Real world effectiveness of warfarin among ischemic stroke patients with atrial fibrillation: observational analysis from Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study

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ABSTRACT

OBJECTIVE

To examine the association between warfarin treatment and longitudinal outcomes after ischemic stroke in patients with atrial fibrillation in community practice.

DESIGN

Observational study.

SETTING

Hospitals (n=1487) participating in the Get With The Guidelines (GWTG)-Stroke program in the United States, from 2009 to 2011.

PARTICIPANTS

12 552 warfarin naive atrial fibrillation patients admitted to hospital for ischemic stroke and treated with warfarin compared with no oral anticoagulant at discharge, linked to Medicare claims for longitudinal outcomes.

MAIN OUTCOME MEASURES

Major adverse cardiovascular events (MACE) and home time, a patient centered outcomes measure defined as the total number of days free from institutional care after discharge. A propensity score inverse probability weighting method was used to account for all differences in observed characteristics between treatment groups.

RESULTS

Among 12 552 survivors of stroke, 11 039 (88%) were treated with warfarin at discharge. Warfarin treated patients were slightly younger and less likely to have a history of previous stroke or coronary artery disease but had similar severity of stroke as measured by the National Institutes of Health Stroke Scale. Relative to those not treated, patients treated with warfarin had more days at home (as opposed to institutional care) during the two years after discharge (adjusted home time difference 47.6 days, 99% confidence interval 26.9 to 68.2). Patients discharged on warfarin treatment also had a reduced risk of MACE (adjusted hazard ratio 0.87, 99% confidence interval 0.78 to 0.98), all cause mortality (0.72, 0.63 to 0.84), and recurrent ischemic stroke (0.63, 0.48 to 0.83). These differences were consistent among clinically relevant subgroups by age, sex, stroke severity, and history of previous coronary artery disease and stroke.

CONCLUSIONS

Among ischemic stroke patients with atrial fibrillation, warfarin treatment was associated with improved long term clinical outcomes and more days at home.

CLINICAL TRIAL REGISTRATION

Clinical trials NCT02146274.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Warfarin is recommended for the prevention of thromboembolism in patients with atrial fibrillation, on the basis of clinical trials in selected patient populations

However, the use and clinical benefit of warfarin for atrial fibrillation outside the clinical trial setting is not well defined, especially among older ischemic stroke patients

WHAT THIS STUDY ADDS

New prescription of warfarin in patients with atrial fibrillation after stroke was associated with a lower risk of major adverse cardiovascular events, all cause mortality, and readmission for ischemic stroke, as well as more institution-free home time

The clinical benefits associated with warfarin treatment were consistent across clinically relevant subgroups

These findings support the routine use of warfarin for eligible ischemic stroke patients with atrial fibrillation, including those over 80 years of age, women, those with more severe strokes, and those with comorbid conditions

Introduction

Approximately 15 million people worldwide have a stroke each year.[1] Atrial fibrillation is an important risk factor, accounting for approximately 15% of all strokes, and the highest incidence is in older patients.[2 3] Clinical studies in selected trial populations have shown the efficacy of warfarin for prevention of stroke in patients with atrial fibrillation.[4-10] On the basis of available data, both European and US guidelines recommend adjusted dose warfarin treatment for stroke prevention in patients with non-valvular atrial fibrillation.[11 12]

Despite the existing evidence, the translation of clinical trial evidence into routine clinical practice is often challenging. Most clinical trials of warfarin for stroke prevention in patients with atrial fibrillation did not specifically enroll patients admitted to hospital for acute ischemic stroke.[8-11] Moreover, clinical trials often have very strict protocols with regard to selection of patients, follow-up, monitoring, and dose adjustment to maximize a patient's time in the therapeutic range. Furthermore, most population based studies are from European countries, and the rate of anticoagulation after stroke in atrial fibrillation patients has improved dramatically in the past decade.[12 13] Whether the efficacy seen in clinical trials translates into effectiveness in contemporary practice is unclear, especially for secondary prevention among older patients who have already had an ischemic stroke and in clinically

relevant subgroups that have higher risks of bleeding and more challenging warfarin management.

