considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

This study qualified as exempt from regulatory review by the University of Pennsylvania, based on retrospective use of

deidentified data. Reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[25]

Data Availability

The data that support the findings of this study are available from Optum's deidentified Clinformatics Data Mart Database, but restrictions apply to the availability of these data, which were used under license for this study and thus are not publicly available. Data may be available from the authors on reasonable request and with explicit permission from Clinformatics.

Results

Patient Characteristics

Among 86,365 adults discharged after an ischemic stroke and without history of intracerebral hemorrhage, subarachnoid hemorrhage, or traumatic brain injury, 8,790 (10.2%) had a diagnosis of active cancer. After excluding those with known AF, less than 3 months of continuous enrollment, or major bleeding or thromboembolic events within 7 days of hospital discharge (due to landmark analysis), 4,781 patients (5.4%) were included in this analysis (Figure 1). Baseline characteristics of patients with and without anticoagulant prescription before and after propensity score matching are presented in Table 1 and eTable 8. In the overall unmatched cohort, the median age was 74 (interquartile range 68–81) years and 48.1% were female. The most frequent cancer types were genitourinary (34%), gastrointestinal (25%), and hematologic (23%) cancers (Figure 2). In our propensity score–matched cohort, 655 individuals prescribed an anticoagulant were matched to 655 individuals not prescribed an anticoagulant.

Anticoagulant Utilization

Anticoagulants were dispensed to 14.7% of individuals within the first week after hospital discharge or presumed to be reinitiated if it was dispensed within 3 months before stroke. In the unmatched cohort, by broad cancer category, anticoagulants were prescribed most frequently to patients with gynecologic (29%), musculoskeletal (22%), and gastrointestinal (22%) cancers. By specific cancer site, anticoagulants were prescribed most frequently to those with pancreatic (35%) and ovarian (32%) cancers. Thromboembolic events were more frequent among those with musculoskeletal (17%) and gynecologic (16%) cancers. Major bleeding events occurred most frequently among patients with gynecologic cancers (9%), skin cancers (9%), and gastrointestinal cancers (9%). Combined thrombotic and major bleeding events occurred most frequently among patients with gynecologic cancers (22%), musculoskeletal cancers (20%), and neurologic cancers (18%) (eTable 9).

Primary Outcome

In the overall cohort, the IR of thromboembolic events was 38.4 (95% CI 35.4–41.6) per 100 person-years, and over two-thirds of these events were recurrent ischemic stroke (IR 26.9; 95% CI 24.4–29.6).

In the propensity-matched cohort, the IR of thromboembolic events was 50.0 (95% CI 43.3–57.6). There was a similar IR for those who were prescribed anticoagulants (55.0 per 100 person-years; 95% CI 45.3–66.6) vs for those not prescribed anticoagulants (45.0 per 100 person-years; 95% CI 36.5–55.6) (HR 1.21; 95% CI 0.91–1.61) (Table 2, Figure 3).

Secondary Outcomes

In the overall cohort, the IR of major bleeding events was 20.9 (95% CI 18.8–23.4) per 100 person-years. In the propensity-matched cohort, the IR of major bleeding events was 28.7 (95% CI 23.8–34.6). Patients with cancer who were prescribed an anticoagulant after an ischemic stroke experienced a similar rate of major bleeding events (IR 30.6; 95% CI 23.6–39.5) compared with those not prescribed an anticoagulant (IR 26.9; 95% CI 20.5–35.3) (HR 1.13; 95% CI 0.78–1.63) (Table 2, Figure 3). The risk of combined thromboembolic and major bleeding events was also similar between these 2 groups (HR 1.14; 95% CI 0.90–1.46).

