Original Contribution

Secondary Versus Primary Stroke Prevention in Atrial Fibrillation

Insights From the Darlington Atrial Fibrillation Registry

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Background and Purpose—Although patients with atrial fibrillation (AF) who experienced an acute stroke are at high risk for recurrence, many patients are untreated or treated suboptimally for stroke prevention. The objective of this study is to compare clinical outcomes of AF patients with versus without previous stroke in relation to guideline-adherent antithrombotic treatment in a contemporary primary care population.

Methods—Community cohort of 105 000 patients from 11 general practices in Darlington, England, was used to assess AF stroke prevention strategies against 2014 National Institute for Health and Care Excellence guidelines.

Results—Overall, 2259 (2.15%) patients with AF were identified, of which 18.9% constituted a secondary prevention cohort. For secondary prevention, antithrombotic treatment was guideline adherent in 56.3%, 18.9% were overtreated, and 24.8% undertreated; corresponding proportions for primary prevention were 49.5%, 11.7%, and 38.8%, respectively. One-year stroke rates were 8.6% and 1.6% for secondary and primary prevention, respectively ($P<0.001$); corresponding all-cause mortality rates were 9.8% and 9.4%, respectively ($P=0.79$). On multivariable analysis, lack of antithrombotic treatment guideline adherence was associated with increased stroke risk for primary prevention (odds ratio, 2.95; 95% confidence interval, 1.26–6.90; $P=0.013$ for undertreatment); for secondary prevention, lack of guideline adherence was associated with increased risk of recurrent stroke (odds ratio, 2.80; 95% confidence interval, 1.25–6.27; $P=0.012$ for overtreatment) and all-cause death (odds ratio, 2.75; 95% confidence interval, 1.33–5.69; $P=0.006$ for undertreatment).

Conclusions—Only approximately half of eligible patients with AF are prescribed oral anticoagulation in line with guidelines. Guideline-adherent antithrombotic treatment significantly reduces the risk of stroke among primary prevention patients and both risk of recurrent stroke and death in patients with previous stroke. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.016146.)**

Key Words: atrial fibrillation ■ general practice ■ secondary prevention ■ stroke

One third of ischemic strokes and >80% of cardioembolic strokes are related to atrial fibrillation (AF).[1] AF may also play a role in approximately a third of cryptogenic strokes, which account for 25% of all strokes.[2] AF-related strokes result in a larger area of brain infarction and greater disability and mortality compared with strokes of other pathogeneses.[3] However, AF remains frequently under-recognized in patients who experience an acute stroke, and it is often left untreated in those with recent AF-related stroke despite high risk for stroke recurrence.[1]

AF-related strokes are highly preventable. A meta-analysis showed that oral anticoagulation (OAC) with vitamin K antagonists, such as warfarin, reduces the risk of stroke in patients with AF by 64% and mortality by 26% compared with placebo, whereas aspirin did not significantly decrease stroke risk and had no impact on mortality.[4] Another meta-analysis demonstrated that nonvitamin K antagonists OACs may offer additional stroke and mortality risk reduction by 19% and 10%, respectively, relative to warfarin.[5] Consequently, in line with current AF guidelines, OAC should be offered to all patients with AF as a default practice unless a truly low-risk category is evident, that is, those with a CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category [female]) score=0 for men or CHA_2DS_2-VASc=1 for women.[6]

Despite these recommendations, contemporary registry data show that more than half of AF patients with no stroke

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risk factors are anticoagulated while at least a third of those at high risk of stroke do not receive OAC where indicated but instead are prescribed antiplatelet monotherapy or remain untreated.[7] Importantly, lack of guideline adherence in antithrombotic treatment for stroke prevention in AF has been shown to increase stroke/thromboembolic and mortality rates compared with recommended therapy.[8–11]

In contrast to previous data on guideline adherence for stroke prevention in AF predominantly implemented by cardiologists,[7–10] we present findings from 11 general practices in the United Kingdom serving the community cohort of 105 000 patients, of whom 2.15% (n=2259) had established AF diagnosis. Our objective was to assess clinical outcomes of community-based AF patients with versus without previous stroke in relation to guideline-adherent antithrombotic treatment for stroke prevention.

Materials and Methods

Study Population

The design of the Darlington AF Registry has been described previously.[12] In brief, the study population comprised 105 000 patients living in Darlington, County Durham, United Kingdom, registered at 1 of 11 general practices. All patients with the diagnosis of AF or atrial flutter and known vital status in March 2013 were eligible for inclusion.

Data Collection

Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation tool was used to collect data.[12,13] All general practices in Darlington were equipped with this electronic record interrogation software that allowed for data collection on demographics, details of AF diagnosis, patient stroke risk profile and antithrombotic treatment, and was primarily developed to facilitate decision making on stroke prevention therapies.