From a patient's perspective, an important measure of the benefit of anticoagulant treatment beyond survival is the prevention of recurrent events or prolonged hospital admissions. Focus groups identify "being alive, without recurrent stroke, and without being hospitalized for complications" as the most desirable outcome.[14-16] This patient centered outcomes measure, which we have called "home time," has not been well studied as an endpoint in clinical trials. Using data from the American Heart Association/American Stroke Association Get With The Guidelines-Stroke (GWTG-Stroke) program linked with Centers for Medicare and Medicaid Services (CMS) claims data, we evaluated the association between warfarin treatment and longitudinal outcomes after ischemic stroke in the general atrial fibrillation population, as well as among clinically relevant subgroups of patients.

Methods

Study design and patient involvement

Details of the design and conduct of the Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study have been previously described.[17] Briefly, PROSPER is a Patient-Centered Outcomes Research Institute (PCORI) sponsored project designed to help patients, physicians, and other stakeholders to make informed decisions about stroke care and to improve outcomes through innovative comparative effectiveness research. The study was conceived and designed by the PROSPER team, a multidisciplinary group of researchers at the Duke Clinical Research Institute, Massachusetts General Hospital, University of California at Los Angeles, University of Texas Southwestern Medical Center, Brigham and Women's Hospital, and University of Calgary, partnering with patient investigators and stakeholders representing the varied interests of patients, caregivers, physicians, nurses, healthcare systems, policy makers, governmental agencies, and professional societies.

To identify the most relevant research topics and meaningful outcomes, we worked with our patient co-investigators and conducted a series of focus groups with stroke survivors and administered a qualitative survey customized to stroke patients. Knowledge gained from these efforts was further reviewed by our patient co-investigators and stakeholder committee, who transformed these identified research needs into patient centered research questions to be studied, including the effectiveness of warfarin among ischemic stroke patients with atrial fibrillation.

The concept of patient involvement also translated to the study design and execution phases of the research. We provided basic educational materials and a research tutorial to help to encourage familiarity with research concepts and terminology. The pros and cons of different types of study design and research method were discussed with patient co-investigators, using laypersons' language to facilitate common understanding and solicit their feedback. We then revisited our aims and revised the research plans to align them better with things that patients cared about the most. As results emerged, we reviewed the results with patient co-investigators to obtain their perspectives and feedback to ensure that we presented the findings in the most effective way beyond the research community to general populations. Through these iterative processes, PROSPER patient co-investigators made high value contributions to both the design and the implementation of the study, while we retained the rigors of the scientific work.

Data sources

PROSPER builds on the American Stroke Association/American Heart Association GWTG-Stroke program, which is an ongoing nationwide quality improvement initiative.[18 19] Standardized data collection in GWTG-Stroke includes patients' demographics, medical history, diagnostic testing, brain imaging, in-hospital treatment, discharge drugs, and inpatient outcomes. The eligibility of each admission is confirmed through chart review. The validity and reliability of data collection in the GWTG-Stroke database has been reported in previous research.[20]

As GWTG-Stroke is an inpatient registry, we linked GWTG-Stroke data to Medicare claims by matching on a series of indirect identifiers, including admission date, discharge date, patient's age or date of birth, and sex, for the assessment of longitudinal outcomes. This linkage method, developed by our analytic team, has been successfully completed and validated using Medicare inpatient claims.[21] Previous work has shown that patients in the linked GWTG-Stroke/CMS database are representative of the national Medicare ischemic stroke population.[22] Quintiles Inc serves as the data collection (through its patient management tool) and coordination center for GWTG-Stroke. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate de-identified data for research purposes.

Study population

Our analysis included Medicare fee for service beneficiaries admitted to GWTG-Stroke hospitals for acute ischemic stroke and discharged alive with documented persistent or paroxysmal atrial fibrillation or flutter between 1 January 2009 and 31 December 2011. Each patient had at least one year of follow-up after the index hospital discharge, using hospital claims data submitted to CMS through December 2012. Figure 1 shows details of the study's inclusion and exclusion criteria. Briefly, we excluded patients with documented contraindications for anticoagulation treatment, as well as those who received comfort measures only or were transferred out to other hospitals. To avoid prevalent user bias, we further excluded patients receiving chronic anticoagulation treatment before the index hospital admission.[23] We abstracted the discharge drug treatment from the medical record of the index hospital admission. We divided patients into two groups according to discharge drug treatment: patients treated with warfarin versus those not treated with any oral anticoagulant at discharge. Patients who refused warfarin but had no contraindications were considered eligible for warfarin but did not receive the treatment (n=1162).