Secondary and Sensitivity Analyses

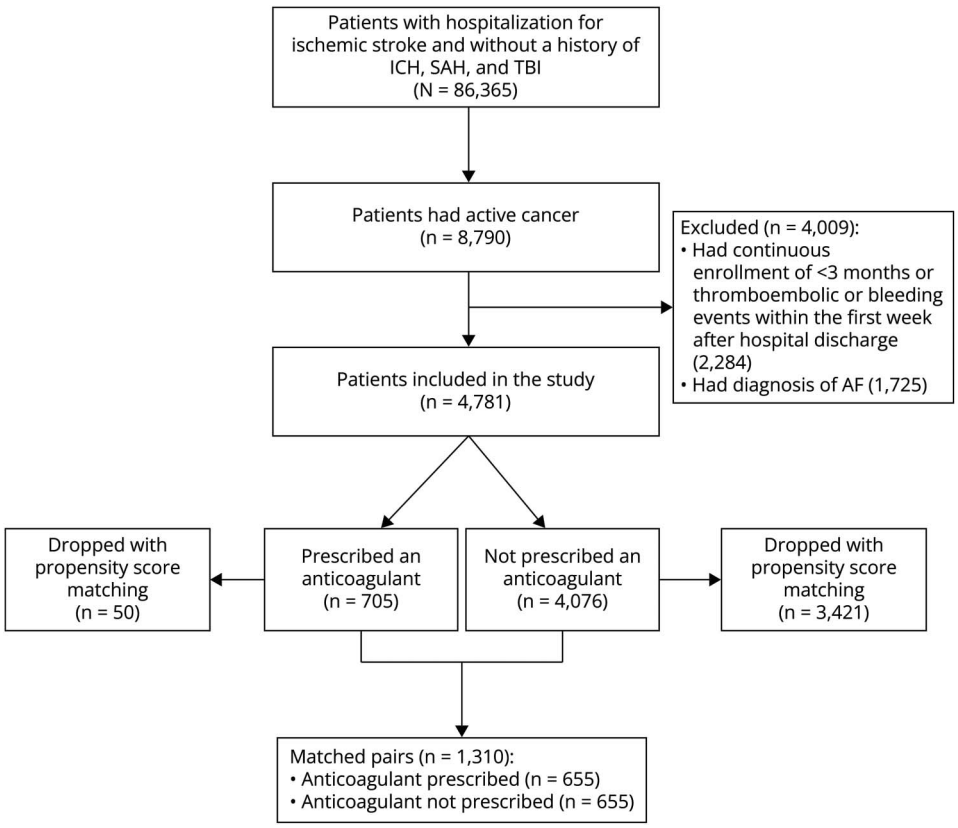
In secondary analysis of the matched cohort, the risk of recurrent ischemic stroke (HR 1.35; 95% CI 0.94–1.95), VTE (HR 1.09; 95% CI 0.70–1.72), and MI (HR 1.29; 95% CI 0.59–2.86) did not differ between patients prescribed anticoagulant and not, although as evidenced by the wide CIs, the results were imprecise and clinically significant differences could not be ruled out (eTable 10). When specific anticoagulants were examined individually, neutral results persisted (eTable 11). In subgroup analyses, no broad cancer type was associated with a differential effect of anticoagulant treatment on the composite outcome of thromboembolic and major bleeding events (eTable 12). Finally, our sensitivity analyses in the unmatched cohort showed fairly similar results to the matched cohort for all study outcomes (eTable 13).

Discussion

In this large-scale retrospective analysis of national claims data from the United States, 1 in 10 patients who were hospitalized with acute ischemic stroke had concomitant active cancer. Thromboembolic events occurred frequently in the 6-month period after stroke in this cohort of patients with active cancer, with recurrent ischemic strokes accounting for most of these events. The observed IR of 38–50 per 100 person-years is several times higher than the rate of recurrent stroke observed after stroke in the broader Medicare population (7.6%)[26] and far exceeds the rate of recurrent stroke after all other specific stroke etiologies.[27-31]

Our finding that 10% of patients with ischemic stroke have active cancer is in keeping with estimates from previous studies[1,32,33] and adds generalizability to those findings, given

Figure 1 Flow Diagram Depicting Inclusion of Patients Hospitalized With Ischemic Stroke and Active Cancer Included in the Matched and Unmatched Cohorts



AF = atrial fibrillation; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.

the large scope of our study population. With the advancement in cancer treatments over the past 2 decades, the survival of patients with cancer has improved. Therefore, the rate of cancer-associated stroke is expected to increase even further, particularly with the aging of populations worldwide.[10] The high rate of recurrent stroke observed here could be explained by a variety of mechanisms that include cancer-mediated hypercoagulability, including nonbacterial thrombotic endocarditis, prothrombotic and vascular toxicities of cancer treatments, paradoxical embolization of deep venous thrombosis, and several non-hypercoagulable underlying mechanisms implicated in stroke in patients with cancer.[10] Cerebral thrombi in patients with cancer-associated stroke contain greater amounts of platelet, thrombin, and tissue factor compared with thrombi in matched patients with non–cancer-associated strokes, which further supports the potential role of different antithrombotic therapies in stroke prevention in this high-risk population.[34] However, clinical practice varies, and no guidelines specifically recommend one type of antithrombotic over another.

