Net Clinical Benefit of Warfarin in Patients With Atrial Fibrillation : A Report From the Swedish Atrial Fibrillation Cohort Study

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Net Clinical Benefit of Warfarin in Patients With Atrial Fibrillation

A Report From the Swedish Atrial Fibrillation Cohort Study

Leif Friberg, MD, PhD; Mårten Rosenqvist, MD, PhD; Gregory Y.H. Lip, MD

Background—Known risk factors for bleeding during anticoagulant treatment are largely the same as those predicting thromboembolic events in patients with atrial fibrillation (AF). Our objective was to investigate how to maximize the likelihood of avoiding both stroke and bleeding.

Methods and Results—All 182 678 subjects with atrial fibrillation in the Swedish Hospital Discharge Register were studied for an average of 1.5 years (260 000 patient-years at risk). Patients were stratified according to risk scores with the use of historic *International Classification of Disease* diagnostic codes in the register. Information about medication was obtained from the Swedish Drug Registry. Our primary end point was net benefit defined as number of avoided ischemic strokes with anticoagulation minus the number of excess intracranial bleedings with a weight of 1.5 to compensate for the generally more severe outcome with intracranial bleedings. The adjusted net clinical benefit favored anticoagulation for almost all atrial fibrillation patients. The exceptions were patients at very low risk of ischemic stroke with a CHA_2DS_2-VASc score of 0 and moderately elevated bleeding risk (−1.7%/y). The results were broadly similar with $CHADS_2$, except for patients with very low embolic risk; the CHA_2DS_2-VASc was able to identify those patients (n=6205, 3.9% of all patients) who had no net clinical benefit or even some disadvantage from anticoagulant treatment.

Conclusions—In almost all patients with atrial fibrillation, the risk of ischemic stroke without anticoagulant treatment is higher than the risk of intracranial bleeding with anticoagulant treatment. Analysis of the net benefit indicates that more patients may benefit from anticoagulant treatment. **(*Circulation*. 2012;125:2298-2307.)**

Key Words: anticoagulants ■ atrial fibrillation ■ hemorrhage ■ stroke ■ warfarin

Atrial fibrillation (AF) confers a substantial mortality and morbidity from stroke and thromboembolism. Oral anticoagulation (OAC) therapy with warfarin is highly effective in reducing stroke and thromboembolism but is associated with increased bleeding risk.[1]

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The risk of stroke and thromboembolism in AF is not homogeneous, and various stroke risk stratification schemes have been derived from various risk factors identified from trials and cohort studies[2,3] so that high-risk patients can be targeted for OAC. The simplest risk scheme is the $CHADS_2$ score (2 points for previous embolic event and 1 point each for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus),[4] but given that this score does not include several other important stroke risk factors, the CHA_2DS_2-VASc score (2 points for previous embolic event and age ≥75 years, and 1 point each for congestive heart failure, hypertension, diabetes mellitus, age 65–74 years, vascular disease, and female sex) has been proposed to complement the $CHADS_2$ score.[5] With the availability of new OACs that may be safer and more effective, a paradigm shift has been made toward improving our identification of truly low-risk patients who do not need any antithrombotic therapy, whereas all those with ≥1 stroke risk factors can be considered for OAC.

Intracranial hemorrhage (ICH) is the most feared hemorrhagic complication of OAC with a high mortality and morbidity.[6,7] Absolute rates of stroke and bleeding are based on clinical trials conducted >15 years ago[1] that suggested a 2-fold increase in ICH with warfarin use. However, contemporary studies have even shown the risk of ICH to be similar to that seen in aspirin-treated patients with AF,[8] and new OAC drugs such as dabigatran, rivaroxaban, and apixaban show noninferior (or even better) efficacy than warfarin, with

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lower ICH rates and similar major bleeding rates.[9–11] Indeed, assessment of bleeding risk is recommended in the most recent guidelines from the European Society of Cardiology[12] and from the Canadian Cardiovascular Society,[13] and use of the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score has been recommended.[14,15]

A previous analysis of cohort data from the ATRIA study (n=13 559) suggested a net benefit of warfarin with a $CHADS_2$ score of ≥2.[16] However, the study was based on a selected cohort of prevalent warfarin users and did not differentiate between patients according to bleeding risk or give any information about whether patients with high bleeding risk could still have a net benefit from anticoagulant treatment. A recent "real-world" Danish nationwide cohort study (n=132 372) dichotomized patients according to whether the bleeding risk was perceived as high or low and found a neutral or positive net clinical benefit (ischemic stroke versus ICH) with vitamin K antagonist use in patients with a $CHADS_2$ score of ≥0 and CHA_2DS_2-VASc score of ≥1.[17]

Thus, the aim of this work was to determine net clinical benefit of OAC in patients with AF in terms of risks of ischemic stroke and intracranial bleeding.

Methods

Patients

All 182 678 individuals (2% of the Swedish population) with a diagnosis of AF at a Swedish hospital between July, 1, 2005, and December 1, 2008, were identified through the Swedish National Hospital Discharge Register (HDR). During the 3.5-year study period, subjects had a total of 1 845 906 hospital contacts. We also used the HDR to obtain information about current and previous diseases and about events that occurred during follow-up. The codes used to define diseases and events during follow-up are specified in Table I in the online-only Data Supplement.

Validity of the HDR

All hospital admissions and outpatient clinic visits have been recorded in the HDR since 1987 for all subjects with Swedish civic registration numbers. Among other things, the HDR lists dates for admission and discharge, *International Classification of Disease* codes for principal diagnosis, up to 7 ancillary diagnoses, and codes for up to 12 surgical procedures on each occasion.

The HDR misses information about principal diagnosis in 0.5% to 0.9% of hospitalizations in somatic care.[18] A diagnosis of AF or flutter in the HDR has a positive predictive value in 97% of the cases.[19] A diagnosis of stroke or transient ischemic attack in the HDR is correct in 98.6% of the cases.[18] The proportion of stroke events identified through the HDR (sensitivity) ranges from 84% to 98% in validation studies. No published studies have validated the diagnosis of intracranial bleeding in the HDR, but the validity could be expected to be at least as good as a diagnosis of ischemic stroke because that diagnosis can be made only after a positive computed tomography or magnetic resonance imaging scanning or at autopsy. Our secondary bleeding end point of any bleed consisted of a set of diagnostic codes relating to bleeding events, which are presented in the Table I in the online-only Data Supplement. This composite end point has not been formally validated.

The positive predictive values of other diagnoses in the HDR, used for determination of risk scores, are as follows: for heart failure, 82% to 88%[20,21]; for diabetes mellitus, 99.6%[22]; and for myocardial infarction, 95% to 100%.[20,23] We have no data on the formal validation of the HDR for hypertension.