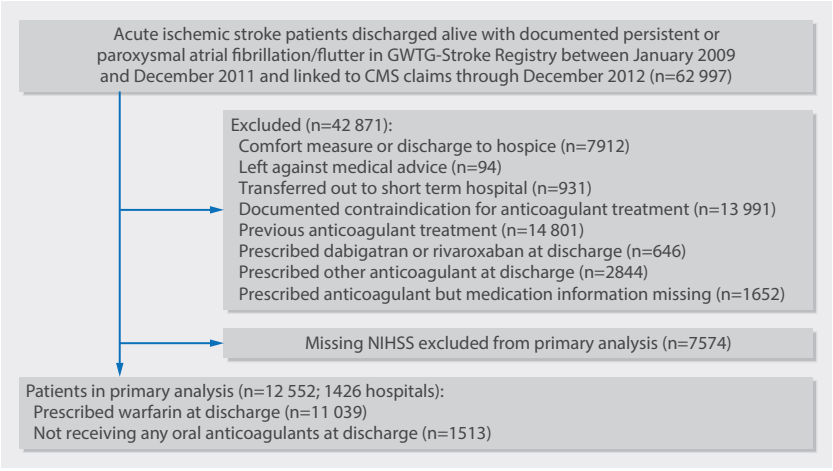

Fig 1 | **Study population from initial cohort, through exclusions, to final population. CMS=Centers for Medicare and Medicaid Services; GWTG-Stroke=Get With The Guidelines-Stroke; NIHSS=National Institutes of Health Stroke Scale**

Novel oral anticoagulants such as dabigatran and rivaroxaban were not recorded in GWTG-Stroke until October 2011. Therefore, we also excluded patients discharged on novel oral anticoagulants or other agents such as low molecular weight heparin or fondaparinux. As the National Institutes of Health Stroke Scale (NIHSS) score (a measure of neurologic deficits ranging from 0 to 42, with a higher score indicating greater severity of stroke) is a critical predictor of outcomes in acute ischemic stroke,[24 25] our primary study population consisted of 12 552 patients with complete NIHSS data from 1487 GWTG-Stroke hospitals in the United States.

Outcome measures

We conducted focus group and surveys of patients to identify outcomes most relevant and meaningful to patients who have survived stroke.[17] The most frequent and important outcome identified was "alive at home, without recurrent stroke, and without being hospitalized for complications."[15 16] On the basis of the interpretation of patients' responses and further refinement by patient co-investigators, we translated this concept into home time, which we defined as the total number of days alive and out of the hospital or a skilled nursing facility within two years after the index hospital discharge. We calculated home time by using Medicare inpatient care, inpatient rehabilitation facility, and skilled nursing home claims.[26] Similarly, a major adverse cardiovascular event (MACE) is a composite measure of all cause mortality or cardiovascular readmission, reflecting patients' desire of "being alive at home, without recurrent stroke, or being hospitalized for complications." Secondary outcomes included all cause mortality, cardiovascular readmission, ischemic stroke readmission, and hemorrhagic stroke readmission.

Where applicable, we determined the date of death through the Medicare denominator files. We ascertained the date and cause of readmission from the hospital claims data submitted to CMS, with the international classification of diseases, ninth revision, clinical modification (ICD-9-CM) primary diagnosis code of 433.x1 or 434.x1 for ischemic stroke and 430 or 431 for hemorrhagic stroke and the Agency for Healthcare Research and Quality's clinical classification software diagnosis category 96-118 for cardiovascular admission. The clinical classification software is a diagnosis and procedure categorization scheme developed by the Agency for Healthcare Research and Quality to identify disease specific or procedure specific hospital admission by grouping individual ICD-9-CM codes into clinically meaningful categories.[27] The use of ICD-9-CM codes 433.x1, 434.x1, 430, and 431 has been proposed by the American Heart Association/American Stroke Association for defining stroke using ICD-9-CM codes and for CMS stroke core measures.[28-30]

Statistical analyses

Our pre-specified statistical analysis plan has been previously described.[17] To summarize, we used means, medians, and percentages to describe the distribution of continuous and categorical variables between patients discharged on warfarin and those discharged not on any oral anticoagulants. We defined warfarin treatment as warfarin prescribed at the time of hospital discharge, as documented in GWTG-Stroke. We used standardized difference to compare baseline characteristics between patient cohorts. An absolute standardized difference greater than 10% indicates significant imbalance of a covariate, whereas a smaller value supports the assumption of balance between treatment groups.[31]

