Prior Antithrombotic Use is Associated with Favorable Mortality and Functional Outcomes in Acute Ischemic Stroke

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Keywords: Ischemic stroke, prognosis, functional outcome, mortality, antiplatelet, anticoagulant, antithrombotic

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Abstract

Background and Purpose: Antithombotics are the mainstay of treatment in primary and secondary prevention of stroke and their use prior to an acute event may be associated with better outcomes.

Methods and Results: Using data from Get With The Guidelines-Stroke with over half a million acute ischemic strokes recorded between Oct 2011 and Mar 2014 (n=540,993) from 1661 hospitals across the US, we examined the unadjusted and adjusted associations between prior antithrombotic use and clinical outcomes. There were 250,104 (46%) stroke patients not receiving any antithrombotic prior to stroke; of whom approximately a third had a documented prior vascular indication. After controlling for clinical and hospital factors, patients who were receiving antithrombotics prior to stroke had better outcomes compared with those who did not, regardless of whether a prior vascular indication was present or not: adjusted odds ratio (OR) (95% confidence intervals [CI]) were 0.82 (0.80-0.84) for in-hospital mortality, 1.18 (1.16-1.19) for home as the discharge destination, 1.15 (1.13-1.16) for independent ambulatory status at discharge, and 1.15 (1.12-1.17) for discharge mRS of 0 or 1.

Conclusion: Prior antithrombotic therapy was independently associated with improved clinical outcomes after acute ischemic stroke. Ensuring use of antithrombotics in appropriate patient populations may be associated with benefits beyond stroke prevention.

Introduction

Even though use of antithrombotic medications for primary and secondary prevention of cardiovascular disease is increasing, many patients with indications are still not receiving antithrombotic medications and suffer an acute ischemic stroke [1]. It also remains unclear if prior therapy can also improve outcomes from those still having an acute ischemic stroke. Possible mechanisms for such a benefit include: attenuating the volume of the initial thrombus, preventing clot propagation, and reducing the risk of early recurrent thrombosis or embolism.

Despite theoretical mechanisms for benefit, existing evidence on the topic is conflicting. Kwok and colleagues found that prior antithrombotic use was not associated with reduced mortality up to one year after stroke presentation [2]. In contrast, a large registry from Canada reported a beneficial association between prior use of antithrombotics and improved functional outcome [3][4]. Indeed, recent studies found a reduction in initial stroke severity in previous antiplatelet users in ischemic stroke [5][6], suggesting prior antithrombotic therapy may moderate ischemic stroke evolution from the earliest moments of onset. To date, however, all these studies were small or moderate in size and some of these conflicts may be due to unstable estimates.

Using data from the American Heart Association/American Stroke Association (AHA/ASA) Get with the Guidelines-Stroke (GWTG-Stroke) database, our study aims were to: (1) describe characteristics of ischemic stroke patients by receipt or non-receipt of antithrombotic medication prior to stroke; (2) determine whether pre-stroke antithrombotic use is related to outcomes at discharge, and whether this relationship varies with indication for antithrombotic use; and (3) determine whether prior warfarin use is associated with outcomes at discharge among patients with atrial fibrillation (AF) or flutter, taking INR control into account.

Methods

The AHA/ASA GWTG-Stroke database data collection methods have been previously described [7][8][9][10]. In brief, 1661 hospitals used an Internet-based "Patient Management Tool" (Quintiles, Cambridge, MA) to enter data, receive decision support, and obtain feedback via on demand reports of performance on quality measures and recorded data from consecutive admissions for acute ischemic stroke. There were a total of 624,883 patients with ischemic stroke at 1,705 participating centres between 1st October 2011 and 31st March 2014. Of them 19,381 were transferred to another acute facility, left against medical advice, or had no data on discharge status; 63,738 had missing data on prior antithrombotic use, and further 771 patients were excluded due to data on vascular indication for use of antithrombotics was missing.

Trained hospital personnel abstracted data using the Internet-based Patient Management Tool with standardized data definitions and detailed coding instructions. The Internet-based system performs checks to ensure that the reported data are complete and internally consistent. In addition, data quality is monitored for both completeness and accuracy. Hospitals that participate must receive approval through their local institutional review boards or a waiver of individual consent under the common rule. Quintiles (Cambridge, MA) is the data collection coordination centre for the American Heart Association/American Stroke Association Get With the Guidelines programs. The Duke Clinical Research Institute (Durham, NC) serves as the data analysis centre. Hospital characteristics (i.e. academic teaching status, bed size) were based on American Hospital Association data [10]. Past medical history was defined on the basis of pre-existing conditions, with the exclusion of conditions that were newly diagnosed during the hospital stay.

Prior antithrombotic use was defined as any anticoagulant or antiplatelet use before the index stroke. Patients were considered to have a vascular indication for antithrombotic use if their *medical history* included coronary artery disease (CAD), previous stroke or transient ischemic attack (TIA), or atrial

fibrillation or flutter. Our study examined patient-relevant outcomes of in-hospital mortality, discharge to home, ability to ambulate independently at discharge, disability at the time of discharged defined using modified Rankin scale (mRS ≥2) and acute hospital length of stay (LOS).