We observed that anticoagulants were prescribed for 14.7% of patients with active cancer after ischemic stroke, in contrast with a previous study using a Surveillance, Epidemiology and End Results (SEER-Medicare) database from 2014 to 2019, which reported that roughly half of the patients with VTE and active cancer were prescribed anticoagulation within 30 days of their index event.[35] The main reason for avoiding anticoagulant therapy after cancer-associated stroke is the heightened risk of bleeding in these patients.[12] However, a study using claims-based data from 2012 to 2019 including 5,100 patients with cancer and VTE showed that the risk of hospitalization for major bleeding after anticoagulation therapy for VTE ranged from 9.9 to 26.7 per 100 person-years depending on the type of the anticoagulants used, which is relatively similar to the risk of bleeding observed in anticoagulant-prescribed patients in our matched ischemic stroke cohort.[36] Our findings suggest that the rate of thromboembolic events in patients with cancer after ischemic stroke is approximately twice that of bleeding events. Nevertheless, owing to a lack of supportive clinical trial data, current guidelines do not recommend routine anticoagulant therapy for this high-risk patient population.

To date, there have only been 2 clinical trials focused on patients with active cancer and ischemic stroke. The TEACH (Trial of Enoxaparin vs Aspirin in Patients With Cancer and Stroke) pilot clinical trial randomized 20 patients to anticoagulant (enoxaparin) or antiplatelet (aspirin) therapy.[37] This pilot study confirmed feasibility, but the sample size was too

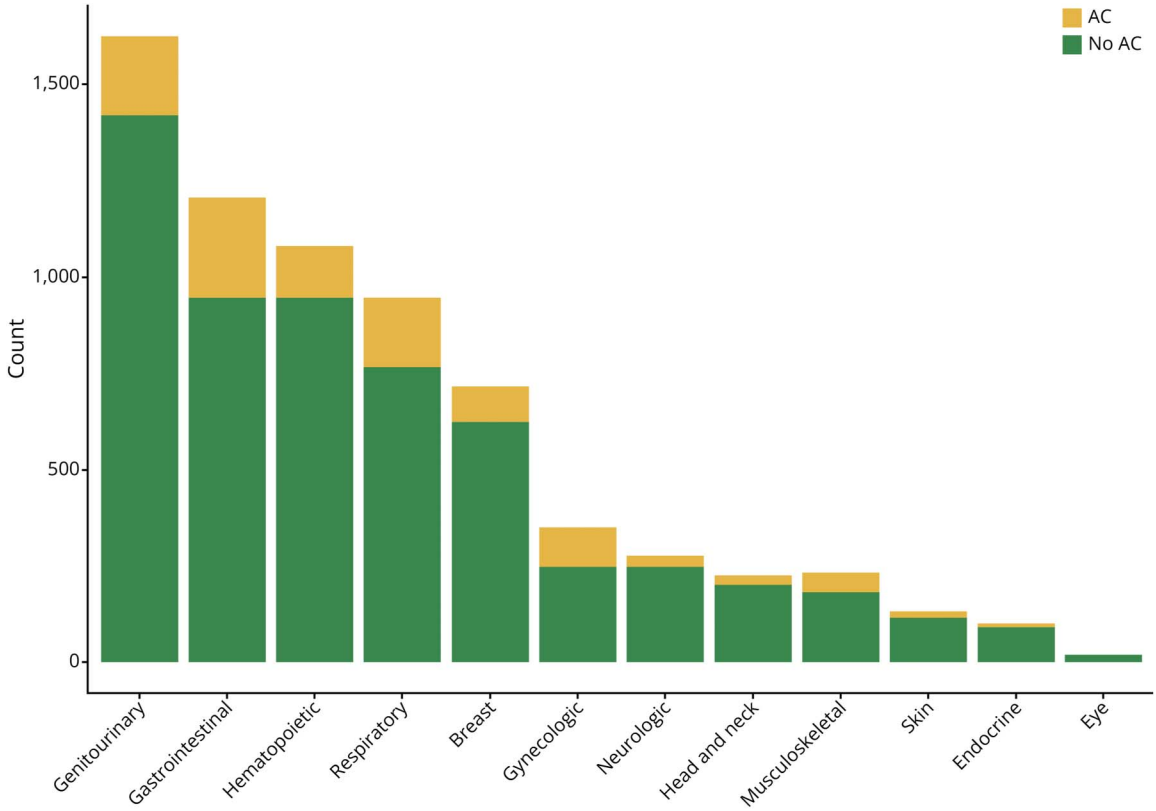
Table 1 Baseline Characteristics of Patients Prescribed an AC vs Not Prescribed (No AC) Before and After Propensity Score Matching