Unlike randomized clinical trials, the decision to treat in "real world" practice is often based on prognostic factors. Therefore, the effectiveness estimate for warfarin might be confounded as a result of treatment selection. We used a stabilized inverse probability weighting approach to control for potential bias. Inverse probability weighting is an extension of the propensity score method used to summarize the conditional probability of assignment for a treatment.[32 33] Using this method, the weights are the inverse probability of assigning a treatment derived from a logistic model with warfarin treatment as the dependent variable and all observed patient level and hospital level characteristics as the independent variables. These variables included age; sex; race/ethnicity; history of previous stroke/transient ischemic attack, coronary artery disease/myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, diabetes, or smoking; emergency medical services transportation; NIHSS at presentation; hospital bed size; annual ischemic stroke volume; American Heart Association/American Stroke Association/Joint Commission certification as a primary stroke center; academic status; rural/urban location; and calendar year. Each patient was then weighted by the inverse of the estimated probability of the treatment received.

We then used inverse probability weighting regression models weighted with warfarin treatment as the independent variable to estimate the adjusted associations between warfarin treatment and each outcome estimated, controlling for other discharge drugs as covariates. Discharge drugs included antihypertensives,

statins, and antiplatelets (aspirin, aspirin/dipyridamole, clopidogrel, aspirin/clopidogrel dual antiplatelet therapy, and other antiplatelet agents). Owing to the presence of over-dispersion in home time and the fact that not all patients had the same length of time in follow-up (for example, patients lost Medicare fee for service coverage or transitioned to Medicaid), we used a negative binomial regression with an offset for log of the proportion of follow-up time to model home time. We used separate Cox proportional hazards models for time to event data including MACE, all cause mortality, all cause readmission, cardiovascular readmission, ischemic stroke readmission, and hemorrhagic stroke readmission.

In addition to the general population of ischemic stroke patients with atrial fibrillation, we did these analyses in clinically relevant subgroups by age (65-80 and >80 years), sex, history of previous stroke/transient ischemic attack and coronary artery disease/myocardial infarction, and stroke severity as measured by NIHSS (mild 0-5, moderate 6-14, and severe 15-42). Our analyses also accounted for within hospital clustering by using random effects for negative binomial models and robust sandwich estimators for Cox proportional hazards models. In a sensitivity analysis, we included 7574 (37.6%) patients with missing NIHSS data and extended our study population to the entire study cohort (total n=20 126). We used a multiple imputation method to impute missing NIHSS values. The characteristics of the patient cohorts including those without NIHSS recorded and only patients with NIHSS recorded are shown in supplementary table A.

All analyses followed the intention to treat principle. All P values are two sided. Owing to multiple outcomes and subgroups assessed, we report 99% confidence intervals and considered P values less than 0.01 to be statistically significant. We used SAS version 9.3 for all statistical analyses.

Results

Of 12 552 patients with ischemic stroke discharged alive with persistent or paroxysmal atrial fibrillation or flutter and untreated with oral anticoagulation before admission, 11 039 (87.9%) were treated with warfarin at discharge. Table 1 shows the baseline demographic, clinical, and hospital characteristics according to warfarin prescription at discharge. The age distribution of the study cohort is shown in supplementary figure A. Compared with patients not receiving warfarin at discharge, those treated with warfarin were slightly younger and were less likely to have a history of previous stroke or coronary artery disease. Fewer patients receiving warfarin were treated with aspirin/dipyridamole, clopidogrel, or aspirin/clopidogrel dual antiplatelet therapy at discharge. By contrast, both groups had similar stroke severity as measured by NIHSS (median 6 (interquartile range 2-13) *v* 5 (2-12)). Results from the warfarin treatment propensity model indicated that older patients with a history of previous stroke, coronary artery disease, diabetes, or smoking were less likely to be treated with warfarin at discharge, whereas patients treated at primary stroke centers were more likely to receive warfarin (supplementary table B). After inverse probability weighting adjustment, patients were well matched on all observed characteristics, with an absolute standardized difference less than 10% (supplementary figure B).