Statistical analysis

Analyses were carried out using SAS version 9.3 or higher (SAS Institute, Cary NC). We compared the baseline characteristics for patients by (a) prior use of antithrombotic (yes vs. no) and (b) prior use of antithrombotic (yes vs. no) and indication (any vs. none) (4 groups). Differences are compared with Pearson chi-square tests for categorical and Wilcoxon rank-sum and Kruskal-Wallis tests for continuous variables and data are presented descriptively.

To evaluate associations, multivariable logistic regression was used for binary outcomes. Multiple regression was used for LOS, which was transformed using the natural log to achieve approximate normality. In addition to the term for prior antithrombotic use, each model also contained a term for antithrombotic indication, and a term for the interaction between them. Models were adjusted for covariates at admission including age, sex, race, BMI, medical history, on-hours arrival, and site characteristics. Missing values of covariates were imputed using multiple imputation (25 imputations). Generalized estimating equations (GEEs) were used to account for clustering within hospitals.

We present prior antithrombotic odds ratios within indication subgroups if the interaction between antithrombotic use and indication is significant and if not, present separate antithrombotic and indication odds ratios (i.e., main effects). For LOS outcome the interaction between prior antithrombotic use and indication was significant, and thus the ratio of expected LOS for the two groups is reported i.e. the data are presented as the *ratio of expected LOS* in the first group compared to the second, that is, (expected

days in group 1)/ (expected days in group 2). Therefore, for LOS outcome, risk relationships are shown for each variable within levels of the other variable.

Because NIHSS is missing in a proportion of patients (23%) a sensitivity analysis was performed in which these models were repeated, including NIHSS as a covariate, in the subset of patients with available NIHSS data.

Persistent or paroxysmal AF/flutter during the index admission and previous medical history of AF/flutter were used to define AF/flutter in this study. To determine whether prior warfarin use is associated with outcomes among patients with AF/flutter, taking INR control into account, patients were grouped as (1) prior use of anticoagulants with INR > 1.4 at admission, (2) prior use of anticoagulants with INR $\leq$ 1.4 at admission, and (3) no anticoagulants prior to admission. Patients who were on an anticoagulant but who do not have INR data were excluded from this analysis. Models used were the same as for the main analysis, except that the three warfarin groups were included in the model in place of the antithrombotic and indication terms, an additional term was added for non-anticoagulant antithrombotics (e.g., aspirin and other antiplatelet drugs), and patients taking new oral anticoagulants (NOACs) were excluded. Each warfarin group was compared to the no-warfarin group (reference group).

Results

A total of 540,993 patients at 1,661 sites admitted with an ischemic stroke during the study period were included in the current study. Over half (53.8%) were receiving an antithrombotic agent (either an antiplatelet/combination or an anticoagulant); 253,552 (46.9%) on were taking antiplatelet drugs and 57,543 (10.6%) were taking an anticoagulant (the sum total is greater than 53.8% because some patients were taking both) (see Supplementary Figure for inclusion and exclusion).

The characteristics of all patients included in the analyses and then separately for those who received antithrombotics prior to the index ischemic stroke and those who did not were shown in **Table 1**. With large numbers the p values are highly significant between the two populations. People who did not take any antithrombotic prior to stroke were younger, more likely to be female, less likely to be Caucasian, more likely to have abnormal lipid profile, more likely to be a current smoker, but with lower prevalence of co-morbid medical conditions including previous history of stroke and AF/flutter, and were more likely to be ambulatory independently prior to stroke. Although many of the acute biochemistry and haematological parameters, and site characteristics, were statistically significantly different between these groups, the magnitudes of differences were negligible.

Sample characteristics comparison by prior antithrombotic use and indication for its use shows pre-stroke antithrombotic users were older and more likely to be white. Patients without pre-stroke antithrombotic use despite an indication show similar characteristics to users who did not have previous cardiovascular diseases. The total number of the subgroups analysed by the presence or absence of prior indications for antithrombotic use and exclusions are presented in the **Figure 1**. Approximately 30% of patients had mismatch between vascular indication and usage in this cohort. **Supplementary Table I** shows the types of antithrombotic use among the users of antithrombotics before the index stroke.

Table 2 shows the regression model results (adjusted for variables described as in Methods), respectively, by prior antithrombotic use and indication. Although crude rates show poor outcome in those with prior use, regression models (with full adjustment) demonstrate that patients taking an antithrombotic prior to the index stroke were less likely to die during the hospitalization and more likely to be discharged to home, able to ambulate independently, and better functional outcomes at discharge compared with patients who were not on an antithrombotic. **Supplementary Table II** shows that patients with a vascular indication for antithrombotic use (medical history of CAD, previous stroke or TIA, or atrial fibrillation or flutter) were more likely to have *unfavourable/negative* outcomes than patients without an indication. There were no significant interactions between antithrombotic use and prior indication for use, indicating that the lower rate of in-hospital death with antithrombotic use was similar for patients with and without a vascular indication for use. Discharge outcome to home among patients discharged alive, and ambulatory status among patients able to ambulate independently prior to the event, showed results which were consistent with the models in the larger set of patients.

Length of stay outcome analysis shows patients taking an antithrombotic prior to stroke had a shorter expected hospital stay than patients not on an antithrombotic prior to the event. The significant interaction indicates that the expected relative length of stay depends on whether or not the patient had an indication — there is more of an associated reduction in LOS, with antithrombotic compared to without, where there is an indication (see **Table 2**).