Because the Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation tool does not collect data on clinical outcomes, separate searches of the database were performed to identify those patients who experienced acute stroke or died within 12 months. The Read Codes were used to identify different types of strokes, comorbidities, current therapies, and contraindications to treatment. All clinical events were manually reviewed and adjudicated.[12]

Definitions

Thromboembolic risk was assessed using the CHA_2DS_2-VASc score.[14] Low-risk patients were men with CHA_2DS_2-VASc=0 and women with CHA_2DS_2-VASc=1 (1 point for sex category only); moderate-risk patients were men with CHA_2DS_2-VASc=1; and high-risk patients were those with CHA_2DS_2-VASc score ≥2, irrespective of sex.

Antithrombotic treatment for stroke prevention was assessed against 2014 National Institute for Health and Care Excellence guidelines.[6] Antithrombotic treatment was considered guideline adherent when the following criteria were applicable:

- OAC in moderate- to high-risk patients with no reported contraindications to OAC therapy
- no OAC in low-risk patients and those who refused treatment with OAC
- OAC+antiplatelet therapy in moderate- to high-risk patients and acute vascular disease (ie, recent acute myocardial infarction)

Lack of guideline adherence in antithrombotic treatment was considered as either overtreatment (OAC overuse) or undertreatment (OAC underuse). Specifically, undertreatment was defined as no OAC (but antiplatelet or no therapy) in moderate- or high-risk patients and no reported contraindications or refusal to treatment. Overtreatment was defined as follows: OAC in low-risk patients or OAC+antiplatelet therapy in moderate- to high-risk patients with no evidence of acute vascular disease (ie, recent acute myocardial infarction); OAC in patients with reported contraindications to anticoagulation; or antiplatelet agents in those who had reported contraindications to both OAC and antiplatelet therapy.

Of note, the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines differ with National Institute for Health and Care Excellence recommendations on stroke risk requiring anticoagulation, that is, OAC is recommended in patients with CHA_2DS_2-VASc score ≥2, whereas those with score 1 may be offered OAC, aspirin, or even no stroke prophylaxis.[15]

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous parameters as mean and SD. Baseline characteristics, antithrombotic therapies, and clinical outcomes were tabulated in relation to prior stroke history. Multivariable logistic regression analyses were performed to determine independent predictors for new/recurrent stroke and all-cause death after adjustment for the components of the CHA_2DS_2-VASc score (age assessed as a continuous variable) and guideline-adherent or nonadherent (overtreatment or undertreatment) antithrombotic treatment, and AF duration. The multivariable analysis was performed separately for patients with prior stroke history (secondary prevention group) and those without previous stroke (primary prevention group). All statistical analyses were performed using IBM SPSS Statistics (version 21) software (Chicago, IL). Statistical significance was set at a 2-sided $P<0.05$.

Results

Overall, 2259 (2.15%) patients with AF were identified, of which 428 (18.9%) constituted a secondary prevention cohort. Patients with previous stroke were older, more often had comorbidities, and were at higher risk of stroke (all patients had CHA_2DS_2-VASc score ≥2, mean score of 5.5, SD of 1.28) as compared with those without prior stroke (CHA_2DS_2-VASc score ≥2 in 82.3%, mean score of 3.0, SD of 1.54; Table 1).

Overall, <50% of patients were prescribed anticoagulation (46.4% vitamin K antagonists and 1.4% non-OACs) while 35.9% received antiplatelet therapy alone and 16.2% remained untreated (Table 1). Antithrombotic drug choice in relation to prior stroke history is summarized in Figure 1. Guideline-adherent antithrombotic treatment for stroke prevention was applied more frequently in the secondary versus primary prevention cohort (56.3% versus 49.5%; $P=0.011$). Overtreatment was more common in patients with prior stroke, whereas undertreatment was more frequent in subjects with no stroke history (Table 1; Figure 2).

Based on the Read Codes, general practitioners reported contraindications to OAC therapy more frequently in patients with previous stroke (13.8%) compared with subjects without prior stroke (7.0%; Table I in the online-only Data Supplement).