MACE and home time

The incidence of MACE was 54.7% in patients treated with warfarin at discharge, compared with 66.8% in those not on warfarin (unadjusted P<0.001). On average, patients receiving warfarin at discharge had 86 more days of home time in the two year follow-up period than those not receiving warfarin at discharge (unadjusted P<0.001) (table 2). After weighting by the inverse probability of treatment and control for other discharge drugs, patients treated with warfarin at discharge had a significantly lower risk of MACE over two years (adjusted hazard ratio 0.87, 99% confidence interval 0.78 to 0.98) and were more likely to spend more days alive and out of the hospital or a skilled nursing facility (adjusted home time difference 47.6, 99% confidence interval 26.9 to 68.2, days) than those not receiving any oral anticoagulants at discharge (table 2, fig 2). The association of warfarin with primary outcomes of MACE (adjusted hazard ratio 0.87, 0.80 to 0.96) and home time (48.5, 36.5 to 60.4, days) remained essentially unchanged after inclusion of patients with missing NIHSS data.

We also evaluated clinical outcomes for clinically relevant subgroups. Of 12 552 patients with ischemic stroke, 6590 (52.5%) were older than 80 years, 7538 (60.1%) were women, 6068 (48.3%) had an NIHSS of 0-5, 3931 (31.3%) had as NIHSS of 6-14, 2553 (20.3%) had an NIHSS of 15-42, 3963 (31.6%) had a history of coronary artery disease, and 2990 (21.6%) had had a previous stroke/transient ischemic attack. We found a similar trend of lower risk of MACE and more home time associated with warfarin treatment in each clinically relevant subgroup, although the benefit in terms of MACE seemed to be more prominent in patients who were older, were female, presented with more severe stroke, and had no history of coronary artery disease (fig 3).

Secondary outcomes

The unadjusted incidences of all cause mortality, all cause readmission, ischemic stroke readmission, and cardiovascular readmission were lower among patients treated with warfarin at discharge (table 2). In contrast, patients receiving warfarin had a higher unadjusted incidence of hemorrhagic stroke than did those not receiving anticoagulation treatment during follow-up (1.4% *v* 1.1%, P=0.50). After inverse probability weighting adjustment and control for other discharge drugs, discharge warfarin treatment was associated with lower risk of all cause mortality (adjusted hazard ratio 0.72, 0.63 to 0.84) and ischemic stroke readmission (0.63, 0.48 to 0.83) but no statistically significant difference in hemorrhagic stroke (1.37, 0.61 to 3.06) in the two years after discharge.

Discussion

Using a large nationwide contemporary registry of patients admitted to hospital with acute ischemic stroke, we found that new prescription of warfarin treatment in patients with atrial fibrillation was associated with a lower risk of

Table 1 | Baseline characteristics of study population. Values are numbers (percentages) unless stated otherwise

Variable	Warfarin (n=11 039)	No oral anticoagulant (n=1513)	Standardized difference (%)
Patients			
Mean (SD) age, years	80.1 (7.5)	83.1 (7.9)	39.1
Women	6582 (59.6)	956 (63.2)	7.3
Race/ethnicity:			
White	9412 (85.3)	1291 (85.3)	4.5
Black	699 (6.3)	105 (6.9)	
Asian	221 (2.0)	26 (1.7)	
Hispanic	379 (3.4)	54 (3.6)	
Other	328 (3.0)	37 (2.4)	
History of:			
Previous stroke	1630 (14.8)	312 (20.6)	15.4
Previous transient ischemic attack	901 (8.2)	147 (9.7)	5.4
Carotid stenosis	443 (4.0)	70 (4.6)	3.0
Coronary artery disease/myocardial infarction	3402 (30.8)	561 (37.1)	13.3
Hypertension	8838 (80.1)	1212 (80.1)	0.1
Dyslipidemia	4879 (44.2)	582 (38.5)	11.7
Peripheral vascular disease	541 (4.9)	98 (6.5)	6.8
Diabetes mellitus	2768 (25.1)	426 (28.2)	7.0
Smoking	785 (7.1)	105 (6.9)	0.7
Mode of arrival, emergency medical services from scene	6283 (56.9)	916 (60.5)	7.4
National Institutes of Health Stroke Scale:			
Median (interquartile range)	6 (2-13)	5 (2-12)	1.8
0-5	5299 (48.0)	769 (50.8)	
6-14	3483 (31.6)	448 (29.6)	
15-42	2257 (20.4)	296 (19.6)	
Discharge drugs:			
Oral anticoagulant	11 039 (100)	0 (0)	–
Antiplatelet	5912 (53.6)	1356 (89.6)	87.3
Aspirin only	5086 (46.1)	714 (47.2)	2.2
Aspirin/dipyridamole	111 (1.0)	112 (7.4)	32.3
Clopidogrel only	398 (3.6)	187 (12.4)	32.7
Aspirin and clopidogrel	298 (2.7)	332 (21.9)	61.2
Other antiplatelet	19 (0.2)	11 (0.7)	8.3
Antihypertensive	8919 (80.8)	1219 (80.6)	0.6
Statin for low density lipoprotein cholesterol ≥100 mg/dL	4710/5082 (92.7)	604/694 (87.0)	18.8
Hospitals			
Mean (SD) No of beds,	441 (292)	420 (306)	6.8
Mean (SD) annual stroke volume	255 (148)	235 (149)	13.6
Hospital type, academic	6440 (58.3)	856 (56.6)	3.6
Primary stroke center	6427 (58.2)	779 (51.5)	13.6
Rural hospital	486 (4.4)	91 (6.0)	7.3