Supplementary Tables III & IV show the results in a subset of patients in whom NIHSS was available with additional adjustment for NIHSS score. Results are generally consistent with those in the full cohort, except for LOS, which here does not have a significant interaction between antithrombotic and the presence or absence of an indication for its use.

Of 118,635 (22.1%) identified as AF/flutter, 29,425/118,636 (24.8%) had no previous medical history of AF/flutter but had either persistent or paroxysmal AF/flutter during the index admission **(Supplementary Table V). Table 3** demonstrates that patients on warfarin with INR>1.4 had better outcomes than patients not on warfarin. Patients on warfarin with INR ≤ 1.4 had a higher risk of in-hospital death, lower likelihood of being discharged home, and a longer length of hospital stay, compared to patients not on warfarin prior to stroke, but a similar probability of being able to ambulate independently and having a low mRS score at the time of discharge.

Discussion

To the best of our knowledge, this study is the largest to examine the association between prior antithrombotic use and important and relevant outcomes in patients admitted with an acute ischemic stroke. We found that the prior use of antithrombotics was associated with a favourable outcome for all outcomes assessed highlighting an important point that antithrombotics not only have effect on vascular outcome but also may reduce the severity of vascular outcomes. Associations between prior antithrombotic medication use and better post-stroke outcomes were seen across patient subgroups. No significant interaction between antithrombotic use and indication was observed except for LOS outcome.

To date, the literature around the impact of prior antithrombotic use on stroke outcome has been inconsistent and shown conflicting results. However, they were limited by relatively small sample size (Sanosian et al, n=260) [11] (Vibo et al, n=433) [12], or focused on mortality alone [2][12], or in a particular patient population or of certain age [13], or examined the stroke severity only [14]. Relatively larger studies again showed conflicting results [2][3][4][5][6][15]. The key advantages of our study are much larger sample size and analysis of diverse relevant and important outcomes for patients.

These findings may have important clinical implications. It appears that in US setting, a substantial proportion of patients who sustained ischemic stroke (78,465/540,993=14.5%) would have potentially benefited from antithrombotic use as a secondary preventive measure were not receiving antithrombotic agents at the time of index stroke onset. Similarly, we found antithrombotic use prior to stroke without a documented vascular indication in a substantial proportion of patients (Supplementary Table 2). This use may be due to other appropriate indications but could also reflect self-medication, which would be concerning due to the potential harm from drug side effects.

White et al [1] highlighted similar mismatches and the fact whilst half of strokes cases were on antithrombotics and yet developed stroke, half of stroke patients might have been identified as high risk and been prescribed an antithrombotic medication that would have prevented a substantial number of stroke events. This, in combination with our current study findings, further strengthens the argument to base antithrombotic medication use on improved risk prediction scores. Indeed, Loke et al [16] recently highlighted the lack of sensitivity of existing cardiovascular risk prediction tools in reliably identifying those groups of patients who are most likely to subsequently develop cardiovascular (CV) adverse events [17]. Most recent guidelines from US [18], Europe [19], UK [20] and ATP III [21] mainly focused on CV risk factors and use of antiplatelets in primary prevention was less well focused perhaps due to presumed adherence to established guidance.

The strengths of our study include the large sample size and prospective data collection. One of the key strengths of the paper includes the robust statistical analysis with ability to control for potential confounders as well as ability to understand the confounding effect by indication through analysis of indication for antithrombotic vs. their effect on the outcomes examined. We were able to examine the outcomes by prior antithrombotic use as well as by vascular indication. We were also able to examine the outcomes by prior warfarin use and INR among patients with AF/flutter. Further, we were able to analyse the data taken into account of the stroke severity at onset (e.g., National Institutes of Health Stroke Scale (NIHSS) score) in this current report.

Our study has some limitations. As a hospital-based registry some cases of stroke might not have been included, such as patients who died before admission. Patients and hospitals may not be entirely representative of the U.S population but the sample population is comparable to all US patients hospitalized with stroke [22]. Residual measured and unmeasured confounders may account for some of these findings such as factors that could have influenced prior use of antithrombotic therapy and

adherence to prescribed therapy. For example, those who use antithrombotic agents may have a 'healthy user' effect or greater use of health care. Whilst a substantial proportion of patients had missing data on NIHSS and that was due to non-random missing, repeating the analyses in those who had NIHSS data yielded the similar results. As an observational study the causality cannot be assumed. Nonetheless, the observed associations have plausible explanations, as we alluded to in the introduction.

In summary, using the AHA/ASA GWTG-Stroke registry data with over half a million of ischemic stroke patients, we present evidence that prior antithrombotic use was associated with favorable outcomes in ischemic stroke and thus highlights the importance of primary and secondary stroke prevention with antithrombotic medications when indicated. A substantial proportion of patients in our study sustained stroke despite being on antithrombotic agents and the fact that patients with INR <1.4 among people with AF/flutter had worse outcomes suggests the urgent need to address issues of medication compliance, and adequate anticoagulation in stroke prevention. Ensuring appropriate use of antithrombotics at a population level may have substantial benefit to patients with stroke and health economy in a global scale.

Disclosures (in alphabetical order):

Dr Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Vice-Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, Takeda.

Dr Fonarow is a member of the GWTG Executive Committee; has served as a consultant to Janssen (modest), receives research support from PCORI (significant), and is an employee of UCLA, which holds a patent on retriever devices for stroke.

Miss. Hellkamp None

Dr Myint has received support from Viforpharma to attend an advisory meeting.