Table 1. Characteristics of the Study Population at Baseline

	Never Warfarin (n=90 706)	Warfarin at Baseline (n=68 306)	*P*
Age			
Median age, y	82	76	<0.00001
Mean age, y	78.38±12.58	73.82±10.17	<0.00001
<65 y	12 748 (14)	12 368 (18)	<0.00001
65–74 y	13 317 (15)	18 997 (28)	<0.00001
≥75 y	64 641 (71)	36 942 (54)	<0.00001
Women, n (%)	46 133 (51)	28 094 (41)	<0.00001
Ischemic stroke, n (%)	14 653 (16)	11 066 (16)	0.90
Unspecified stroke, n (%)	2481 (2.7)	1495 (2)	<0.00001
TIA, n (%)	5114 (6)	4544 (7)	<0.00001
Peripheral systemic emboli, n (%)	1001 (1.1)	1348 (2.0)	<0.00001
Pulmonary embolism, n (%)	1585 (1.7)	2777 (4.1)	<0.00001
Intracranial bleeding, n (%)	2319 (2.6)	616 (0.9)	<0.00001
Gastric/duodenal bleed, n (%)	4183 (5)	1509 (2)	<0.00001
Any severe bleeding, n (%)	8288 (9)	2941 (4)	<0.00001
Anemia, n (%)	12 401 (14)	4178 (6)	<0.00001
Platelet/coagulation defect, n (%)	1218 (1.3)	1208 (1.8)	<0.00001
Myocardial infarction, n (%)	19 404 (21)	12 331 (18)	<0.00001
Ischemic heart disease, n (%)	31 786 (35)	21 542 (32)	<0.00001
PCI procedure, n (%)	4275 (5)	4120 (6)	<0.00001
CABG procedure, n (%)	3317 (4)	3610 (5)	<0.00001
Peripheral arterial disease, n (%)	5451 (6)	3453 (5)	<0.00001
Vascular disease, n (%)	22 970 (25)	14 607 (21)	<0.00001
Heart failure, n (%)	30 471 (34)	23 259 (34)	0.039
Valvular disease, n (%)	5142 (6)	6599 (10)	<0.00001
Pacemaker or ICD, n (%)	3971 (4)	4320 (6)	<0.00001
Hypertension, n (%)	38 383 (42)	30 284 (44)	<0.00001
Diabetes mellitus, n (%)	15 121 (17)	11 958 (18)	<0.00001
Obesity, n (%)	916 (1.6)	1229 (1.8)	<0.00001
Renal failure, n (%)	5624 (6)	2489 (4)	<0.00001
Liver disease, n (%)	1340 (1.5)	462 (0.7)	<0.00001
Thyroid disease, n (%)	5901 (7)	3781 (6)	<0.00001
Thyrotoxicosis, n (%)	988 (1.1)	804 (1.2)	0.098
COPD/emphysema, n (%)	7555 (8)	4619 (7)	<0.00001
Cancer ≤3 y, n (%)	13 009 (14)	6903 (10)	<0.00001
Alcohol abuse, n (%)	3305 (3.6)	995 (1.5)	<0.00001
Dementia, n (%)	5941 (6.5)	782 (1.1)	<0.00001
Frequent falls, n (%)	9294 (10)	2647 (4)	<0.00001
Aspirin, n (%)	60 927 (67)	18 884 (28)	<0.00001
Clopidogrel, n (%)	6263 (7)	2412 (4)	<0.00001
$CHADS_2$, mean±SD	1.96±1.37	1.82±1.32	<0.00001
CHA_2DS_2-Vasc, mean±SD	3.70±1.89	3.41±1.82	<0.00001
HAS-BLED, mean±SD	2.20±1.15	2.25±0.93	<0.00001

TIA indicates transient ischemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter-defibrillator; and COPD, chronic obstructive pulmonary disease. For definitions of cofactors, see Table I in the online-only Data Supplement.

Table 2. Ischemic Stroke and Intracranial Bleeding Events Presented as Crude, Unadjusted Incidence, and Events per 100 Years at Risk

	Ischemic Stroke Without Warfarin (n=90 706; Time at Risk=188 470 y) HAS-BLED Score								
	0	1	2	3	4	5	6	7	All
$CHADS_2$ Score									
0	26 (0.2)	84 (0.9)	18 (1.8)	4 (2.9)	1 (10.1)	. . .	. . .	. . .	133 (0.6)
1	11 (1.5)	201 (2.1)	659 (3.4)	86 (3.9)	6 (3.5)	. . .	. . .	. . .	963 (3.0)
2	. . .	120 (3.5)	612 (4.0)	556 (4.6)	68 (4.3)	5 (4.4)	. . .	. . .	1361 (4.2)
3	. . .	23 (4.7)	258 (6.3)	833 (7.4)	155 (7.4)	12 (7.7)	2 (10.5)	1 (9125)	1284 (7.1)
4	. . .	0 (0)	57 (8.4)	411 (9.3)	516 (13.2)	76 (13.7)	3 (13.1)	. . .	1063 (11.1)
5	. . .	. . .	8 (26.3)	74 (10.0)	287 (13.2)	55 (12.6)	5 (10.0)	. . .	429 (12.5)
6	. . .	. . .	. . .	12 (16.4)	60 (11.5)	21 (16.6)	4 (18.2)	. . .	97 (13.0)
CHA_2DS_2-VASc Score									
0	8 (0.1)	4 (0.1)	2 (0.6)	1 (2.1)	. . .	. . .	. . .	. . .	15 (0.2)
1	9 (0.2)	34 (2.1)	13 (0.8)	5 (2.2)	2 (6.6)	. . .	. . .	. . .	63 (0.6)
2	15 (0.3)	102 (1.4)	196 (2.8)	34 (3.5)	2 (1.8)	. . .	. . .	. . .	349 (2.2)
3	5 (0.1)	155 (1.1)	441 (3.3)	130 (3.4)	22 (4.4)	1 (2.4)	. . .	. . .	754 (3.2)
4	. . .	86 (0.8)	485 (4.4)	501 (5.4)	76 (5.3)	4 (3.6)	1 (9.9)	1 (1000)	1154 (4.8)
5	. . .	35 (0.7)	296 (5.8)	665 (7.4)	207 (9.1)	34 (13.2)	2 (12.2)	. . .	1239 (7.2)
6	. . .	11 (0.6)	137 (8.1)	416 (8.1)	419 (13.1)	49 (11.0)	3 (10.9)	. . .	1035 (9.7)
7	. . .	1 (0.2)	35 (8.2)	168 (91)	257 (12.9)	51 (15.8)	5 (14.8)	. . .	517 (11.1)
8	. . .	. . .	6 (10.5)	50 (10.5)	88 (11.0)	21 (12.0)	3 (14.1)	. . .	168 (11.0)
9	. . .	. . .	1 (49.5)	6 (8.3)	20 (13.5)	4 (14.2)	. . .	. . .	31 (12.2)
All	37 (0.3)	428 (1.9)	1612 (4.0)	1976 (6.4)	1093 (10.4)	164 (11.6)	14 (12.2)	1 (57.5)	10650 (4.5)

Events per 100 years at risk are given in parentheses.