One-Year Outcomes

After 12 months of follow-up, the observed stroke rates were 8.6% (n=37) and 1.6% (n=30) for the secondary and primary prevention cohorts, respectively ($P<0.001$). No difference was observed in the incidence of hemorrhagic strokes (0.2% in both groups; Table 2). All-cause death rates were comparable in patients with prior stroke (9.8%; n=42) and those without previous stroke (9.4%; n=172). The causes of death were also similar in both groups, except that in the secondary prevention

Table 1. Baseline Characteristics Overall and in the Primary and Secondary Prevention Groups

	All	Previous Stroke	No Previous Stroke	*P* Value
n (%)	2259 (100)	428 (18.9)	1831 (81.1)	
Demographics				
Females	1041 (46.1)	193 (45.1)	848 (46.3)	0.68
Age, y, mean (SD)	75.6 (12.2)	79.6 (9.6)	74.7 (12.6)	
<65	367 (16.2)	28 (6.5)	339 (18.5)	
65–74	554 (24.5)	93 (21.7)	461 (25.2)	
≥75	1338 (59.2)	307 (71.7)	1031 (56.3)	<0.001
Medical history				
Heart failure	514 (22.8)	106 (24.8)	408 (22.3)	0.27
Hypertension	1404 (62.2)	305 (71.3)	1099 (60.0)	0.001
Diabetes mellitus	490 (21.7)	120 (28.0)	370 (20.2)	0.001
Vascular disease	389 (17.2)	97 (22.7)	292 (15.9)	0.001
Acute myocardial infarction	152 (6.7)	41 (9.6)	111 (6.1)	0.008
Thromboembolic risk				
CHA_2DS_2-VASc, mean (SD)	3.5 (1.79)	5.5 (1.28)	3.0 (1.54)	
Score=0	118 (5.2)	0	118 (6.4)	
Score=1	206 (9.1)	0	206 (11.6)	
Score≥2	1935 (85.7)	428 (100)	1507 (82.3)	<0.001
Antithrombotic treatment				
None	367 (16.2)	28 (6.5)	339 (18.5)	
Antiplatelets	812 (35.9)	136 (31.8)	676 (36.9)	
OAC	971 (43.0)	225 (52.6)	746 (40.7)	
OAC+antiplatelets	109 (4.8)	39 (9.1)	70 (3.8)	<0.001
Oral anticoagulation				
Contraindicated	187 (8.3)	59 (13.8)	128 (7.0)	<0.001
Declined	113 (5.0)	28 (6.5)	85 (4.6)	0.11
Antithrombotic therapy				
Guideline adherent	1147 (50.8)	241 (56.3)	906 (49.5)	0.011
Overtreatment	296 (13.1)	81 (18.9)	215 (11.7)	<0.001
Undertreatment	816 (36.1)	106 (24.8)	710 (38.8)	<0.001

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category (female); and OAC, oral anticoagulant.

cohort, more patients died of noncerebral bleeding (0.5%; n=2) compared with the primary prevention cohort (0.1%; n=1; Table 2).

Clinical Outcomes in Relation to Guideline-Adherent Antithrombotic Therapy

In the primary prevention group, the 1-year stroke rates were similar in guideline-adherent (0.8%) and overtreated patients (0.5%) while the undertreated patients had an ≈4-fold higher stroke rate (3.1%). The corresponding event rates for 12-month all-cause mortality were 7.1%, 6.0%, and 13.2%, respectively (Table 3).

In the secondary prevention cohort, the lowest rate of stroke recurrence, at 5.4%, was in patients receiving guideline-recommended treatment, whereas the event rates for undertreatment and overtreatment were 9.4% and 17.3%, respectively (*P*=0.011). There was no significant difference in all-cause mortality between guideline-adherent (6.6%) and overtreated patients (6.2%; *P*=0.88), whereas the mortality was 3-fold higher in the undertreated subjects (19.8%; *P*<0.001).

On multivariable logistic regression analysis (Table 4), nonadherence with guideline-recommended antithrombotic treatment was associated with an increased risk of stroke in the primary prevention cohort (odds ratio, 2.95; 95% confidence interval, 1.26–6.90; *P*=0.013 for undertreatment), whereas in the secondary prevention cohort, nonadherence with guideline-recommended antithrombotic treatment was associated with an increased risk of recurrent stroke (odds ratio, 2.80; 95% confidence interval, 1.25–6.27; *P*=0.012 for overtreatment) and all-cause death (odds ratio, 2.75; 95% confidence interval, 1.33–5.69; *P*=0.006 for undertreatment). No association was found between AF duration and outcome events.

As a sensitivity analysis, the impact of OAC therapy per se on clinical outcomes after completely excluding patients who denied treatment or had any contraindications is shown in the online-only Data Supplement (Tables II and III in the online-only Data Supplement). The results show broadly similar trends as our principal analysis, with an even more pronounced effect of OAC on outcomes.

Discussion

In this article, we provide antithrombotic treatment patterns in an unselected (ie, consecutive all-comers) contemporary, community-based AF population. The main findings of this study are that despite a high thromboembolic risk, particularly among secondary prevention patients, only ≈50% of patients with AF in primary care were prescribed OAC in line with guidelines. Second, guideline-adherent antithrombotic treatment reduces the risk of stroke among primary prevention patients, and in those with prior stroke, there was a significant reduction in both recurrent stroke and mortality.