Dr Peterson has received research funding from Janssen Pharmaceuticals, Sanofi-Aventis, Genentech, Daiichi Sankyo, Eli Lilly and Astra Zeneca. He has served as a consultant for Boehringer Ingelheim, Astra Zeneca, and Janssen. Dr Peterson is also the PI of the AHA Data Coordinating Centre at Duke Clinical Research Institute.

Dr Reeves has received salary support from the Michigan Stroke GWTG Registry and is a member of the American Heart Association's GWTG Quality Improvement Subcommittee and Stroke Science Subcommittee.

Dr Saver is a member of the GWTG-Stroke Science Subcommittee; is an employee of the University of California which received funding for his scientific consulting services for trial design and conduct to Medtronic, Stryker, Neuravia, Boehringer Ingelheim (prevention only), Mitsubishi, and St. Jude Medical; and is an employee of the University of California, which holds a patent on retriever devices for stroke.

Dr Schulte None

Dr Schwamm is Chair of the GWTG Clinical Workgroup; serves as a consultant to the Massachusetts Department of Public Health, and as a member of the steering committee for the VICTORY AF and REACT AF trials of stroke prevention in AF (Medtronic).

Dr Smith is a member of the American Heart Association Get With The Guidelines Steering Committee; has received research support from the National Institutes of Health (National Institute of Neurological Disorders and Stroke R01NS062028), the Canadian Stroke Network, and the Canadian Institute

for Health Research; has received speaking or writing fees from QuantiaMD, the BMJ Group, and the Canadian Conference on Dementia; and has served on an advisory board to Genentech.

Dr Suter is employed as Vice-President of Quality and Health IT by the American Heart Association/American Stroke Association, which has received grant support from numerous entities including Genentech, Boehringer Ingelheim, Janssen Pharmaceuticals, Daiichi Sankyo, Medtronic,

Bristol-Myers Squibb, and Astra Zeneca; he has previously served as a consultant for Genentech and Daiichi Sankyo.

Dr Ying Xian: None

Sources of Funding

The GWTG-Stroke program is currently supported in part by a charitable contribution from Bristol-Myers Squibb/Sanofi Pharmaceutical Partnership and the American Heart Association Pharmaceutical Roundtable. GWTG-Stroke has been funded in the past through support from Boehringer-Ingelheim and Merck. These funding agencies did not participate in design or analysis, manuscript preparation, or approval of this study.

Contributors

PKM and EES conceived the idea and developed the analysis plan with critical input from co-authors. ASH analysed the data. PKM and EES drafted the paper with input from all co-authors. All authors contributed in interpretation of results and in making an important intellectual contribution to the manuscript.

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Table 1: Baseline Patients Descriptive Statistics by Prior Antithrombotic Use

Variable	Overall (N=540,993)	Prior antithrombotic (N=290,889)	No prior antithrombotic (N=250,104)	P-value
Demographics				
Age (years), median (IQR)	72 (61-82)	75 (65-84)	67 (56-80)	<0.0001
Female Sex, n (%)	276687 (51.18)	148179 (50.97)	128508 (51.41)	0.001
Race, n (%)				<0.0001
White	379289 (70.23)	214862 (73.97)	164427 (65.86)	
Black	91176 (16.88)	42793 (14.73)	48383 (19.38)	
Hispanic	35268 (6.53)	16394 (5.64)	18874 (7.56)	
Asian	14338 (2.65)	6474 (2.23)	7864 (3.15)	
Other	20026 (3.71)	9930 (3.42)	10096 (4.04)	
Presentation				
On-hour arrival (M-F 7a-6p), n (%)	292989 (54.16)	158233 (54.40)	134756 (53.88)	0.0001

Variable	Overall (N=540,993)	Prior antithrombotic (N=290,889)	No prior antithrombotic (N=250,104)	P-value
NIH Stroke Scale, median (IQR)	4 (1-10)	4 (1-10)	4 (1-9)	<0.0001
N (% missing)	415034 (23.3)	223243 (23.3)	191791 (23.3)	
Systolic BP (mmHg), median (IQR)	155 (136-177)	153 (135-174)	156 (137-179)	<0.0001
N (% missing)	427326 (21.0)	229521 (21.1)	197805 (20.9)	
Heart rate (per min), median (IQR)	79 (68-91)	78 (68-89)	80 (70-93)	<0.0001
N (% missing)	420998 (22.2)	226011 (22.3)	194987 (22.0)	
BMI (kg/m^2), median (IQR)	27.2 (23.7-31.6)	27.2 (23.7-31.5)	27.1 (23.6-31.6)	0.004
N (% missing)	389151 (28.1)	209930 (27.8)	179221 (28.3)	
Lab results				
Serum creatinine (mg/dL), median (IQR)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	<0.0001
N (% missing)	424629 (21.5)	228171 (21.6)	196458 (21.5)	
Total cholesterol (mg/dL), median (IQR)	165 (137-198)	156 (130-188)	175 (147-207)	<0.0001