The Prescribed Drugs Registry

Information about medication was obtained from the National Prescribed Drugs Registry, which has been in operation since July 1, 2005, in its present form in which it is possible to link prescriptions to individual patients. All pharmacies in the country are required to be linked to this registry, which therefore by definition should include information on dates, dosages, and quantities for every prescription that was dispensed in the country, without exceptions. For the study cohort, we had access to >18 million prescriptions of cardiovascular and antithrombotic drugs. Medication at baseline was defined as a drug that had been collected at a pharmacy within ±3 months of the index date. The choice of 3 months is based on the condition that a prescription in Sweden can be made for consumption only during a maximum of 3 months, which makes 3 months the standard prescription interval. We made separate analyses according to whether the patient had been exposed to warfarin and identified patients with warfarin at baseline and patients who never collected warfarin during the study period. Warfarin is the only registered OAC in Sweden, although phenprocoumon is available on license for patients intolerant to warfarin.

Time at Risk and Exclusions

The index date was defined as the date of the first occurrence in a patient with a diagnosis of AF (I489) after July 1, 2005. For the registration of events during follow-up, we applied a blanking period of 14 days after the index date because transfers between hospitals and clinics are common, eg, from the emergency clinic to the stroke clinic and then on to the rehabilitation clinic. Reappearances of a diagnosis of an ischemic stroke or intracranial bleeding that occur within the first few days after the first diagnosis are generally related to each other and do not signify a new event. In our view, it would be improper to count such reappearances of diagnoses that were already present at the index contact as follow-up events. Diagnoses that were given on the index date and up to 2 weeks after that date were therefore considered to reflect comorbidity and were not considered end points during follow-up. Thus, for 5720 patients with a diagnosis of stroke within 14 days of index, the event was counted a risk factor for the subsequent follow-up but not as an end-point event. We also excluded 7167 patients who died in conjunction with the index-generating hospital contact (who could not contribute with follow-up time), 528 patients with valvular AF resulting from mitral stenosis, and 5112 patients who had undergone valvular heart surgery.

Primary and Secondary End Points

For the end point of thromboembolism, we used ischemic stroke (*International Classification of Disease*, 10th edition, code I63), and for the composite thromboembolism end point, we used ischemic stroke, unspecified stroke, transient ischemic attack, and systemic embolism (I63, I64, G45, I74). The primary bleeding end point was ICH (I60–I62), although data on major bleeding, including all intracranial bleeds, all gastrointestinal bleeds, and diagnosis for anemia secondary to bleeding, were also analyzed (see Table I in the online-only Data Supplement for the specific *International Classification of Disease* codes used). In addition, we compared the outcome with regard to a combined end point consisting of death resulting from any cause, ischemic stroke, or intracranial bleeding for patients on warfarin at baseline with that of patients who never used warfarin during follow-up.

Definitions

Components of the $CHADS_2$ score were defined by age ≥75 years at inclusion and a diagnosis of heart failure (I50), hypertension (I10–I15), diabetes mellitus (E10–E14), previous ischemic stroke

Table 2. Continued

Intracranial Bleeding Warfarin At Baseline (n=68 306, Time at Risk=114 569 y) HAS-BLED Score								
0	1	2	3	4	5	6	7	All
. . .	48 (0.2)	8 (0.9)	. . .	. . .	. . .	. . .	. . .	56 (0.3)
. . .	14 (0.2)	138 (0.6)	17 (1.0)	2 (3.0)	. . .	. . .	. . .	171 (0.5)
. . .	3 (0.3)	96 (0.6)	80 (0.7)	17 (1.9)	. . .	. . .	. . .	196 (0.6)
. . .	. . .	21 (0.6)	104 (0.8)	20 (1.5)	1 (1.2)	. . .	. . .	146 (0.8)
. . .	. . .	4 (3.3)	32 (0.7)	45 (1.2)	6 (2.0)	. . .	. . .	87 (1.0)
. . .	. . .	. . .	5 (0.9)	10 (0.5)	5 (2.0)	. . .	. . .	20 (0.7)
. . .	. . .	. . .	. . .	5 (1.0)	2 (2.3)	. . .	. . .	7 (1.1)
. . .	10 (0.1)	3 (1.0)	. . .	. . .	. . .	. . .	. . .	13 (0.2)
. . .	27 (0.3)	10 (0.4)	1 (0.5)	. . .	. . .	. . .	. . .	38 (0.3)
. . .	19 (0.2)	63 (0.6)	7 (0.8)	. . .	. . .	. . .	. . .	89 (0.5)
. . .	3 (0.1)	92 (0.6)	32 (0.8)	12 (3.4)	. . .	. . .	. . .	139 (0.6)
. . .	5 (0.5)	66 (0.6)	82 (0.8)	15 (1.7)	. . .	. . .	. . .	168 (0.8)
. . .	1 (0.4)	23 (0.6)	75 (0.8)	23 (1.2)	2 (1.2)	. . .	. . .	124 (0.8)
. . .	. . .	1 (0.1)	23 (0.5)	31 (1.1)	4 (1.7)	. . .	. . .	59 (0.7)
. . .	. . .	1 (0.3)	13` (0.8)	10 (0.6)	5 (2.8)	. . .	. . .	29 (0.8)
. . .	. . .	. . .	5 (1.3)	8 (1.2)	3 (2.9)	. . .	. . .	16 (1.3)
. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
. . .	. . .	258 (0.6)	225 (0.7)	89 (1.0)	9 (1.2)	. . .	. . .	646 (0.6)

(I63), unspecified stroke (I64), transient ischemic attack (G45), or systemic emboli (I74). Components of the CHA_2DS_2-VASc score were, in addition to these factors used for definition of the $CHADS_2$ score, age of 65 to 74 years, female sex, and vascular disease (prior myocardial infarction, peripheral arterial disease; I21, I252, I70–I73).

For the HAS-BLED score, we used (apart from the above factors) a number of codes for intracranial, gastrointestinal, and other bleeding events as specified in Table I in the online-only Data Supplement. We had to modify the score because some information was impossible to extract from the registers. For example, the L in HAS-BLED stands for labile international normalized ratio, which we had no information on and had to ignore.