	Unmatched		Matched		SMD[a]	
	AC (N = 705)	No AC (N = 4,076)	AC (N = 655)	No AC (N = 655)	Prematch	Postmatch
Age, y, median (IQR)	72 (67–79)	75 (68–81)	73 (67–79)	73 (67–80)	−0.223	−0.056
Female, n (%)	336 (51.9)	1,962 (48.1)	337 (51.5)	341 (52.1)	0.076	0.012
Race and ethnicity, n (%)						
Asian	14 (2.0)	84 (2.1)	13 (2.0)	16 (2.4)	−0.005	−0.031
Black	126 (17.9)	677 (16.6)	121 (18.5)	118 (18.0)	0.033	0.012
Hispanic	72 (10.2)	399 (9.8)	69 (10.5)	66 (10.1)	0.014	0.015
White	458 (65.0)	2,661 (65.3)	417 (63.7)	414 (63.2)	−0.007	0.010
Unknown	35 (5.0)	255 (6.3)	35 (5.3)	41 (6.3)	−0.056	−0.039
Education, n (%)						
High school or less	246 (34.9)	1,378 (33.8)	229 (35.0)	234 (35.7)	0.023	0.016
Some college	459 (65.1)	2,698 (66.2)	426 (65.0)	421 (64.3)	−0.023	−0.016
Comorbidities, n (%)						
Hypertension	506 (71.8)	3,067 (75.2)	472 (72.1)	491 (75.0)	−0.079	−0.066
Complicated diabetes	178 (25.2)	1,238 (30.4)	170 (26.0)	209 (31.9)	−0.115	−0.133
Myocardial infarction	38 (5.4)	174 (4.3)	35 (5.3)	42 (6.4)	0.052	−0.050
Heart failure	173 (24.5)	919 (22.5)	164 (25.0)	176 (26.9)	0.047	−0.043
Prosthetic heart valve	17 (2.4)	60 (1.5)	15 (2.3)	17 (2.6)	0.068	−0.022
Stroke	153 (21.7)	1,025 (25.1)	144 (22.0)	161 (24.6)	−0.081	−0.061
TIA	39 (5.5)	380 (9.3)	35 (5.3)	38 (5.8)	−0.145	−0.018
Peripheral vascular disease	201 (28.5)	1,063 (26.1)	188 (28.7)	206 (31.5)	0.055	−0.062
Renal failure	181 (25.7)	1,215 (29.8)	175 (26.7)	200 (30.5)	−0.092	−0.085
Liver disease	126 (17.9)	448 (11.0)	106 (16.2)	105 (16.0)	0.197	0.004
DVT/PE	275 (39.0)	242 (5.9)	225 (34.4)	229 (35.0)	0.862	−0.016
Coagulopathy	132 (18.7)	505 (12.4)	120 (18.3)	122 (18.6)	0.175	−0.008
Major bleeding	142 (20.1)	763 (18.7)	135 (20.6)	127 (19.4)	0.036	0.031
Cerebrovascular malformation	1 (0.1)	8 (0.0)	1 (0.1)	0 (0.0)	−0.013	0.037

Abbreviations: AC = anticoagulant; DVT = deep vein thrombosis; IQR = interquartile range; PE = pulmonary embolism; SMD = standardized mean difference.
[a] SMDs are a measure of distance between 2 groups used to evaluate balance of individual covariates after propensity score matching. An absolute value ≥0.10 denotes persistent imbalances.

small to draw any meaningful conclusion regarding the safety and efficacy of anticoagulation.[37] The Edoxaban for the Treatment of Hypercoagulability in Patients with Active Cancer and Acute Ischemic Stroke (ENCHASE) trial randomized 40 patients to edoxaban, a direct oral anticoagulant, or enoxaparin, a low-molecular-weight heparin. This biomarker-focused pilot trial demonstrated that short-term changes in serum D-dimer and transcranial Doppler microembolic signals were comparable between the study groups. There was no antiplatelet arm in ENCHASE.[38] There are also 2 relevant subgroup analyses from previous clinical trials, including only patients with cryptogenic stroke, which further heightened the uncertainty regarding antithrombotic agents among those with cancer. The Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke trial suggested a numerically lower, though not statistically significant, risk of major ischemic or hemorrhagic events with apixaban compared with aspirin in patients with cancer[33] while the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source trial reported similar rates of recurrent stroke in patients with cancer who

