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Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study

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Aims The impact of some risk factors for stroke and bleeding, and the value of stroke and bleeding risk scores, in atrial fibrillation (AF), has been debated, as clinical trial cohorts have not adequately tested these. Our objective was to investigate risk factors for stroke and bleeding in AF, and application of the new CHA_2DS_2-VASc and HAS-BLED schemes for stroke and bleeding risk assessments, respectively.

Methods and results We used the Swedish Atrial Fibrillation cohort study, a nationwide cohort study of 182 678 subjects with a diagnosis of AF at any Swedish hospital between 1 July 2005 and 31 December 2008, who were prospectively followed for an average of 1.5 years (260 000 years at risk). With the use of the National Swedish Drug Registry, all patients who used an oral anticoagulant anytime during follow-up were identified. Most of the analyses were made on a subset of 90 490 patients who never used anticoagulants. Risk factors for stroke, the composite thromboembolism endpoint (stroke, TIA, or systemic embolism), and bleeding, and the performance of published stroke and bleeding risk stratification schemes were investigated. On multivariable analysis, significant associations were found between the following 'new' risk factors and thromboembolic events; peripheral artery disease [hazard ratio (HR) 1.22 (95% CI 1.12–1.32)], 'vascular disease' [HR 1.14 (1.06–1.23)], prior myocardial infarction [HR 1.09 (1.03–1.15)], and female gender [HR 1.17 (1.11–1.22)]. Previous embolic events, intracranial haemorrhage (ICH), hypertension, diabetes, and renal failure were other independent predictors of the composite thromboembolism endpoint, while thyroid disease (or hyperthyroidism) was not an independent stroke risk factor. C-statistics for the composite thromboembolic endpoint with the $CHADS_2$ and CHA_2DS_2-VASc schemes were 0.66 (0.65–0.66) and 0.67 (0.67–0.68), respectively. On multivariable analysis, age, prior ischaemic stroke or thromboembolism, prior major bleeding events, and hypertension were significant predictors of ICH and major bleeding. Heart failure, diabetes, renal failure, liver disease, anaemia or platelet/coagulation defect, alcohol abuse, and cancer were other significant predictors for major bleeding, but not ICH. The ability for predicting ICH and major bleeding with both bleeding risk schemes ($HEMORR_2HAGES$, HAS-BLED) were similar, with c-statistics of ~0.6.

Conclusion Several independent risk factors (prior ICH, myocardial infarction, vascular disease, and renal failure) predict ischaemic stroke and/or the composite thromboembolism endpoint in AF, but thyroid disease (or hyperthyroidism) was not an independent risk factor for stroke. There is a better performance for CHA_2DS_2-VASc over $CHADS_2$ schemes for the composite thromboembolism endpoint. While both tested bleeding risk schemes have similar predictive value, the HAS-BLED score has the advantage of simplicity.

Keywords Stroke • Bleeding • Risk assessment • Atrial fibrillation

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Introduction

Atrial fibrillation (AF) is associated with a substantial risk of stroke and thromboembolism. Nonetheless, this risk is not homogeneous and various risk factors have been identified that cumulatively add to stroke risk in AF.[1,2] These risk factors have been formulated into stroke risk stratification schemes.[3]

Over the past 15 years, such risk stratification schemes have had modest predictive value for stroke and thromboembolism, especially if they categorized patients into low, moderate, and high risk strata.[3] One reason for this division was to help clinicians identify the 'high risk' category who could be targeted for warfarin, given its inconvenience and dis-utility. Nonetheless, these risk strata are artificial divisions of a continuous stroke risk burden especially in the presence of multiple stroke risk factors.[3,4] Thus, the recent 2010 European Society of Cardiology (ESC) guidelines de-emphasizes the low/moderate/high risk categories and promotes a risk factor based approach to stroke risk assessment.[4]