The letter D stands for drugs (eg, concomitant antiplatelet therapy or nonsteroidal antiinflammatory drugs) or alcohol abuse. We used information from the national Prescribed Drug Registry on aspirin, clopidogrel, ticlopidine, and low-molecular-weight heparins, but we had no information about use of nonsteroidal antiinflammatory drugs, which are often intermittent and difficult to adjust for. We always counted 1 point for antiplatelet agents (HAS-BLED), no matter what reason there was for treatment, when it was used concomitantly with OAC. A patient on warfarin did not receive a point for warfarin use only because D refers to concomitant drugs with warfarin. For the definition of alcohol abuse, for which it is particularly difficult to obtain reliable information, we used the same collection of diagnostic codes that the Swedish Board of Health of Welfare uses for accounts of alcohol-related deaths ("alcohol index"), which is presented in Table I in the online-only Data Supplement.

Net Clinical Benefit

We initially compared the risk for ischemic stroke without OAC with warfarin against the risk of ICH when treated with warfarin for all combinations of CHA_2DS_2-VASc and HAS-BLED scores as follows: Net benefit=$(IS_{\text{off warfarin}}-ICH_{\text{on warfarin}})$, where IS is ischemic stroke.

We also calculated the net clinical benefit using the method of Singer et al.[16] The number of ICH events attributable to warfarin treatment was subtracted from the number of ischemic strokes avoided by warfarin treatment with the weight of 1.5 as was used in the net clinical benefit analysis by Singer et al to account for the generally more disastrous effects of an intracranial bleed compared with an ischemic stroke: Net Benefit=$(IS_{\text{off warfarin}}-IS_{\text{on warfarin}})-1.5\times(ICH_{\text{on warfarin}}-ICH_{\text{off warfarin}})$.

Statistical Methods

For pairwise comparisons, t tests and χ^2 tests were used. For survival analyses, Kaplan-Meier analysis and univariable and multivariable Cox regression was used. Age was used as a categorical variable when presented in the tables for the sake of comprehensiveness but otherwise was used as a continuous variable in the analyses. Hazard ratios for the composite end point were calculated for all combinations of risks on the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores when there were at least 100 patients in both the warfarin and nonwarfarin groups. Although 2-dimensional stratification of risks on these 2 scales is a type of multivariable adjustment of confounding, we added multivariable Cox regression on top. Event rates were calculated as events per 100 patient-years at risk but are presented in the text as annualized individual risks (percent) for the sake of comprehensibility. We calculated 95% confidence intervals when relevant. Values of $P<0.05$ were considered significant. All analyses were performed in SPSS 20.0 (IBM SPSS Statistics, IBM Corp, Somers, NY).

This study was approved by the ethics committee of Karolinska Institute (EPN 2008/433-32).

Results

We studied 182 678 subjects with AF, of whom 170 292 (mean age, 76.2 years; 53% male) fulfilled our inclusion criteria. Of these patients, 90 706 (53%) never used warfarin and 68 306 (40%) had warfarin at index (Table 1). The group of patients who did not use warfarin at any time during follow-up was heterogeneous, consisting of elderly patients with multiple comorbidities and younger patients with lone AF. Patients without warfarin were generally older and more often had a history of previous bleeds, frequent falls, and dementia compared with warfarin-treated patients (Table 1).

During 1.5±1.1 years of follow-up representing 260 000 patient-years at risk, 43 712 patients died; 9296 had an ischemic stroke; 13 281 had any kind of thromboembolic event, including unspecified strokes, transient ischemic attacks, and systemic emboli; 1600 suffered an ICH; and 5810 had a bleeding that resulted in a diagnosis in the HDR. An unadjusted presentation of incident ischemic strokes and intracranial bleedings in relation to risk scores is given in Table 2.

Stroke and Thromboembolism

Ischemic stroke rates increased with increasing CHA_2DS_2-VASc scores from almost 0% to 12% annually in patients without warfarin and to 7% annually in patients with warfarin at baseline (Figure 1, left). For the composite thromboembolism end point, the annual event rate in high-risk patients approached 16% in untreated and 10% in warfarin-treated patients (Figure 1, right).

Bleeding Events

Intracranial bleedings occurred at an annual rate of 0.6% in warfarin-treated and untreated patients alike, whereas bleeding of any type occurred at an annual rate of 2.3% (1.9% in patients on warfarin at baseline and 2.7% in patients who never used warfarin during the study period). There was a positive association between CHA_2DS_2-VASc scores and the risk of bleeding in general but not in relation to ICH because the rates were relatively constant across all strata.

The HAS-BLED score showed a better association with both the risk of ICH, increasing from 0% to almost 2% annually, and the risk of any bleeding event, with incidence rates increasing almost linearly to almost 8% in those with the highest HAS-BLED scores (Figure 2). Unadjusted data did not show increased bleeding rates in patients using warfarin compared with patients who did not.

Regardless of whether the CHA_2DS_2-VASc or the HAS-BLED score was used, the risk of ischemic stroke increased more than the risk of bleeding as the risk score increased. This was true for patients with and without warfarin, regardless of whether strict or wide definitions of events were used.

Net Clinical Benefit

The net clinical benefits of anticoagulation for the main end point in relation to CHA_2DS_2-VASc and HAS-BLED scores are shown in Table 3. The net result favored warfarin treatment for all patients except for those at very low risk of ischemic stroke using the CHA_2DS_2-VASc score (score=0). Those who appeared to have the best net benefit from warfarin were patients with the highest risk scores in both risk score schemes. In these high-risk groups, warfarin treatment was associated with up to 12 fewer events per 100 years at risk than if warfarin was not given.

The adjusted net clinical benefit (which puts a weight of 1.5 for ICH to account for the generally more disastrous consequences of ICH over thromboembolic stroke) was greatest for patients with an HAS-BLED score of 4 and CHA_2DS_2-VASc score of 6 (Table 3). In this group of patients, the adjusted net clinical benefit was >6%/y. Patients at very low risk of ischemic stroke (CHA_2DS_2-VASc score=0) and moderately elevated bleeding risk appeared to