Several studies have found that guideline-adherent thromboprophylaxis in AF is associated with fewer stroke and lower mortality rates compared with nonguideline stroke prevention.[8–11] However, these studies assessed adherence to guidelines in patients managed solely by cardiologists[8–10] or internal medicine specialists.[11] Unlike in previous studies, we present findings from a community-based AF cohort managed by primary care physicians; however, it should be noted that the vast majority of strokes are diagnosed and managed in a hospital setting, and specialist input is provided at that stage, unless AF was not present at the time of the event. Our analysis also provides novel data on the clinical implications of nonadherence with recommended antithrombotic treatment for stroke prevention in AF and how this affects clinical outcomes in patients who have already experienced an acute stroke.

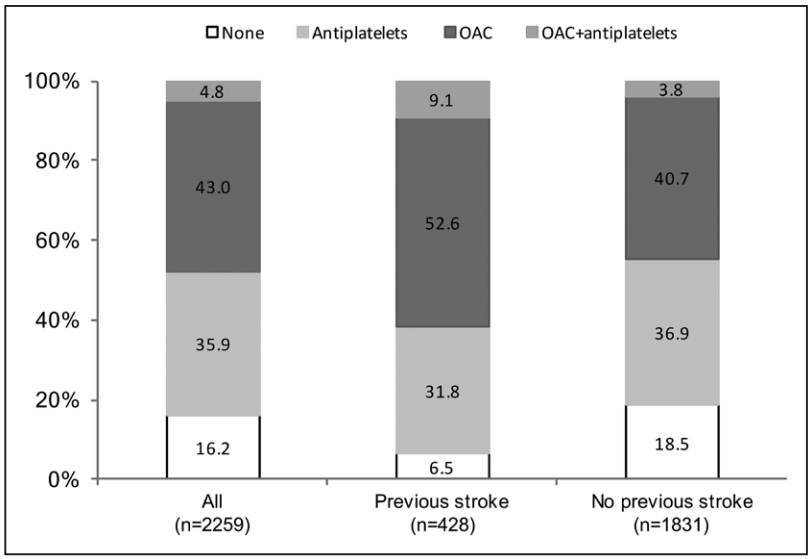

Figure 1. Antithrombotic treatment in relation to prior stroke history. OAC indicates oral anticoagulation.

As expected, we observed higher 1-year stroke rates in AF patients with versus without prior stroke. The magnitude of the stroke rate difference was 6-fold higher in secondary versus primary prevention patients, thereby reflecting a high thromboembolic risk among those with a previous stroke. Despite such high risk, only about half of the patients with prior strokes were prescribed OAC in line with current National Institute for Health and Care Excellence guidelines.[6]

More importantly, the lowest stroke recurrence was observed in patients who were guideline adherent, whereas it was higher for undertreatment and unexpectedly highest for overtreatment. Although higher stroke rates for overtreatment compared with guideline adherence may be surprising, the EORP-AF (EURObservational Research Programme Atrial Fibrillation) Pilot Registry also found a similar association between overtreatment and higher 1-year incidence of thromboembolic events, defined as any of the following: stroke, transient ischemic attack, acute coronary syndrome, coronary intervention, cardiac arrest, peripheral embolism, or pulmonary embolism.[10] By contrast, other studies have not reported such an association[8,11] or have found a lower risk of thromboembolism for overtreatment.[9]

The possible explanation of more is not better is not straightforward and may include various contributing factors. First, in contrast to the present analysis, none of other studies considered the presence of contraindications to antithrombotic treatment or patient's declining therapy when defining adherence versus nonadherence to antithrombotic treatment.[8–11] Prior papers base OAC prescribing solely on thromboembolic risk (and thus, this assumes that 100% must be given OAC, no exceptions). Such an approach fails again to reflect real-life everyday clinical practice by not taking into account an unselected population of consecutive patients, as well as many clinical- and patient-related factors affecting the final decision making needed for OAC prescribing. In addition, only the present study and the EORP-AF registry corrected the definition of nonadherence for the presence of acute vascular disease.[10]

Second, although Gorin et al[9] found significantly fewer event rates in overtreated patients and suggested that a more aggressive antithrombotic treatment (ie, combination of OAC and antiplatelet therapy) may be advocated in selected patients with AF, the authors used the older $CHADS_2$ score (Congestive Heart Failure, Hypertension, Age≥75, Diabetes, Stroke/TIA) that resulted in classifying some patients as low-risk (ie, with