To complement the widely used and simple $CHADS_2$ [congestive heart failure, hypertension, age >75 and diabetes (1 point each) and stroke/TIA (2 points)] scheme,[5] the ESC guidelines recommend the use of the new CHA_2DS_2-VASc scheme[4,6] to allow a more comprehensive stroke risk assessment, and to improve our ability to predict the 'truly low risk' subjects with AF, who may not even need antithrombotic therapy. Also, the CHA_2DS_2-VASc scheme categorizes the lowest proportion into the 'intermediate/moderate' risk category where older guidelines recommended 'warfarin or aspirin', hence minimizing therapeutic uncertainty over which to prescribe. Since its original validation,[6–9] the CHA_2DS_2-VASc scheme has been validated in several independent cohorts, including an elderly 'real world' cohort,[7] an anticoagulated trial cohort,[8] and a large general practice prescriptions database cohort.[9] In the latter study of nearly 80 000 AF subjects, the CHA_2DS_2-VASc scheme performed similarly well to the $CHADS_2$ scheme in predicting thromboembolism, but was better than the $CHADS_2$ scheme at identifying 'truly low risk' patients and placed the lowest proportion of subjects into the intermediate/moderate risk category.[9]

Apart from using stroke risk stratification schemes, clinicians also need to assess the bleeding risk, and the new ESC guidelines[4] provide a simple bleeding risk score (HAS-BLED[10]) which is simpler than previously published schemes, only one of which ($HEMORR_2HAGES$[11]) has been derived and validated in an AF cohort. The HAS-BLED scheme has been validated in an European cohort[10] as well as an anticoagulated AF trial cohort,[12] where it performs at least as good as other published bleeding risk stratification schemes, but is much simpler to use. The utility of having comprehensive yet simple stroke and bleeding risk schemes is evident, given the availability of new oral anticoagulant drugs that overcome the dis-utility of warfarin, and if they come in different doses, clinicians could potentially need some help in decision making for whether to prescribe a low or high dose for a particular patient, subject to validation studies of these new scores in patients treated with the new drugs.[13]

The objective of this study is to investigate risk factors for stroke and bleeding, and application of the CHA_2DS_2-VASc and HAS-BLED schemes for stroke and bleeding risk assessments, respectively (as recommended in the ESC guidelines) in a large database of AF patients ($n = 182.678$) prospectively followed up in a nation-wide Swedish AF cohort. These schemes would be compared against other published stroke and bleeding risk schema.

Methods

All individuals with a diagnosis of AF at any Swedish hospital between 1 July 2005 and 31 December 2008 were identified through the Swedish National Hospital Discharge Registry (HDR) by the ICD-10 code I489 with or without any of the specifying subcodes A–F. In this registry, all hospital admissions, and all visits to hospital out-patients clinics, have been recorded for all subjects with a Swedish civic registration number since 1987. Patients with 'silent' AF and patients with AF who were taken care of in the primary care or in other open clinics not affiliated with a hospital during follow-up were not included. From this nationwide registry, we obtained information about current and previous diseases as well as information about stroke, bleedings, and other outcome events that occurred during follow-up. The codes we used for definition of diseases are specified in the Supplementary material online, *Table S2*. The validity of the registry has been evaluated repeatedly and is considered to be well suited for epidemiological studies by the National Board of Health and Welfare.[14,15]

We identified 182 678 unique individuals (2% of the Swedish population) who had a diagnosis of AF during the 3.5 years we studied. The median duration of follow-up, which ended 31 December 2008 was 1.4 years (interquartile range 1.8 years). We excluded 7167 patients who died in conjunction with the index generating hospital contact, 528 patients with valvular AF due to mitral stenosis, and 5112 patients who had undergone valvular surgery. Information about medication was obtained from the National Prescribed Drugs Registry. Medication at baseline was defined as a drug that had been collected at a pharmacy within ± 3 months of the index date.

We made separate analyses according to whether the patient had been exposed to oral anticoagulation or not. Warfarin is the only registered oral anticoagulant in Sweden, with a minority of patients using Marcoumar (phenprocoumon) which is available on license. From the drug registry, it was easy to identify patients who never had warfarin prescribed during follow-up. It was, however, more difficult to identify patients who used warfarin continuously during follow-up because doses vary widely between individuals and over time. We therefore decided that the warfarin-treated group should be represented by patients who took warfarin at baseline, bearing in mind that the reported discontinuation rates among warfarin-treated patients are high[16] and that many patients in this group may not actually had warfarin during the remainder of the follow-up period.