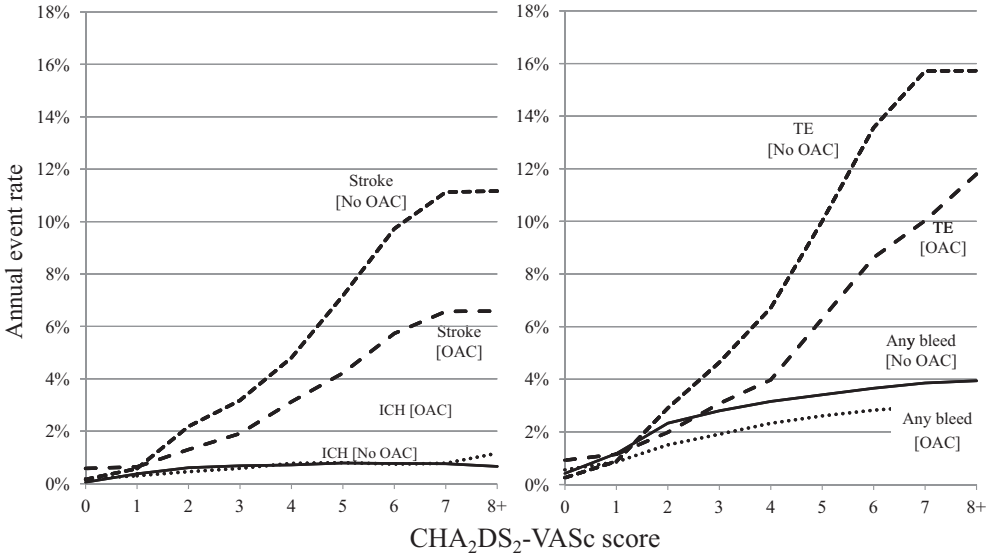

Figure 1. Relation between CHA_2DS_2-VASc scores and annual event rates of ischemic stroke and intracranial hemorrhage (ICH; left) and more widely defined thromboembolic events and bleedings (right) in relation to use of oral anticoagulation (OAC; n=159 013). Stroke indicates ischemic stroke; TE, thromboembolic event (including ischemic stroke, unspecified stroke, transient ischemic attack, or systemic emboli).

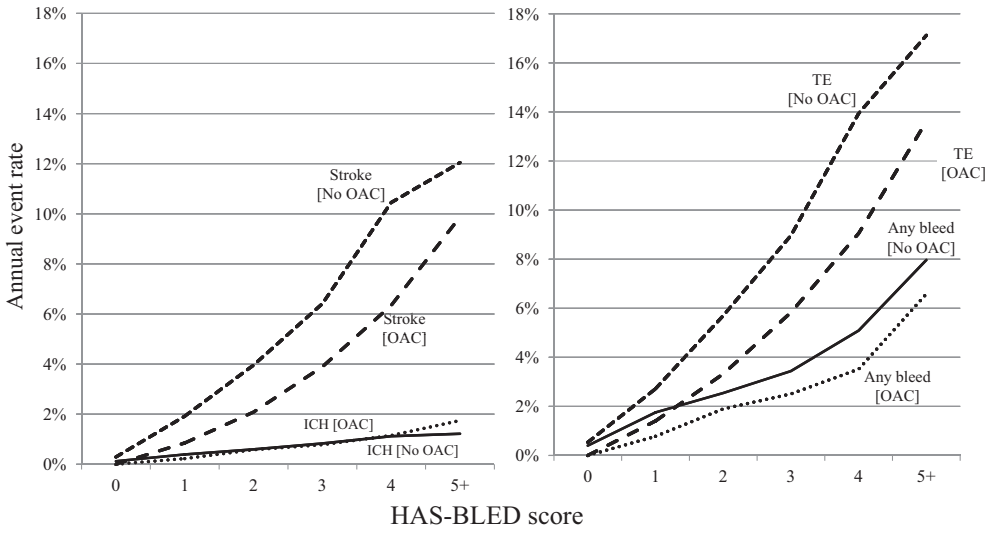

Figure 2. Relation between HAS-BLED scores and annual event rates of ischemic stroke and intracranial hemorrhage (ICH; left) and more widely defined thromboembolic events (TEs) and bleedings (right) in relation to use of oral anticoagulation (OAC; n=159 013).

have a net clinical disadvantage from warfarin treatment (ie, −1.7%/y).

The results were broadly similar with $CHADS_2$ except for patients with very low embolic risk; the CHA_2DS_2-VASc was able to identify those patients (n=6205, 3.9% of all patients) who had no net clinical benefit or even some disadvantage from anticoagulant treatment. Of these, all but 667 patients (0.4% of all) belonged to the group with the lowest embolic risk with a CHA_2DS_2-VASc score of 0. Thus, the $CHADS_2$ score was less discriminatory for truly low-risk patients, whereas all patients regardless of $CHADS_2$ score appeared to benefit from OAC.

Freedom From Death, Ischemic Stroke, or Intracranial Bleed

We compared the outcome with regard to a composite end point consisting of death resulting from any cause, ischemic stroke, or intracranial bleed for patients on warfarin at baseline with that of patients who never used warfarin during follow-up. Patients were stratified according to low or high

Table 3. Net Clinical Benefit of Warfarin: Ischemic Stroke Versus Intracranial Hemorrhage

	Net Benefit, Embolic Strokes With Warfarin Minus Intracranial Bleeds With Warfarin, Net Difference in Annualized Event Rate (95% CI) HAS-BLED Score							Net Benefit, Avoided Embolic Strokes With Warfarin Minus Excess Intracranial Bleeds With Warfarin With a Weight of 1.5, Net Difference in Annualized Event Rate HAS-BLED Score						
	1	2	3	4	5	6	All	1	2	3	4	5	6	All
$CHADS_2$														
0	0.7 (0.5–0.9)	0.9 (−0.1 to 2.0)	. . .	. . .	. . .	. . .	0.3 (0.2–0.5)	0.3	0.5	. . .	. . .	. . .	. . .	−0.3
1	2.0 (1.6–2.3)	2.8 (2.5–3.1)	2.9 (1.9–3.9)	. . .	. . .	. . .	2.5 (2.3–2.7)	1.7	1.7	1.2	. . .	. . .	. . .	1.6
2	3.3 (2.6–4.0)	3.5 (3.1–3.8)	3.9 (3.5–4.3)	2.4 (1.1–3.8)	. . .	. . .	3.6 (3.3–3.8)	2.3	1.7	2.2	0.3	. . .	. . .	1.8
3	. . .	5.7 (4.9–6.5)	6.6 (6.1–7.1)	5.8 (4.5–7.2)	6.5 (1.5–11)	. . .	6.3 (5.9–6.7)	. . .	2.8	3.0	3.2	. . .	. . .	4.5
4	. . .	. . .	8.6 (7.7–9.5)	12.1 (10.9–13)	11.6 (8.1–15)	13.0 (−1.7 to 28)	10.1 (9.4–11)	. . .	. . .	3.9	5.8	1.8	2.7	4.5
5	. . .	. . .	9.1 (6.6–11)	12.7 (11–14)	10.7 (6.9–14)	10.0 (1.2–19)	11.8 (10–13)	. . .	. . .	2.2	6.6	1.0	0.8	5.2
6	. . .	. . .	. . .	10.5 (7.5–14)	. . .	. . .	11.9 (9.2–15)	. . .	. . .	. . .	1.4	. . .	. . .	3.5
CHA_2DS_2-VASc														
0	0.0 (−0.2 to 0.2)	−0.5 (−1.9 to 1.0)	. . .	. . .	. . .	. . .	0.0 (−0.1 to 0.1)	−0.6	−1.7	. . .	. . .	. . .	. . .	−0.6
1	0.4 (0.2–0.7)	0.5 (0.0–0.9)	1.7 (−0.5 to 3.8)	. . .	. . .	. . .	0.3 (0.1–0.4)	0.2	0.6	2.3	. . .	. . .	. . .	0.0
2	1.5 (1.1–1.8)	2.2 (1.8–2.6)	2.7 (1.4–5.0)	. . .	. . .	. . .	1.7 (1.5–2.0)	1.2	1.4	2.1	. . .	. . .	. . .	1.1
3	2.7 (2.2–3.1)	3.0 (2.6–3.3)	2.6 (2.0–3.3)	1.0 (−1.7 to 3.6)	. . .	. . .	2.6 (2.3–2.8)	2.2	1.5	1.4	−0.7	. . .	. . .	1.4
4	3.1 (2.2–4.0)	3.8 (3.4–4.2)	4.6 (4.1–5.1)	3.6 (2.1–5.1)	. . .	. . .	4.0 (3.7–4.3)	1.0	1.5	2.0	1.2	. . .	. . .	1.6
5	5.1 (3.1–7.1)	5.3 (4.6–6.0)	6.5 (5.9–7.1)	8.0 (6.6–9.3)	12.8 (8.3–17.3)	. . .	6.3 (5.9–6.8)	3.2	2.7	3.0	3.3	3.0	. . .	2.9
6	7.4 (3.0–12)	7.4 (5.9–8.8)	7.6 (6.8–8.4)	12.1 (11–13)	9.3 (5.8–13)	. . .	9.1 (8.5–9.7)	3.4	3.9	2.8	6.3	3.4	. . .	4.2
7	. . .	7.9 (5.1–10.7)	8.3 (6.8–9.7)	12.3 (11–14)	13.1 (8.1–18)	. . .	10.4 (9.4–11)	. . .	4.5	3.7	5.8	−0.9	. . .	4.5
8	. . .	. . .	9.2 (6.1–12)	9.8 (7.4–12)		. . .	9.7 (7.9–11)	. . .	. . .	4.7	1.6	. . .	. . .	9.7
9	. . .	. . .	. . .	. . .	. . .	. . .	12.2 (7.9–16)	. . .	. . .	. . .	. . .	. . .	. . .	11.5
All	1.7 (1.5–1.9)	3.4 (3.2–3.6)	5.7 (5.4–6.0)	9.4 (8.8–10)	10.4 (8.5–12)	12.1 (5.8–19)	3.9 (3.8–4.1)	1.3	1.9	2.6	4.0	1.3	5.6	1.9