Variable	Overall (N=540,993)	Prior antithrombotic (N=290,889)	No prior antithrombotic (N=250,104)	P-value
N (% missing)	393327 (27.3)	207828 (28.6)	185499 (25.8)	
HDL (mg/dL), median (IQR)	42 (34 -52)	41 (34 -51)	42 (34 -53)	<0.0001
N (% missing)	387763 (28.3)	204917 (29.6)	182846 (26.9)	
LDL (mg/dL), median (IQR)	95 (72 -123)	88 (67 -114)	104 (80 -132)	<0.0001
N (% missing)	470591 (13.0)	248304 (14.6)	222287 (11.1)	
Triglycerides (mg/dL), median (IQR)	111 (79 -161)	109 (78 -159)	113 (80 -164)	<0.0001
N (% missing)	389988 (27.9)	205899 (29.2)	184089 (26.4)	
Glucose (mg/dL), median (IQR)	119 (101 -156)	120 (101 -158)	117 (100 -153)	<0.0001
N (% missing)	418499 (22.6)	224843 (22.7)	193656 (22.6)	
Medical History, n (%)				
Hypertension	414163 (76.56)	241323 (82.96)	172840 (69.11)	<0.0001

Variable	Overall (N=540,993)	Prior antithrombotic (N=290,889)	No prior antithrombotic (N=250,104)	P-value
Diabetes mellitus	181960 (33.63)	112281 (38.60)	69679 (27.86)	<0.0001
CAD/prior MI	136054 (25.15)	104966 (36.08)	31088 (12.43)	<0.0001
Smoker	98326 (18.18)	41038 (14.11)	57288 (22.91)	<0.0001
Prosthetic heart valve	7179 (1.33)	6059 (2.08)	1120 (0.45)	<0.0001
CHF	49611 (9.17)	36665 (12.60)	12946 (5.18)	<0.0001
PVD	25807 (4.77)	19700 (6.77)	6107 (2.44)	<0.0001
Prior stroke	137221 (25.36)	101765 (34.98)	35456 (14.18)	<0.0001
Atrial fib/flutter	101520 (18.77)	78077 (26.84)	23443 (9.37)	<0.0001
Carotid stenosis	19915 (3.68)	15930 (5.48)	3985 (1.59)	<0.0001

Variable	Overall (N=540,993)	Prior antithrombotic (N=290,889)	No prior antithrombotic (N=250,104)	P-value
Ambulatory status prior to index stroke				<0.0001
Independent with or without a device	388622 (84.09)	203870 (81.93)	184752 (86.61)	
Needs assistance from another person	26327 (5.70)	17194 (6.91)	9133 (4.28)	
Unable to ambulate	17752 (3.84)	11172 (4.49)	6580 (3.08)	
Missing (%)	21.0	21.1	20.7	
Antithrombotics at admission, n (%)				
Antiplatelet		253552 (87.34)		
Anticoagulant		57543 (19.82)		
Type unspecified		574 (0.20)		
INR (patients on warfarin), median (IQR)		1.69 (1.22-2.30)		
N		21743		
Missing (%)		23.7		

Variable	Overall (N=540,993)	Prior antithrombotic (N=290,889)	No prior antithrombotic (N=250,104)	P-value
Hospital characteristics				
Teaching hospital, n (%)	322708 (60.72)	172461 (60.41)	150247 (61.07)	<0.0001
Number of beds, median (IQR)	327 (252-567)	370 (250-561)	374 (255-569)	<0.0001
Annual ischemic stroke admissions, median (IQR)	213 (145-333)	214 (145-333)	213 (144-333)	0.41
Annual volume of IV t-PAs, median (IQR)	15.5 (8.8-25.4)	15.4 (8.7-25.3)	15.6 (8.8-26.0)	<0.0001
Geographic region, n (%)				<0.0001
West	100506 (18.58)	52650 (18.10)	47856 (19.13)	
South	193037 (35.68)	100423 (34.52)	92614 (37.03)	
Midwest	107701 (19.91)	61039 (20.98)	46662 (18.66)	
Northeast	139749 (25.83)	76777 (26.39)	62972 (25.18)	
Rural location, n (%)	26767 (4.99)	15570 (5.39)	11197 (4.51)	<0.0001

Abbreviations: IQR = inter quartile range; CAD = coronary artery disease; CHF = chronic heart failure; MI = myocardial infarction; PVD = peripheral vascular disease; BP= blood pressure; BMI = body mass index; INR = international normalized ratio; HDL = high density lipoprotein; LDL = low density lipoprotein

Data for each variable are missing in <5% of patients unless noted. Percentages are calculated using only non-missing values.

P-values for categorical variables are from Pearson chi-square tests, and for continuous variables are from Wilcoxon rank sum tests.

Table 2: Outcomes by prior antithrombotic use and indication

	Interaction between anti-thrombotic use and indication	Prior antithrombotic use vs. no prior use		Indication for antithrombotic use vs. no indication	
Outcome	**P**	**OR (95%CI)**	**P**	**OR (95% CI)**	**P**
In-hospital death	0.29	0.82 (0.80, 0.84)	<0.0001	1.49 (1.45, 1.54)	<0.0001
Discharge to home	0.33	1.18 (1.16, 1.19)	<0.0001	0.72 (0.71, 0.72)	<0.0001
–where discharged alive	0.55	1.16 (1.15, 1.18)	<0.0001	0.73 (0.72, 0.74)	<0.0001
Able to ambulate independently at discharge	0.43	1.15 (1.13, 1.16)	<0.0001	0.70 (0.69, 0.71)	<0.0001
–where able to ambulate independently prior to index stroke	0.61	1.17 (1.15, 1.19)	<0.0001	0.77 (0.76, 0.78)	<0.0001
mRS = 0 or 1 at discharge	0.55	1.15 (1.12, 1.17)	<0.0001	0.66 (0.65, 0.67)	<0.0001