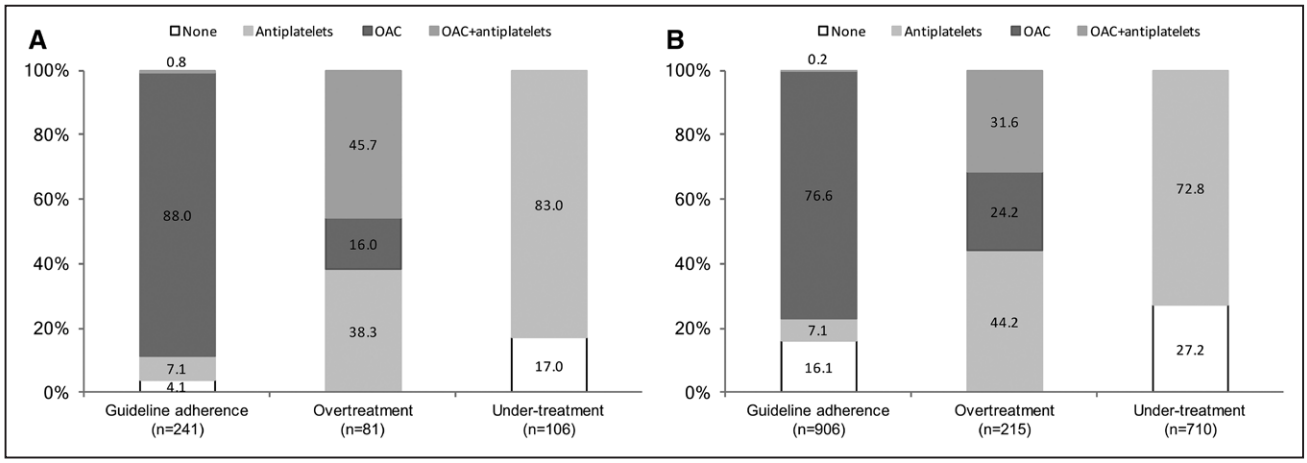

Figure 2. Antithrombotic treatment in relation to guideline adherence and prior stroke history. **A**, Prior stroke history. **B**, No prior stroke history. OAC indicates oral anticoagulation.

Table 2. One-Year Outcomes Overall and in the Primary and Secondary Prevention Groups

	All	Previous Stroke	No Previous Stroke	*P* Value
n (%)	2259 (100.0)	428 (18.9)	1831 (81.1)	
Recurrent/new stroke*	67 (3.0)	37 (8.6)	30 (1.6)	<0.001
Ischemic	62 (2.7)	36 (8.4)	26 (1.4)	
Hemorrhagic	5 (0.2)	1 (0.2)†	4 (0.2)†	
Cause of death				
All-cause	214 (9.5)	42 (9.8)†	172 (9.4)†	0.79
Cardiovascular				
Cardiac death	14 (0.6)	3 (0.7)†	11 (0.6)†	
Heart failure	24 (1.1)	3 (0.7)†	21 (1.1)†	
Stroke	11 (0.5)	3 (0.7)†	8 (0.4)†	
PE or STE	3 (0.1)	1 (0.2)†	2 (0.1)†	
Intracranial bleeding	5 (0.2)	1 (0.2)†	4 (0.2)†	
Noncardiovascular				
Bleeding noncerebral	3 (0.1)	2 (0.5)	1 (0.1)	
Cancer	42 (1.9)	4 (0.9)†	38 (2.1)†	
Other	67 (3.0)	16 (3.7)†	51 (2.8)†	
Unknown	45 (2.0)	9 (2.1)†	36 (2.0)†	

Values in the same row not sharing the same symbol (†) are significantly different at $P<0.05$. PE indicates pulmonary embolism; and STE, systemic thromboembolism.

*Confirmed by imaging (computer tomography was predominantly used).

Table 3. Event Rates at 1-Year in Relation to Prior Stroke History, Thromboembolic Risk, and Antithrombotic Guideline Adherence

n (%)	Undertreatment	Adherent Treatment	Overtreatment	*P* Value
Prior stroke history	n=106	n=241	n=81	
CHA_2DS_2-VASc, mean (SD)	5.5 (1.40)*	5.5 (1.26)*	5.9 (1.11)*	0.050
Recurrent stroke	10 (9.4)*,†	13 (5.4)*	14 (17.3)†	0.011
All-cause death	21 (19.8)	16 (6.6)*	5 (6.2)*	0.006
No prior stroke	n=710	n=906	n=215	
CHA_2DS_2-VASc, mean (SD)	3.1 (1.39)*	3.2 (1.51)*	2.4 (1.95)	<0.001
New stroke	22 (3.1)	7 (0.8)*	1 (0.5)*	0.003
All-cause death	94 (13.2)	65 (7.1)*	13 (6.0)*	0.003

Values in the same row not sharing the same symbol (*,†) are significantly different at $P<0.05$. CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category (female).