CI indicates confidence interval. Values have been suppressed if they represented <100 patients in either the treated or untreated group.

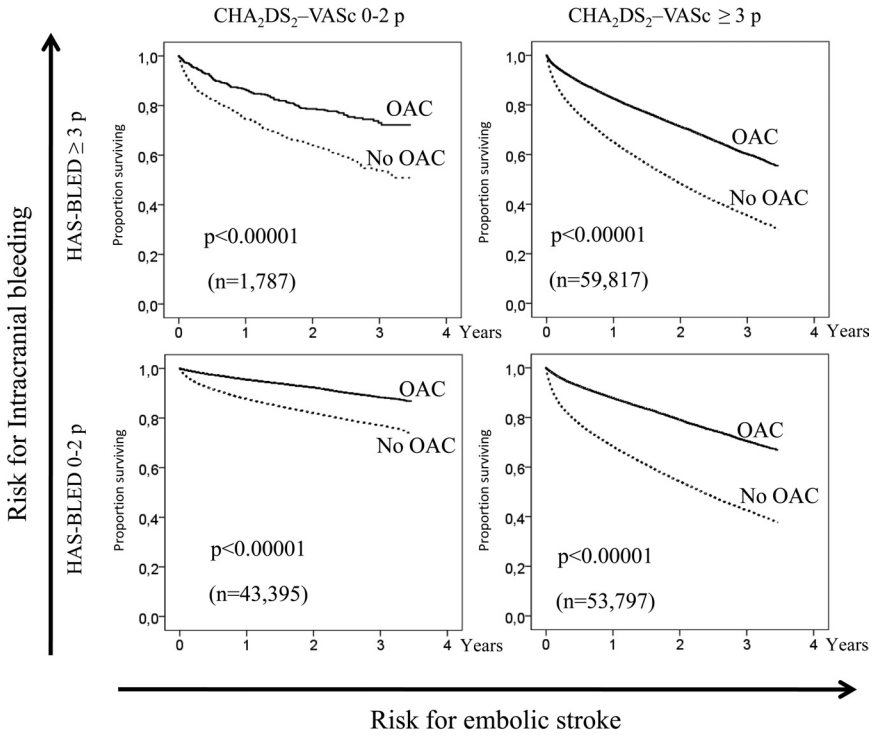

Figure 3. All-cause mortality, ischemic stroke, and intracranial bleeds in relation to oral anticoagulant (OAC) treatment in patients with different combinations of stroke and bleeding risks on the CHA_2DS_2-VASc and HAS-BLED risk scores.

risk for embolic stroke and according to low or high risk for ICH. In all 4 scenarios with CHA_2DS_2-VASc and HAS-BLED schemes, warfarin-treated patients had a better outcome than patients without warfarin, with the Kaplan-Meier plots shown in Figure 3. The results obtained with $CHADS_2$ (Table 4) were broadly similar to those obtained with CHA_2DS_2-VASc.

Hazard ratios were calculated for all combinations of risks on the CHA_2DS_2-VASc and HAS-BLED scores when there were at least 100 patients in both the warfarin and the nonwarfarin groups. Hazard ratios in all instances favored warfarin treatment (HRs ranging from 0.26–0.72; Table 4). Multivariable Cox regression did not change the main results, which still showed a more favorable prognosis for warfarin-treated patients (Table 4). The results were broadly similar when $CHADS_2$ rather than CHA_2DS_2-VASc was used to stratify patients.

Discussion

The main finding of this study is that the risk of ischemic stroke without anticoagulant treatment exceeds the risk of intracranial bleeding with anticoagulant treatment at almost every combination of stroke and bleeding risks that we were able to study. When the risk of bleeding is high, according to the HAS-BLED scale, the risk of ischemic stroke or of a thromboembolic event is even higher. Indeed, the higher the bleeding risk is, the wider the gap is between the embolic risk and the bleeding risk; thus, there is more to be gained from OAC treatment.