Length of Stay					
	Interaction between anti-thrombotic use and indication	**Prior antithrombotic use vs. no prior use Ratio (95%CI)**		**Indication for antithrombotic use vs. no indication Ratio (95%CI)**	
Outcome	**P**	**Indication for antithrombotic use**	**No indication for antithrombotic use**	**Prior antithrombotic use**	**No prior antithrombotic use**
Length of stay	0.0049	0.95 (0.94, 0.95)	0.96 (0.95, 0.97)	1.12 (1.11, 1.12)	1.13 (1.12, 1.14)

	Interaction between anti-thrombotic use and indication	Prior antithrombotic use vs. no prior use		Indication for antithrombotic use vs. no indication	
Outcome	**P**	**OR (95%CI)**	**P**	**OR (95% CI)**	**P**
Length of stay (ratio)	0.0049	0.96 (0.95, 0.97)	<0.0001	1.13 (1.12, 1.14)	<0.0001

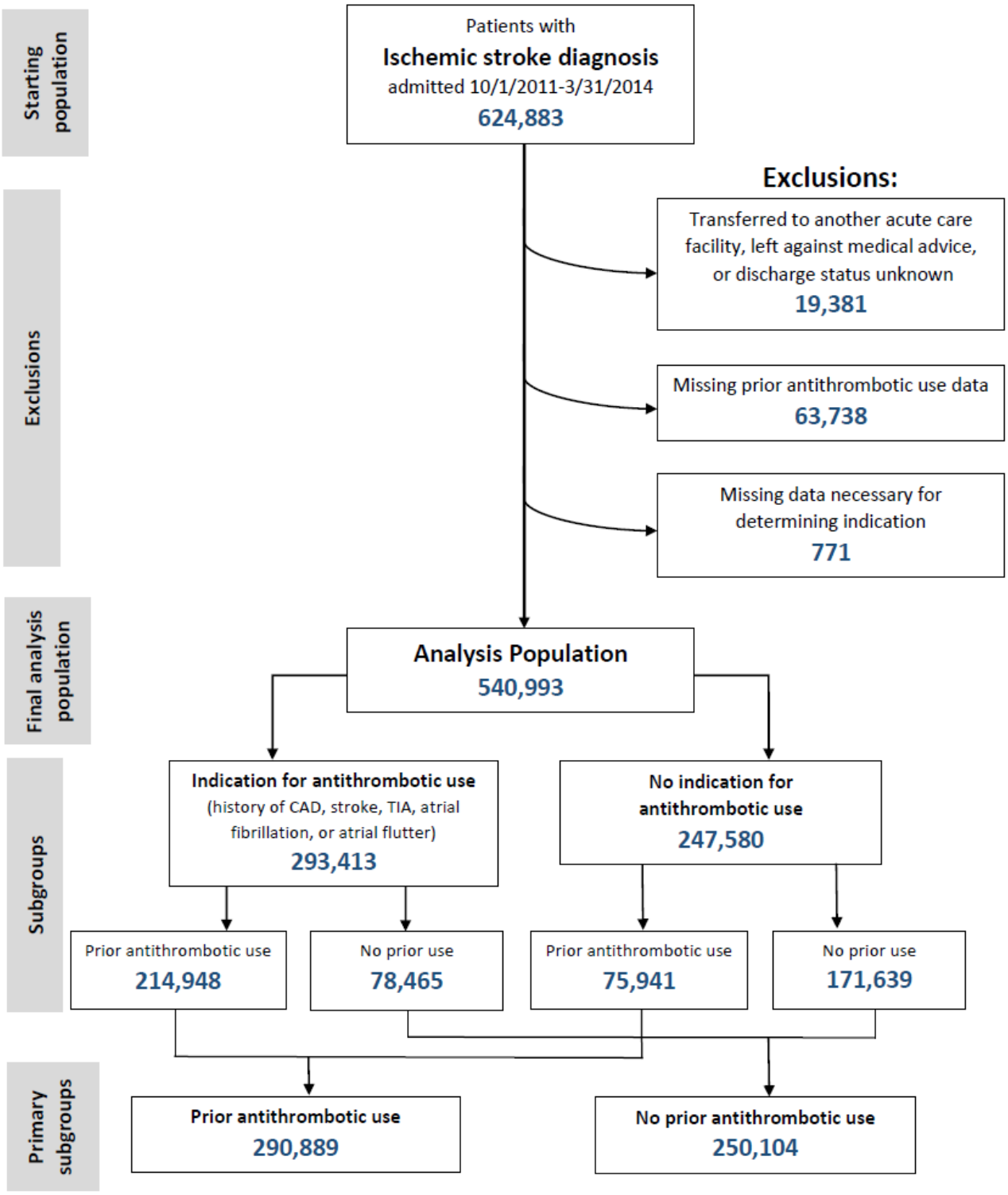
For the all endpoints, there was no significant interaction between prior antithrombotic use and indication; therefore, odds ratios are shown for these two variables separately.*Modeling for LOS:* A multiple regression model was used. Patients were excluded if they transferred in or transferred out to acute care, or had an in-hospital stroke. In all other respects the LOS model is the same as for the binary endpoints.