$CHADS_2$=0) and thus overtreated, whereas in the present analysis, many of them would be categorized as high-risk patients and consequently guideline adherent. In addition, overtreated patients were significantly younger and had lower risk of stroke compared with those undertreated or guideline adherent.[9] By contrast, in the present analysis, overtreated versus guideline-adherent patients were at significantly lower risk of stroke in the primary prevention while an opposite relation with a trend toward a higher thromboembolic risk was noted in the overtreated, secondary prevention cohort.

Third, unlike previous studies, we analyzed the population of AF patients with prior stroke, which are at the highest risk for stroke recurrence, 8.6% after 1 year of observation despite antithrombotic treatment. Our analysis did not show overtreatment to be associated with increased stroke rates in patients without prior stroke. Also, some physicians may consider that combination therapy (OAC+antiplatelets) was more effective and superior to OAC monotherapy for stroke prevention in patients with prior stroke. Our data suggest that despite such an aggressive antithrombotic treatment, the risk of stroke recurrence remains high. However, we may speculate that fear of bleeding complications while being more aggressive with antithrombotic treatment results in suboptimal quality of anticoagulation. For patients with AF undergoing percutaneous coronary interventions and thus requiring combination OAC and antiplatelet therapy, the average time in therapeutic range was only 52.6% with an international normalized ratio of 1.6 to 2.6.[16] Consequently, instead of a decrease in stroke rates, an increase in both stroke and major bleeding rates was observed when compared with patients who were not receiving combination antithrombotic treatment.

Nonetheless, despite stroke rates being 3× higher in the overtreated versus guideline-adherent group, we have observed similar mortality rates in both treatment cohorts. This finding would suggest that even though a more aggressive antithrombotic regimen is not sufficient to protect against stroke recurrence in at high risk of stroke AF patients, while many of these strokes are not fatal, reduction in all-cause mortality with antithrombotic therapy exceeds the reduction of stroke-related deaths only.[17]

Despite being at high risk for stroke, some patients may have genuine contraindications to anticoagulation because many stroke and bleeding risk factors do overlap.[18] In the present analysis, contraindications to OAC were reported in 13.8% and 7.0% of patients with versus without previous stroke, respectively. However, contraindications to OAC therapy are frequently not absolute and may be transient and depend on individually perceived lack of benefit from OAC prescription.[6] A considerable variation in the rates of reported contraindications to OAC (ranging from 2.6% to 12.0%) was observed across 1857 general practices in England.[13] Contemporary registry data also show that ≈50% of eligible patients with AF are not offered OAC or have stroke prevention treatment discontinued because of physician's preference.[19,20] Many physicians have concerns with regard to prescribing OAC to frail, elderly patients with many comorbidities, cognitive impairment, and frequent falls[21] although the available data show that even these patients, including the very elderly (>85 years of age), also benefit from anticoagulation.[22,23]

Bleeding risk assessment scores, such as the HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio s, age ≥65 years,

Table 4. Multivariable Logistic Regression Analysis for New/Recurrent Stroke and Death in Relation to Prior Stroke History

	New Stroke OR (95% CI)	*P* Value	Death OR (95% CI)	*P* Value
Prior stroke history				
Age (per 1-y increase)	1.00 (0.97–1.04)	0.83	1.08 (1.04–1.13)	<0.001
Female sex	1.32 (0.63–2.74)	0.46	1.02 (0.49–2.12)	0.96
Hypertension	0.91 (0.43–1.95)	0.81	0.81 (0.38–1.72)	0.81
Diabetes mellitus	1.72 (0.83–3.56)	0.14	2.21 (1.08–4.52)	0.03
Heart failure	0.91 (0.39–2.12)	0.83	1.55 (0.73–3.30)	0.26
Vascular disease	0.89 (0.38–2.10)	0.80	1.52 (0.70–3.28)	0.29
ATT undertreatment	1.39 (0.58–3.30)	0.46	2.75 (1.33–5.69)	0.006
ATT overtreatment	2.80 (1.25–6.27)	0.01	0.66 (0.23–1.89)	0.44
No prior stroke				
Age (per 1-y increase)	1.07 (1.03–1.12)	0.002	1.11 (1.09–1.14)	<0.001
Female sex	2.29 (0.96–5.50)	0.06	1.32 (0.91–1.91)	0.15
Hypertension	0.79 (0.36–1.73)	0.56	0.97 (0.67–1.41)	0.88
Diabetes mellitus	2.11 (0.94–4.73)	0.07	1.31 (0.88–1.97)	0.19
Heart failure	1.38 (0.60–3.15)	0.44	2.11 (1.46–3.05)	<0.001
Vascular disease	2.12 (0.94–4.78)	0.07	3.28 (2.25–4.78)	<0.001
ATT undertreatment	2.95 (1.26–6.90)	0.01	1.36 (0.94–1.97)	0.10
ATT overtreatment	0.56 (0.07–4.57)	0.58	0.83 (0.43–1.61)	0.58