Table 2 | Warfarin treatment and clinical outcomes up to 2 years after ischemic stroke

Outcome*	Warfarin (n=11 039)	No oral anticoagulant (n=1513)	Unadjusted hazard ratio (99% CI)	Adjusted hazard ratio (99% CI)	P value
No (%) MACE	5683 (54.7)	952 (66.8)	0.73 (0.67 to 0.80)	0.87 (0.78 to 0.98)	0.003
Mean (SD) home time, days	468.3 (254.7)	389.0 (266.7)	86.1 (68.0 to 104.1)†	47.6 (26.9 to 68.2)†	<0.001
No (%) all cause mortality	3285 (32.4)	699 (50.0)	0.57 (0.51 to 0.63)	0.72 (0.63 to 0.84)	<0.001
Readmission:					
All cause	6794 (64.5)	951 (65.9)	0.88 (0.81 to 0.97)	1.01 (0.91 to 1.13)	0.79
Ischemic stroke	814 (7.9)	169 (11.8)	0.58 (0.47 to 0.72)	0.63 (0.48 to 0.83)	<0.001
Hemorrhagic stroke	140 (1.4)	16 (1.1)	1.10 (0.56 to 2.16)	1.37 (0.61 to 3.06)	0.31
Cardiovascular	3673 (35.3)	515 (36.0)	0.87 (0.77 to 0.98)	1.00 (0.86 to 1.16)	0.97

MACE=major adverse cardiovascular event (composite of death and cardiovascular readmission).
*Weighted by proportion of follow-up.
†Differences in days.

MACE, all cause mortality, and readmission for ischemic stroke, as well as more institution-free home time. The clinical benefits associated with warfarin treatment were consistent across clinically relevant subgroups and risk adjustment methods. Collectively, our findings suggest that the efficacy of anticoagulation in clinical trials may translate into real world clinical practice and support the current guideline recommendations of warfarin treatment as an anticoagulation approach for the prevention of recurrent stroke in patients with atrial fibrillation.[11 12]

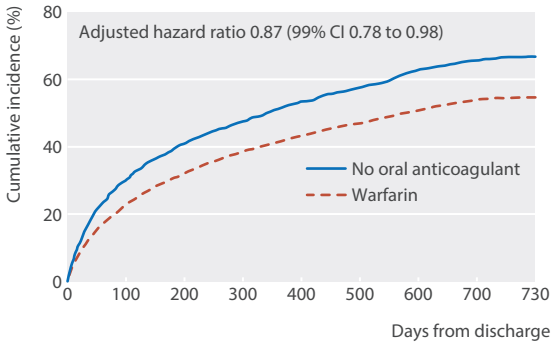

Fig 2 | Cumulative incidences for major adverse cardiovascular event during two year follow-up for patients receiving warfarin versus no oral anticoagulant