Table 3: Outcomes by prior warfarin use and INR, among patients with AF/flutter

Outcome / subgroup	**N**	**Event rate**	**Adjusted Odds ratio (95% CI)**	**P**
All patients with AF/flutter*	121,287			
In-hospital mortality				
Prior warfarin, INR > 1.4	10,774	7.9% (853)	0.99 (0.92, 1.07)	0.79
Prior warfarin, INR ≤ 1.4	5,255	9.2% (482)	1.19 (1.08, 1.31)	0.0005
No warfarin	105,258	8.6% (9,060)	ref	
Discharge to home				
Prior warfarin, INR > 1.4	10,774	36.6% (3,942)	1.12 (1.08, 1.18)	<.0001
Prior warfarin, INR ≤ 1.4	5,255	31.2% (1,637)	0.81 (0.76, 0.87)	<.0001
No warfarin	105,258	32.6% (34,312)	ref	
Able to ambulate independently				
Prior warfarin, INR > 1.4	8,979	42.7% (3,834)	1.20 (1.15, 1.26)	<.0001
Prior warfarin, INR ≤ 1.4	4,308	38.5% (1,658)	0.96 (0.90, 1.03)	0.29
No warfarin	78,401	37.4% (29,343)	ref	
Modified Rankin Scale = 0 or 1				
Prior warfarin, INR > 1.4	5,846	20.0% (1,169)	1.09 (1.01, 1.17)	0.028
Prior warfarin, INR ≤ 1.4	2,866	17.7% (507)	0.89 (0.80, 0.99)	0.028
No warfarin	47,183	17.8% (8,395)	ref	
Length of stay		*median (25^{th}, 75^{th} percentiles)*	*Ratio (95% CI)*	
Prior warfarin, INR > 1.4	8,947	4 (3, 6)	0.93 (0.92, 0.95)	<.0001
Prior warfarin, INR ≤ 1.4	4,294	5 (3, 8)	1.10 (1.08, 1.13)	<.0001
No warfarin	86,319	4 (3, 7)	ref	

* Model covariates as described in the methods, including a model term for non-anticoagulant antithrombotic medications (e.g. aspirin). Of 130,945 with known or newly diagnosed atrial fibrillation or flutter during the hospital stay, 143 (0.1%) were excluded for missing antithrombotic information, 4,930 (3.8%) were excluded for missing INR, and 4,585 (3.5%) for taking novel oral anticoagulants (NOACs).

Figure 1: Consort Diagram of Patient Exclusion



Supplementary Table I: The frequency distribution by type of prior antithrombotic agents

Antiplatelet	**Percent (n) of pts on an antiplatelet**
N	167,791
Aspirin	86.6% (145,255)
Clopidogrel	23.1% (38,696)
Aspirin/dipyridamole	3.1% (5,128)
Other antiplatelet	0.4% (681)
Prasugrel	0.1% (100)
Ticlopodine	<0.1% (67)
Ticagrelor	<0.1% (48)
Anticoagulant	**Percent (n) of pts on an anticoagulant**
N	36,704
Warfarin	77.7% (28,503)
Dabigatran	7.8% (2,876)
Rivaroxaban	6.6% (2,423)
LMW heparin	6.3% (2,299)
Other anticoagulant	1.4% (514)
Unfractionated heparin	1.1% (416)
Apixaban	0.5% (181)
Fondaparinux	0.4% (133)
Argatroban	<0.1% (13)
Desirudin	<0.1% (4)
Lepirudin	<0.1% (3)

Supplementary Table II: Outcomes (event rates) by prior antithrombotic use and indication

	Indication for antithrombotic use		No indication for antithrombotic use	
Outcomes	**Prior antithrombotic use**	**No prior use**	**Prior antithrombotic use**	**No prior use**
N	214,948	78,465	75,941	171,639
In-hospital death	5.5% (11,829)	6.5% (5,121)	3.6% (2,730)	3.8% (6,538)
Discharge destination				
Home	43.5% (93,599)	41.4% (32,478)	53.9% (40,932)	56.7% (97,235)
Other health care facility*	45.1% (96,995)	45.3% (35,522)	39.1% (29,691)	36.7% (63,071)
Hospice	5.8% (12,525)	6.8% (5,344)	3.4% (2,588)	2.8% (4,795)
Died	5.5% (11,829)	6.5% (5,121)	3.6% (2,730)	3.8% (6,538)
Ambulatory status at discharge				
N	184,071	66,732	63,221	144,761
Able to ambulate independently	42.5% (78,200)	40.2% (26,834)	53.5% (33,823)	56.1% (81,185)
Able to ambulate with assistance	30.7% (56,546)	30.0% (19,988)	27.4% (17,300)	25.8% (37,369)
Unable to ambulate	17.5% (32,142)	19.1% (12,717)	11.9% (7,546)	10.9% (15,728)
Died	6.4% (11,829)	7.7% (5,121)	4.3% (2,730)	4.5% (6,538)
ND	2.9% (5,354)	3.1% (2,072)	2.9% (1,822)	2.7% (3,941)
Modified Rankin Scale at discharge				
N	95,000	35,026	32,330	75,631
0	10.1% (9,589)	9.4% (3,281)	15.2% (4,912)	16.7% (12,650)
1	14.8% (14,080)	13.9% (4,869)	19.9% (6,421)	20.9% (15,838)
2	9.9% (9,435)	9.2% (3,239)	11.7% (3,790)	11.6% (8,736)
3	14.2% (13,512)	13.9% (4,858)	13.9% (4,489)	13.5% (10,202)
4	27.1% (25,700)	26.7% (9,337)	23.5% (7,582)	22.1% (16,731)
5	12.8% (12,162)	14.0% (4,890)	8.3% (2,671)	7.4% (5,606)
6	11.1% (10,522)	13.0% (4,552)	7.6% (2,465)	7.8% (5,868)
Length of stay (days)				
N	179,908	65,737	63,074	142,686
Median (25^{th}, 75^{th} percentiles)	4 (2, 6)	4 (3, 6)	3 (2, 5)	3 (2, 6)

*Skilled nursing facility, inpatient rehabilitation facility, long term care hospital, intermediate care facility, or other.