ATT indicates antithrombotic treatment; CI, confidence interval; and OR, odds ratio.

drugs or alcohol),[6,24] were predominantly designed to flag up patients at increased risk for bleeding to allow for correction of the reversible risk factors (eg, uncontrolled hypertension, labile international normalized ratio values, concomitant drugs, alcohol abuse, etc)[25] but were by no means intended to withhold or preclude OAC therapy.[26] Importantly, the net clinical benefit of systemic anticoagulation, when balancing stroke risk reduction versus increased risk of bleeding, is still positive and even greater in patients at increased risk of bleeding.[27] Therefore, once the reasons for interrupting OAC therapy have been corrected, a change from 1 anticoagulant to another may seem more reasonable than complete withdrawal of OAC therapy, even in patients who have survived major bleeds or those with prior intracranial hemorrhage.[28,29] Similarly, in patients who have experienced an ischemic stroke despite being on OAC, a switch to a more effective anticoagulant to prevent a recurrent thromboembolic event, that is, dabigatran 150 mg twice daily, could be considered.[30]

Foregoing anticoagulation may also result from patient's refusal to use OAC. However, this shared decision making has to be based on detailed and clear explanation to a patient of their individual benefits and risks with OAC therapy.[31] One recent study showed that 12% of patients with AF would refuse OAC even if it was 100% effective in preventing strokes while those who accepted anticoagulation were willing to accept 4.4 major bleeds to prevent 1 stroke.[32]

Limitations and Strengths

A limitation of this study is that the analysis focused on the quantity but not quality of antithrombotic treatment. Despite having precise data on various antithrombotics used, as well as corrections made for antithrombotic drug uptake preceding the outcome events, neither international normalized ratio nor time in therapeutic range values were available. In addition, although the contraindications to, and reasons for patients declining antithrombotic therapy were reported precisely using Read codes, specific reasons for withholding or precluding OAC could not be identified. We could not establish the cause of death with certainty in 45 patients because death certificates could not be retrieved. However, it is unlikely that any significant number of strokes were missed that way. It cannot be also excluded that some strokes were missed by being not coded although this is also unlikely as stroke rates contribute to the stroke prevalence recording, which is linked to therapy reimbursement. Incorrect coding was addressed by a wide search of related conditions.

Although the cohort was a broad patient representation from 11 general practitioners practices serving the population of >100 000 patients, it was confined to 1 UK region, and, therefore, the results may not be representative of other primary care populations in different regions. Unfortunately, data on sociodemographic characteristics were not available for the purpose of this analysis. However, in contrast to previous studies, we used precise and robust criteria for study end points used in randomized clinical trials, with stroke confirmed by cerebral imaging and every outcome event was manually adjudicated. The usefulness of the Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation tool used for diagnostic and data collection purposes has been also previously confirmed.[13]

Our definition of adherence to guidelines is different from previously published papers because we have analyzed the unselected cohort of consecutive all-comers and thus included also those patients who declined OAC or had reported contraindications to therapy. We aimed to assess the impact of guideline adherence, rather than the specific impact of OAC therapy per se on clinical outcomes after completely excluding patients who denied treatment or had any contraindications. The results of the latter approach (broadly similar trends and showing even more pronounced effect of OAC on outcomes) have been summarized as a sensitivity analysis.

Summary

Despite a high thromboembolic risk profile, particularly among secondary prevention patients, only ≈50% of patients with AF in primary care are prescribed OAC in line

with current guidelines. Guideline-adherent antithrombotic therapy significantly reduces the risk of stroke among primary prevention patients, but in those with prior stroke, there is also a significant reduction in both recurrent stroke and death rates.

Disclosures

Dr Lane has received investigator-initiated educational grants from Bayer Healthcare, Bristol Myers Squibb, and Boehringer Ingelheim and has been a speaker and consulted for Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/Pfizer. Dr Wolff has been a clinical advisor to Boehringer Ingelheim, Pfizer, Bristol Myers Squibb (BMS), Sanofi Aventis, and Daiichi-Sankyo and also received educational grants and investigator payments from the above. In addition, he served as speaker for Boehringer Ingelheim, Sanofi, and Pfizer. Dr Proietti has received consultancy fee from Boehringer Ingelheim. Dr Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. He served as speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other authors report no conflicts.