Warfarin has been shown to be superior to placebo in primary stroke prevention trials among patients with atrial fibrillation, but the data on secondary prevention among patients who have already had an ischemic stroke and in clinically relevant subgroups, including patients older than 80 years and women, are much more limited.[7-11] A meta-analysis of six randomized clinical trials found a 64% reduction in stroke associated with adjusted dose warfarin treatment in selected atrial fibrillation populations.[34] We evaluated the clinical effectiveness of warfarin treatment for secondary prevention among older ischemic stroke patients with atrial fibrillation in community practice. We found that those treated with warfarin at discharge had 86 more days (48 days after adjustment) on average free from institutional care than did their untreated counterparts during the two years after their stroke. We also observed a favorable association of warfarin treatment with reduced risks of MACE, all cause mortality, and recurrent ischemic stroke. Although the observed benefits are smaller than those reported in clinical trials, our observations are not surprising, given that the efficacy of warfarin treatment is dependent on the the intensity of anticoagulation.[35] This partially mitigates the concern that the benefits of warfarin reported in clinical trials may not translate into usual clinical care, particularly among older patients and those with multiple comorbid conditions.

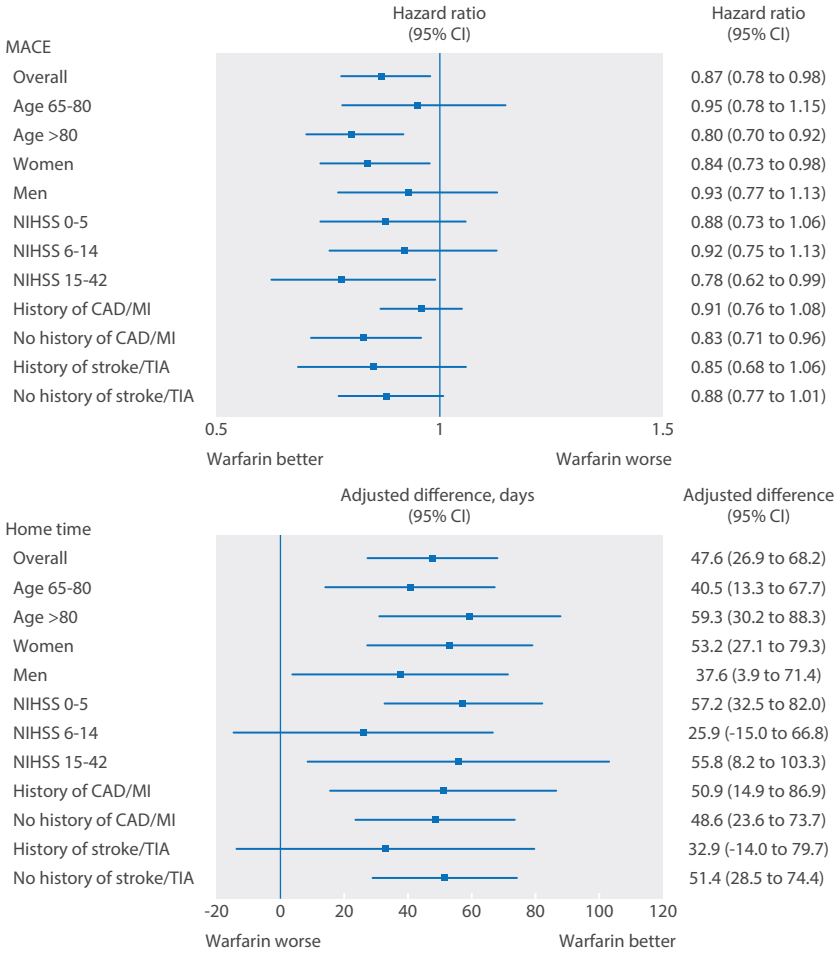

Fig 3 | Major adverse cardiovascular event (MACE) and home time according to warfarin treatment at discharge, overall and in clinically relevant subgroups. CAD=coronary artery disease; MI=myocardial infarction; NIHSS=National Institutes of Health Stroke Scale; TIA=transient ischemic attack

Importantly, we found that the benefits associated with warfarin treatment were consistent across clinically relevant groups by age, sex, stroke severity, and history of stroke and coronary artery disease. A salient finding is that older patients (age >80), women, and those with more severe stroke (NIHSS 15-42) seemed to have greater benefit from warfarin treatment, yet these patients were less likely to be treated with warfarin in clinical practice. Reasons for the treatment-risk paradox are complex, but they might be related to physicians' misperceptions, uncertainty of risk and benefit, and reluctance to cause harm in patients at high risk who are often underrepresented in clinical trials.[36 37] Our study attempted to fill this gap by evaluating the clinical effectiveness of warfarin treatment in clinically relevant subgroups. Although we did not have information on the exact clinical circumstance of a treatment decision, physicians may tend to be risk averse and not prescribe more aggressive treatment to high risk patients who might be perceived to have a poor prognosis. An objective and precise benefit/risk prediction tool will help to overcome the paradox by promoting a better understanding of the clinical factors contributing to patients' outcomes.