Supplementary Table III: Outcomes (event rates) by prior antithrombotic use and indication – among patients with NIHSS data

	Indication for antithrombotic use		No indication for antithrombotic use	
Outcomes	**Prior antithrombotic use**	**No prior use**	**Prior antithrombotic use**	**No prior use**
N	165,339	59,512	57,904	132,279
In-hospital death	5.2% (8,539)	5.9% (3,505)	3.2% (1,856)	3.3% (4,408)
Discharge destination				
Home	44.1% (72,985)	42.2% (25,108)	54.3% (31,450)	57.0% (75,394)
Other health care facility*	45.1% (74,531)	45.5% (27,077)	39.3% (22,742)	37.1% (49,101)
Hospice	5.6% (9,284)	6.4% (3,822)	3.2% (1,856)	2.6% (3,376)
Died	5.2% (8,539)	5.9% (3,505)	3.2% (1,856)	3.3% (4,408)
Ambulatory status at discharge				
N	142,333	50,855	48,859	112,394
Able to ambulate independently	43.6% (62,075)	41.4% (21,064)	54.7% (26,719)	57.0% (64,117)
Able to ambulate with assistance	30.5% (43,440)	30.0% (15,266)	27.1% (13,256)	25.8% (28,977)
Unable to ambulate	17.2% (24,454)	18.8% (9,584)	11.8% (5,764)	10.8% (12,180)
Died	6.0% (8,539)	6.9% (3,505)	3.8% (1,856)	3.9% (4,408)
ND	2.7% (3,825)	2.8% (1,436)	2.6% (1,264)	2.4% (2,712)
Modified Rankin Scale at discharge				
N	76,860	27,831	26,285	61,429
0	10.7% (8,229)	10.1% (2,801)	15.7% (4,131)	17.3% (10,628)
1	15.2% (11,720)	14.3% (3,988)	20.3% (5,342)	21.4% (13,130)
2	10.1% (7,755)	9.4% (2,604)	11.9% (3,138)	11.7% (7,193)
3	14.2% (10,929)	14.1% (3,928)	13.9% (3,661)	13.4% (8,248)
4	27.1% (20,826)	26.9% (7,479)	23.5% (6,167)	22.4% (13,746)
5	12.7% (9,738)	14.0% (3,889)	8.2% (2,155)	7.4% (4,527)
6	10.0% (7,663)	11.3% (3,142)	6.4% (1,691)	6.4% (3,957)
Length of stay (days)				
N	138,914	50,083	48,243	110,383
Median (25^{th}, 75^{th} percentiles)	4 (2, 6)	4 (3, 6)	3 (2, 5)	3 (2, 5)

*Skilled nursing facility, inpatient rehabilitation facility, long term care hospital, intermediate care facility, or other.

Supplementary Table IV: Outcomes (model results) by prior antithrombotic use and indication among patients with NIHSS data

	Interaction between anti-thrombotic use and indication	Prior antithrombotic use vs. no prior use		Indication for antithrombotic use vs. no indication	
Outcome	**P**	**OR (95%CI)**	**P**	**OR (95% CI)**	**P**
In-hospital death	0.74	0.92 (0.89, 0.96)	<0.0001	1.10 (1.06, 1.14)	<0.0001
Discharge to home	0.22	1.13 (1.11, 1.15)	<0.0001	0.90 (0.88, 0.91)	<0.0001
–where discharged alive	0.16	1.12 (1.11, 1.14)	<0.0001	0.91 (0.89, 0.92)	<0.0001
Able to ambulate independently at discharge	0.41	1.11 (1.09, 1.13)	<0.0001	0.85 (0.83, 0.86)	<0.0001
–where able to ambulate independently prior to index stroke	0.12	1.13 (1.11, 1.15)	<0.0001	0.91 (0.89, 0.93)	<0.0001
mRS = 0 or 1 at discharge	0.74	1.09 (1.07, 1.12)	<0.0001	0.83 (0.81, 0.85)	<0.0001
LOS (ratio)	0.31	0.97 (0.96, 0.97)	<0.0001	1.07 (1.06, 1.07)	<0.0001

For the endpoints above, there was no significant interaction between prior antithrombotic use and indication; therefore, odds ratios are shown for these two variables separately.

Supplementary Table V: Sample distribution of AF/Flutter by medical history and recorded persistent paroxysmal AF/flutter during index admission

	Persistent or paroxysmal AF/Flutter during index admission			
	Yes	**No**	**Unknown**	**Total**
Medical history of AF/Flutter				
Yes	89,210	12,001	309	101,520
No	29,425	408,471	1577	473,473
Total	118,635	420,472	1866	540,993