Usefulness of Risk Stratification Schemes

The CHA_2DS_2-VASc score was more sensitive in identifying patients who were truly low risk in whom OAC treatment may be associated with a net disadvantage, and in this respect, CHA_2DS_2-VASc was clearly superior to $CHADS_2$. Our findings are consistent with other data showing that the CHA_2DS_2-VASc score was better than the $CHADS_2$ score in identifying truly low-risk subjects with AF.[5,24,25] The HAS-BLED score was also useful as a tool for prediction of bleeding risk, but there was a similar relation of this score to ischemic stroke risk. Nonetheless, the risk of stroke is usually much higher than the risk of bleeding.[25]

Anticoagulation Is the Rule, With Few Exceptions

An alternative and simpler approach to the anticoagulation issue could be to regard anticoagulation as the general rule for all AF patients except those at very low risk of stroke (who would not derive any net benefit, as shown in the present study to be those with a CHA_2DS_2-VASc score of 0) and those at extremely high risk of bleeding. In short, when managing patients with AF, we essentially need to ask the question, "Who are the patients with bleeding risks that exceed the risk of ischemic stroke?" Indeed, the present study managed to identify only a very small minority (0.4% of all patients) in whom this was the case. Of note, in patients with malignant hypertension, ongoing occult gastrointestinal bleeds, or recurrent spontaneous ICH (eg, cerebral amyloid angiopathy), bleeding risks far exceed the risk for ischemic stroke.[26]

Improving Net Benefit Further

Bleeding risk with OAC treatment is not static. A great deal may be done to reduce bleeding risks, and the HAS-BLED score makes the clinician think of the common bleeding risk factors that are correctable such as uncontrolled blood pressure, labile international normalized ratios, and concomitant drugs such as nonsteroidal antiinflammatory drugs, aspirin, or clopidogrel (ie, the H, L, and D in HAS-BLED, respectively).[26] Indeed, a good time in therapeutic range has been related to a low rate of thromboembolism and major hemorrhage.[27]

Table 4. Net Benefit From Warfarin Treatment on Embolic Strokes, Intracranial Bleeds, or Death

	Net Benefit From Warfarin Treatment on Embolic Strokes, Intracranial Bleeds, or Death, Hazard Ratios (95% CI) HAS-BLED Score					
	1	2	3	4	5	All
Unadjusted						
CHA_2DS_2-VASc						
0	0.46 (0.35–0.61)	0.40 (0.21–0.75)	. . .	. . .	. . .	0.60 (0.48–0.75)
1	0.49 (0.42–0.58)	0.37 (0.27–0.49)	0.36 (0.19–0.68)	. . .	. . .	0.47 (0.42–0.54)
2	0.26 (0.23–0.30)	0.36 (0.33–0.40)	0.56 (0.44–0.70)	. . .	. . .	0.35 (0.33–0.38)
3	0.29 (0.26–0.34)	0.40 (0.38–0.43)	0.46 (0.42–0.51)	0.62 (0.46–0.83)	. . .	0.40 (0.38–0.41)
4	0.26 (0.21–0.32)	0.44 (0.42–0.47)	0.47 (0.44–0.50)	0.66 (0.56–0.78)	. . .	0.44 (0.42–0.46)
5	0.26 (0.18–0.38)	0.39 (0.36–0.43)	0.45 (0.42–0.47)	0.50 (0.44–0.56)	0.46 (0.33–0.65)	0.42 (0.41–0.44)
6	0.39 (0.22–0.71)	0.44 (0.38–0.50)	0.50 (0.46–0.54)	0.46 (0.42–0.50)	0.61 (0.47–0.80)	0.47 (0.45–0.50)
7	. . .	0.28 (0.21–0.38)	0.43 (0.38–0.49)	0.48 (0.42–0.54)	0.64 (0.49–0.85)	0.45 (0.41–0.48)
8	. . .	. . .	0.53 (0.43–0.66)	0.50 0.42–0.60)	. . .	0.53 (0.47–0.60)
9	. . .	. . .	. . .	. . .	. . .	0.47 (0.34–0.64)
All	0.20 (0.19–0.21)	0.37 (0.36–0.39)	0.46 (0.44–0.47)	0.50 (0.47–0.53)	0.63 (0.54–0.72)	0.41 (0.40–0.42)
Multivariable						
CHA_2DS_2-VASc						
0	0.78 (0.46–1.33)	0.89 (0.26–3.05)				0.74 (0.58–0.93)
1	0.62 (0.46–0.83)	0.84 (0.50–1.40)	0.66 (0.23–1.91)			0.50 (0.43–0.57)
2	0.37 (0.30–0.45)	0.60 (0.52–0.69)	0.59 (0.42–0.84)			0.46 (0.42–0.49)
3	0.40 (0.32–0.50)	0.57 (0.51–0.63)	0.66 (0.55–0.78)	0.62 (0.37–1.04)		0.50 (0.47–0.53)
4	0.32 (0.24–0.44)	0.58 (0.53–0.64)	0.59 (0.53–0.66)	0.81 (0.63–1.04)		0.53 (0.50–0.56)
5	0.37 (0.22–0.61)	0.41 (0.36–0.46)	0.49 (0.45–0.54)	0.61 (0.51–0.73)	0.45 (0.27–0.75)	0.47 (0.45–0.50)
6		0.42 (0.36–0.50)	0.51 (0.46–0.57)	0.51 (0.44–0.58)	0.71 (0.48–1.05)	0.51 (0.47–0.54)
7			0.44 (0.38–0.52)	0.60 (0.51–0.71)	1.12 (0.75–1.67)	0.49 (0.45–0.54)
8			0.52 (0.40–0.68)	0.55 (0.43–0.71)		0.55 (0.47–0.64)
9						0.45 (0.31–0.65)
All	0.41 (0.37–0.45)	0.52 (0.49–0.54)	0.53 (0.51–0.56)	0.58 (0.53–0.62)	0.73 (0.60–0.89)	0.51 (0.50–0.52)

CI indicates confidence interval. In the multivariate Cox analysis, adjustment was made for age (continuous), sex, previous thromboembolism, major bleed, vascular disease, heart failure, hypertension, renal failure, hepatic disease, anemia, diabetes, chronic obstructive pulmonary disease, alcohol abuse, dementia, frequent falls, cancer within the preceding 3 years, aspirin at baseline, clopidogrel at baseline, and warfarin at baseline. Only boxes with at least 100 individuals in both of the treatment groups are shown.

Limitations

Selection Bias

An important limitation of this large cohort study is that it was not a randomized, blinded, or prospective study. Such a study perhaps would have been easier to interpret (notwithstanding the selective nature of a clinical trial population that randomizes only a proportion of subjects screened) but impossible to perform for ethical reasons, considering the well-documented protective effect of anticoagulation in AF. This limitation would also be intrinsic to all other real-world cohorts such as the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study,[16] although the present study is substantially much larger than previous published cohorts.

In addition, this study is limited by its reliance on a cohort of patients who were in contact with a hospital as either outpatients or inpatients. Therefore, such patients could have more illness burden than AF patients who are cared for exclusively by their primary care physician. Similar hospital-centered data sets have been used to study previous stroke and bleeding risk evaluations.[4,24,28]

Dependence on Validity of Registers

Our analysis cannot account for all of the clinical variables and changes in therapy over time and is reliant on the accuracy of diagnostic recording. In a similarly organized cohort study of AF, the hospital diagnosis for AF was well validated; evidence for AF was found in 99%.[29] Another possible limitation is the underreporting of some comorbidities, especially hypertension.