To the best of our knowledge, our research is the first comparative effectiveness study on warfarin use after stroke with atrial fibrillation that has incorporated input from patients throughout the entire research process, reflecting their healthcare priorities, choice of outcome measures, and input into the statistical analysis plan. One of the strengths of our study is the integration of home time, which is a patient centered measure of longitudinal functional outcomes prioritized by stroke survivors and stakeholders.[15 16] Home time is a simple objective measure and is closely associated with the modified Rankin scale and Barthel index.[26 38] Owing to data limitations, we could not fully distinguish whether home time meant that patients were living in their own home, living at a relative's or friend's house, at home with home care services, at home with other community support, in assisted living, homeless, or exceeding the Medicare benefit for post-acute care and transitioning to Medicaid because of poverty. We also recognize

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that being at home does not equate to the absence of disability. Even with these imperfections, home time indicates the absence of institutional care, which is a highly valued health state prioritized by stroke survivors.[15 16] More importantly, home time reflects the overall health status of the patient following stroke, is meaningful from patients' perspectives, and is easy to measure using claims data.

The benefit of more days at home with warfarin treatment could be partially explained by the lower MACE rates—in particular, reduction in death and recurrent ischemic stroke events after discharge. Despite numerically more bleeding events in patients treated with warfarin, the association between warfarin treatment and hemorrhagic stroke was not statistically significant after risk adjustment. This finding should be interpreted with caution, as our study was not adequately powered for assessing hemorrhagic stroke, owing to the overall low incidence. Nevertheless, the fact that the overall incidence of hemorrhagic stroke was low is reassuring, suggesting that the net benefit of warfarin is likely to be greater than the effect of bleeding, even if the difference was statistically significant.

Limitations of study

Our study should be interpreted in the context of certain limitations. Firstly, this was an observational analysis of registry data. Despite use of propensity score techniques to minimize observed confounding, residual and unmeasured confounding may exist. To help to limit bias, we used a new user design as well as a pre-specified study protocol and statistical analysis plan similar to those used in clinical trials. Secondly, our analysis was based on warfarin status at discharge and we do not have data on adherence to treatment and international normalized ratio during follow-up. Early discontinuation of treatment or poor adherence could potentially bias some of these findings. This being said, the level of anticoagulation with warfarin treatment is often managed less well in community practice than in clinical trials. A recent study indicates that 50% of Medicare beneficiaries who were advised to take an oral anticoagulant filled only one prescription.[39] Therefore, it could be argued that our study represents an intention to treat comparison that reflects real world effectiveness. The benefit associated with warfarin treatment would have been even larger if higher adherence could be achieved. Thirdly, our study is restricted to fee for service Medicare beneficiaries and, as a result, may not be generalizable to other populations. Fourthly, we were unable to report direct functional outcome measures such as disability and the modified Rankin scale. Instead, our study was able to report home time, an objective outcome correlated closely with the modified Rankin scale and increasingly being examined in stroke research.[26] Furthermore, home time better reflects patients' preference of living independently in the community. Presenting the benefit of warfarin in patient centric terms rather than through traditional clinical endpoints and outcomes may help to improve adherence to anticoagulant treatment. Finally, GWTG-Stroke is a voluntary program. Despite being the largest stroke registry in the United States, capturing more than a third of annual ischemic stroke admissions, these results might not be extrapolated to patients treated in non-GWTG-Stroke hospitals or to patients in other countries.

Conclusions

Among ischemic stroke patients with atrial fibrillation, new prescription of warfarin treatment at discharge was associated with lower mortality, fewer major adverse cardiovascular events, fewer recurrent ischemic stroke events, and more time spent at home during the two years after stroke. These findings support the routine use of warfarin treatment for eligible ischemic stroke patients with atrial fibrillation, including those over 80 years of age, women, those with more severe strokes, and those with comorbid conditions. With the availability of new oral anticoagulants in clinical practice, further studies should evaluate the safety and clinical effectiveness of other anticoagulation regimens.

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