Figure 2 Number of Patients With Active Cancer Hospitalized With Acute Stroke Who Were Prescribed vs Not Prescribed an AC by Cancer Group in the Unmatched Cohort (N = 4,781)



AC = anticoagulant.

were assigned to rivaroxaban vs aspirin and nominally fewer major bleeding events with aspirin.[13]

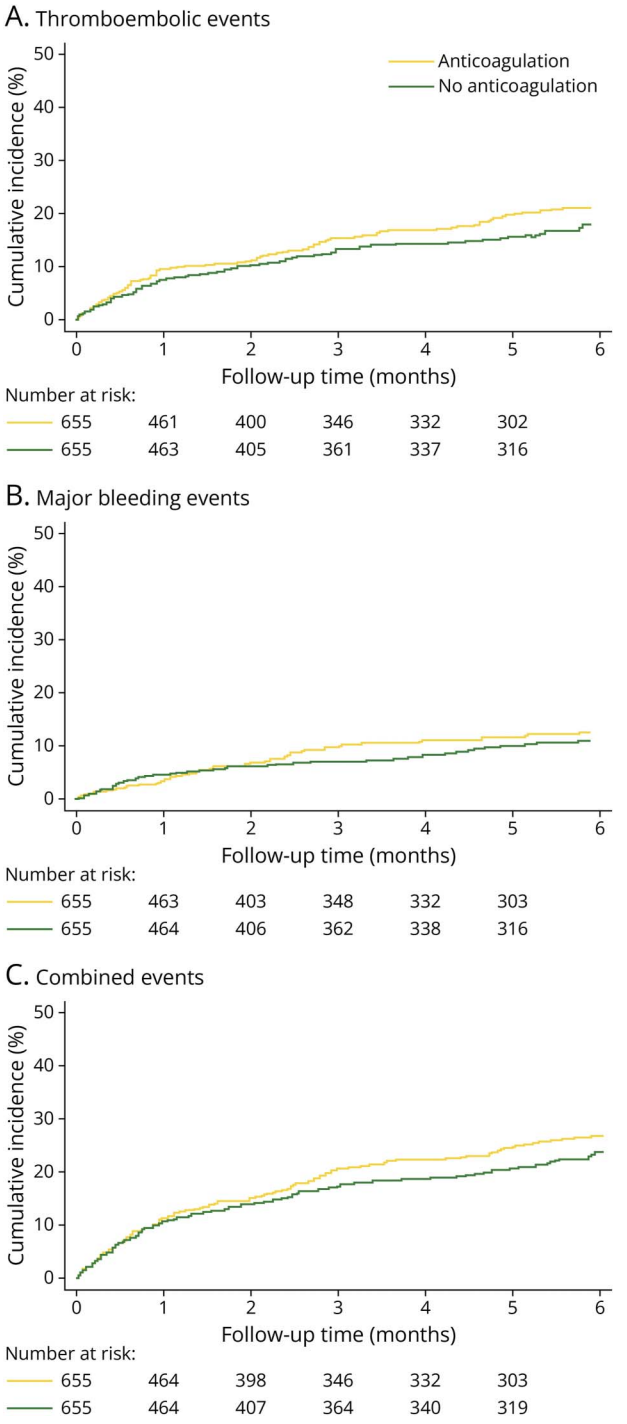
In this large cohort study, we observed no difference in thromboembolic events in patients with vs those without anticoagulant prescriptions. The propensity score matching was successful to some extent in excluding patients at lower risk of thromboembolic events, as the IR of thromboembolic events for those without anticoagulant prescription increased from 36.0 in the unmatched cohort to 45.1 in the matched cohort. However, decision making regarding anticoagulation could be influenced by many patient-level factors, including the severity of stroke, atherothrombotic vs embolic or multiterritory infarction patterns, stroke recurrence during hospitalization, impaired ambulation resulting from the index stroke, smoking history, and life expectancy. All of these are potential reasons that could not be included in the propensity score matching or adjusted for in our sensitivity analysis