The rate of major bleeding complications with warfarin in our study (2.7% annually) was lower than in the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial (3.36%),[9] which could indicate a lower sensitivity of bleeding events than in RE-LY and thus bias the study toward a greater net benefit of warfarin. However, the bleeding rates in RE-LY stand out as rather high compared with other studies such as Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III (1.8%), Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS; 1.4%), Stroke Prevention in Atrial Fibrillation (SPAF; 2.3%),

Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE; 3.1%), Atrial Fibrillation Ablation Trial (AFI; 1.3%), and Canadian Atrial Fibrillation Anticoagulation (CAFA; 2.5%).[30–35] Furthermore, the rate of intracranial bleeds among warfarin-treated patients was not lower but actually higher in our study compared with RE-LY (0.60% versus 0.38%, respectively) and ARISTOTLE (0.47%), which is consistent with the higher mean age of the patients in our study (73.8 versus 71.6 years in RE-LY) and a higher median age than in ARISTOTLE (82 versus 70 years).

Confounding by Indication

It is important to note that the patients in this study were not randomized to receive warfarin, and we did not have detailed information about the time in therapeutic range for individual patients. Warfarin-treated AF patients as a group may differ in many ways from those who do not receive warfarin.[36] Indeed, the patients in the anticoagulated group were generally lower risk than those who were not anticoagulated, and stratification according to risk scoring schemes or multivariable adjustments for confounding factors can never fully account for these differences. In comparisons of bleeding risk with (and thromboembolic risk without) anticoagulation therapy, residual confounding from differences between the groups may have boosted the apparent beneficial net effect of anticoagulant treatment. The importance of such unaccounted differences should not be exaggerated because all comparisons of risks are performed within groups, in addition to comparisons between groups.

Applicability of Results

We had no information on how anticoagulant treatment was managed with regard to international normalized ratio values and the average time in therapeutic range. Clearly, patients with well-managed warfarin treatment have lower risk of ischemic stroke and of bleeding than patients with labile international normalized ratios. The HAS-BLED risk stratification score includes labile international normalized ratios. We had to ignore this criterion when calculating patients' bleeding risk, and this is an important limitation. Nonetheless, we know that warfarin treatment in Sweden is generally very well managed compared with most other countries.[37] Thus, the results in the present study may not be applicable in countries with less well-managed anticoagulant treatment.

When we compared bleeding and embolic events in various risk strata with and without warfarin treatment, we could not do so for all combinations of risks. Patients cannot by definition have the maximal point on one of the scales and no points on the other scale because several components appear in both scales (age, hypertension, previous stroke). Despite the huge number of patients in this study, few patients with high HAS-BLED scores were treated with warfarin. Finally, we were unable to assess the severity of the consequences of individual thromboembolic or bleeding events and were forced to rely on a weight of 1.5 to compensate for the graver prognosis in cerebral bleedings compared with ischemic strokes.

Conclusions

In almost all patients with AF, the risk of ischemic stroke without anticoagulant treatment is far higher than the risk of intracranial bleeding with treatment. Analysis of the net benefit indicates that more patients should be offered OAC treatment. Furthermore, the CHA_2DS_2-VASc score was more sensitive than the $CHADS_2$ score in identifying patients who were truly low risk in whom anticoagulation may be associated with a net disadvantage.

Sources of Funding

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Disclosures

Dr Friberg is a consultant to Sanofi-aventis, Boehringer-Ingelheim, and BMS. Dr Rosenqvist is a consultant to Sanofi-aventis and Nycomed, Sweden. He has also been national coordinator for the RECORD, REALISE, and ARISTOTLE studies and is a member of the steering group for the REALISE study. He has been reimbursed by Sanofi-aventis and Boehringer Ingelheim for lectures. Dr Lip has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of AF and thrombosis.

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CLINICAL PERSPECTIVE

Atrial fibrillation is a major cause of ischemic stroke. Oral anticoagulants give good protection against ischemic stroke but also increase the risk of bleeding. Intracranial hemorrhage is the most feared complication with high mortality and morbidity. We investigated how to maximize the net clinical benefit by balancing ischemic stroke against intracranial hemorrhage in 182 678 atrial fibrillation patients in the Swedish National Hospital Discharge Register. Patients were classified according to stroke risk ($CHADS_2$ and CHA_2DS_2-VASc) and bleeding risk (HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly]). As the risk of ischemic stroke increased, the risk of intracranial hemorrhage and other bleeding also increased. Patients with high bleeding risk scores suffered more ischemic strokes than bleeding events, so the net clinical benefit favored anticoagulation for almost all patients except those patients with very low embolic risk; the CHA_2DS_2-VASc was able to identify those patients (3.9% of all patients) who had no net clinical benefit or even some disadvantage from anticoagulant treatment with warfarin. Thus, we conclude that in almost all patients with atrial fibrillation, the risk of ischemic stroke without anticoagulant treatment is far higher than the risk of intracranial hemorrhage with anticoagulant treatment and that most atrial fibrillation patients should be offered effective thromboprophylaxis with oral anticoagulation.

Supplemental Table 1

Definitions of comorbidity and outcome by ICD-10 codes

Diagnosis	ICD-10 code beginning with
Ischemic stroke	I63
Stroke, unspecified	I64
TIA	G45
Peripheral systemic embolism	I74
Thromboembolic event	I63-64, G45, I74
Pulmonary embolism	I26
Intracranial bleeding	I60-62
Gastric/duodenal bleeding	K25-28 (subcodes 0-2 and 4-6 only)
Any severe bleeding	I60-62, I850,I983, K25-28 (subcodes 0-2 and 4-6 only) K625, K922, D629
Anemia	D50-64
Platelet or coagulation defect	D65-69
Myocardial infarction	I21, I252
Ischemic heart disease	I20-25
PCI-procedure	Z955 or local procedure code
CABG-procedure	Z951 or local procedure code
Peripheral arterial disease	I70-73
Vascular disease	I21, I252, I70-73
Heart failure	I50
Valvular disease	I05-09, I33-39
Mitral stenosis	I342, I050, I052, Q232
Pacemaker/ICD	Z950, Z450 or local implant code
Hypertension	I10-15
Diabetes mellitus	E10-14
Obesity	E65-66
Renal disease	N17-19 or local code for renal transplantation or dialysis
Liver disease	K70-77, or local code for liver transplantation or resection
Thyroid disease	E00-07
Thyreotoxicosis	E05
COPD/ Emphysema	J43-44
Cancer within preceding 3 years	entire C-series
Alcohol abuse ("Alcohol Index" used by the National Board of Health and Welfare)	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Dementia	F00-F03
Frequent falls (≥2 hospitalizations)	W00-19