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Secondary Versus Primary Stroke Prevention in Atrial Fibrillation: Insights From the Darlington Atrial Fibrillation Registry

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Table I Reported Contraindications to Oral Anticoagulation Overall and in the Primary and Secondary Prevention Groups

	All	Previous Stroke	No Previous Stroke
n (%)	2259 (100)	428 (18.9)	1831 (81.1)
OAC contraindications by Read Codes	187 (8.3)	59 (13.8) [a]	128 (7.0) [a]
Adverse reaction to warfarin (TJ421)	9 (0.4)	5 (1.2) [a]	4 (0.2) [a]
OAC causing AE in therapeutic use (U6042)	7 (0.3)	3 (0.7)	4 (0.2)
Warfarin side effects (66 Q3)	2 (0.1)	0	2 (0.1)
Warfarin allergy (Xa5yS)	1 (0.0)	0	1 (0.1)
Warfarin contraindicated (XaFsz)	114 (5.0)	38 (8.9) [a]	76 (4.2) [a]
Warfarin not tolerated (XaJ5b)	5 (0.2)	2 (0.5)	3 (0.2)
History of warfarin allergy (XaJ60)	1 (0.0)	0	1 (0.1)
OAC not tolerated (XaKA0)	5 (0.2)	1 (0.2)	4 (0.2)
OAC contraindicated (XaKAB)	10 (0.4)	3 (0.7)	7 (0.4)
Adverse reaction to OAC – NOS (TJ42z)	33 (1.5)	7 (1.6)	26 (1.4)

Values in the same row sharing the same subscript are significantly different at $p<0.05$

AE, adverse effect; NOS, not specified; OAC, oral anticoagulant

Table II Event Rates at One-Year in Relation to Prior Stroke History, Thromboembolic Risk and Antithrombotic Guideline-Adherence

(after exclusion of patients who denied treatment or had any contraindications)

n (%)	**Under-treatment**	**Adherent treatment**	**Over-treatment**	P-value
Prior stroke history	n=106	n=206	n=32	
CHA_2DS_2-VASc, mean (SD)	5.5 (1.40) [a]	5.4 (1.27) [a]	5.6 (1.21) [a]	0.85
Recurrent stroke	10 (9.4) [a]	13 (6.3) [a]	8 (25.0)	0.003
All-cause death	21 (19.8)	13 (6.3) [a]	1 (3.1) [a]	<0.001
No prior stroke	n=710	n=771	n=142	
CHA_2DS_2-VASc, mean (SD)	3.1 (1.39) [a]	3.1 (1.53) [a]	1.6 (1.81)	<0.001
New stroke	22 (3.1)	7 (0.9)	0	0.002
All-cause death	94 (13.2)	52 (6.7)	2 (1.4)	0.001

Values in the same row not sharing the same subscript are significantly different at $p<0.05$

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); SD, standard deviation

Table III Multivariable Logistic Regression Analysis for New/Recurrent Stroke *and* Death in Relation to Prior Stroke History (after exclusion of patients who denied treatment or had any contraindications)

	New Stroke		**Death**	
	OR (95% CI)	P value	OR (95% CI)	P value
Prior stroke history				
Age (per 1 y increase)	1.01 (0.97-1.06)	0.67	1.08 (1.03-1.14)	0.002
Female sex	1.43 (0.64-3.19)	0.39	1.32 (0.59-2.97)	0.49
Hypertension	1.17 (0.49-2.80)	0.73	0.82 (0.35-1.90)	0.64
Diabetes	2.01 (0.86-4.68)	0.10	2.38 (1.05-5.37)	0.04
Heart failure	0.74 (0.27-1.98)	0.55	1.75 (0.75-4.06)	0.19
Vascular disease	1.23 (0.50-3.02)	0.65	1.77 (0.77-4.09)	0.18
ATT under-treatment	1.30 (0.53-3.21)	0.56	2.99 (1.37-6.57)	0.006
ATT over-treatment	5.29 (1.95-14.36)	0.001	0.46 (0.06-3.78)	0.47
No prior stroke				
Age (per 1 y increase)	1.06 (1.02-1.11)	0.007	1.11 (1.08-1.13)	<0.001
Female sex	2.23 (0.92-5.43)	0.08	1.36 (0.90-2.05)	0.14
Hypertension	0.74 (0.33-1.65)	0.46	0.91 (0.61-1.37)	0.65
Diabetes	2.01 (0.87-4.69)	0.10	1.66 (1.07-2.57)	0.02
Heart failure	1.57 (0.67-3.67)	0.30	2.32 (1.55-3.49)	<0.001
Vascular disease	1.97 (0.84-4.63)	0.12	3.22 (2.12-4.88)	<0.001
ATT under-treatment	2.72 (1.10-6.71)	0.03	1.53 (1.02-2.31)	0.04
ATT over-treatment	NE	0.99	0.44 (0.10-1.90)	0.27

ATT, antithrombotic treatment; CI, confidence interval; NE, not estimable; OR, odds ratio; y, year