Table 2 Estimated IRs and HRs for Thromboembolic, Major Bleeding, and Combined Events in Patients With Active Cancer Hospitalized With Ischemic Stroke With vs Without an AC Prescription in the Propensity Score–Matched Cohort

	Matched cohort				
	AC		No AC		
	Events/PY	IR[a] (95% CI)	Events/PY	IR[a] (95% CI)	HR (95% CI)
Thromboembolic events	104/189.2	55.0 (45.3–66.6)	87/193.2	45.0 (36.4–55.5)	1.21 (0.91–1.61)
Major bleeding events	58/189.8	30.6 (23.6–39.5)	52/193.6	27.0 (20.5–35.3)	1.13 (0.78–1.63)
Combined events	136/189.0	72.0 (60.8–85.1)	120/192.9	62.2 (52.0–74.4)	1.14 (0.90–1.46)

Abbreviations: AC = anticoagulant; HR = hazard ratio; IR = incidence rate; PY = person years of follow-up.
[a] IRs are calculated and reported per 100 person-years.

Figure 3 Cumulative Incidence of Thromboembolic Events (Panel A), Major Bleeding Events (Panel B), and Combined Events (Panel C) in the Matched Cohort



because of the lack of corresponding data in the Clinformatics database. Thus, we suspect that the numerically higher IR of thromboembolic events in the anticoagulant group is likely due to residual confounding by indication, as those at greatest risk of recurrent thromboembolism may have been most likely to be treated with anticoagulation, thereby biasing our results toward the null. Therefore, clinical equipoise persists.

Strengths of this study include the large sample size and the use of propensity score matching to balance measurable covariates across individuals treated with and without anticoagulants. However, this study also has several important limitations, primarily owing to its reliance on administrative data and nonrandomized design, particularly regarding the comparison of those with vs without anticoagulant prescriptions.

First, this study used claims-based data from a US population with private or Medicare Advantage insurance and, therefore, the results may not generalize to other populations. Furthermore, the socioeconomic status of this cohort may be higher than average for the United States. Second, because the data are claims-based, only outcomes with an associated diagnostic code are observed. We lacked imaging data and thus were unable to confirm stroke diagnoses by review of CT and/or MRI. Differential misclassification of outcomes is possible, as patients prescribed anticoagulation may have been monitored more frequently, which in turn could have led to overestimation of the magnitude of association between anticoagulation and clinical outcomes. However, thromboembolic and major bleeding events are often associated with a hospital visit or other claims, which would not likely be missed. Third, data on diagnoses and dispensed prescriptions covered by secondary insurance were unavailable. In addition, Clinformatics provides data regarding the dispensation of medications, but not their adherence, thereby limiting the accuracy of anticoagulant exposure classification in this analysis. Fourth, our employment of landmark analysis, while preventing immortal time bias, limits the generalizability of our results to those who survived, remained outcome free, and were not lost to follow-up until the selected landmark time (i.e., 7 days after hospital discharge).[16] Fifth, our definition of active cancer was determined by previously established diagnostic code algorithms, although we are unable to identify cancer grade/stage or the presence of metastatic disease with this approach. Sixth, while we aimed to focus on strokes with no apparent cause other than the cancer, we could only reliably exclude those with known AF before hospitalization. Seventh, we lacked data on measures of stroke severity and etiology. In addition, we lacked data on relevant laboratory values (such as D-dimer) and AF or VTE diagnoses occurring during or immediately after the index hospitalization. Eighth, a substantial number of patients were excluded from this analysis because of lack of continuous enrollment, a known limitation of claims-based studies.[39-42] Finally, mortality events were unavailable in the Clinformatics data set, and thus, we could not account for this competing risk in our analysis. Similarly, we lacked outcome data on patients who left the cohort, which could have led an underestimated risk of outcomes in this analysis.

In this analysis of administrative claims data, approximately 10% of patients with acute ischemic strokes had active cancer. The risk of early recurrent thromboembolic events in this population is substantial, and dedicated research is warranted

to improve their outcomes. In clinical practice, anticoagulants are not frequently prescribed for these patients and their potential benefits and risks are unclear. Future clinical trials are required to assess optimal antithrombotic strategies in this thromboembolism-prone population.

Author Contributions

P. Balali: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E.K. Acton: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. H. Elser: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. B.B. Navi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. S.E. Kasner: drafting/revision of the manuscript for content, including medical writing for content; study concept or design.

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