The index date was defined as the date of the first occurrence of the patient with a diagnosis of AF (ICD-10 code I489) after 1 July 2005. For the registration of events during follow-up, we applied a 'blanking period' of 14 days after index. This was because transfers between hospitals and clinics were common and early re-appearances of a diagnosis often were intimately related to a preceding hospital period, for example, a new code for an event that had been registered at another clinic a few days earlier. Also, events that occurred within the first 14 days of the index date were not counted as events during follow-up because they were most likely diagnoses given at discharge of a hospital period that started with an event, which in itself would have been a much more severe limitation for this analysis. Diagnoses that were given on the index date and up to 2 weeks after that date were considered reflecting comorbidity and were not counted as endpoints during the follow-up period. 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 endpoint for that follow-up.

Endpoints

In this study, we relied on diagnoses given at hospital discharge. As definitions, we have used the appropriate ICD-10 codes which are listed in the Supplementary material online, *Table S2*. The validity of diagnoses in the Swedish Hospital Discharge registry has been evaluated for some diagnoses, like myocardial infarction where it has been found to be good. For the endpoints of thromboembolism, we used *ischaemic stroke* (ICD-10 code I63), and a composite thromboembolism endpoint of 'ischaemic stroke, unspecified stroke, TIA, and systemic embolism' (I63–64, G45, I74). The primary bleeding endpoint of interest was intracranial haemorrhage (ICH) (I60–62), although data on major bleeding including all intracranial bleeds, all gastrointestinal bleeds, and diagnosis for anaemia secondary to bleeding were also analysed (see Supplementary material online, *Table S2* for the specific ICD-codes used).

Definition of stroke and bleeding risk schemes

The various stroke risk schema compared and/or validated in this cohort are summarized in Supplementary material online, *Table S2*. While the primary focus was a comparison of $CHADS_2$[5] and CHA_2DS_2-VASc, we also compared these two schemes with the schemes published by the AF Investigators,[17] Stroke Prevention in AF (SPAF) Investigators,[18] the 2006 American College of Cardiology/American Heart Association/ European Society of Cardiology (ACC/AHA/ESC) guidelines,[19] Framingham,[20] and the National Institute for Health and Clinical Excellence (NICE).[21] The Framingham, $CHADS_2$, and CHA_2DS_2-VASc schemes are point-based scores, with the Framingham one based on a mathematical formula.[20]

In order to compare their predictive ability with other schemes for distinguishing low, intermediate, and high risk, we categorized the scores into three groups. We defined the $CHADS_2$ score in two ways: (i) classical, whereby scores of 0: low, 1–2: intermediate, >2: high risk; or (ii) revised, whereby scores of 0: low, 1: intermediate, ≥2: high risk. We categorized the Framingham score in a similar manner to that proposed by Fang *et al.*,[22] as follows: score 0–7: low, 8–15: intermediate, 16–31: high risk. In addition to these categorized definitions (commonly used in clinical practice), the Framingham, $CHADS_2$, and CHA_2DS_2-VASc scores were also tested (perhaps more appropriately) as continuous variables.

Components of the $CHADS_2$ score were defined by age at inclusion, a diagnosis of heart failure (I50), hypertension (I10–15), diabetes mellitus (E10–14) and previous ischaemic stroke (I63), unspecified stroke (I64), TIA (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, sex and vascular disease (prior myocardial infarction, peripheral arterial disease; I21, I252, I70–73).

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 the Supplementary material online, *Table S2*. We only used those risk factors that were available to us, and thus, the maximal HAS-BLED score in this study was seven rather than nine as we did not include the 'labile INR' (which only applies if the patient were taking warfarin) and we know nothing about genetic factors for the $HEMORR_2HAGES$ score as genetic factors are not commonly tested in 'real world' cohorts. The last letter of HAS-BLED stands for drugs or alcohol abuse. Drugs of interest are such that may lead to bleeding, such as aspirin, clopidogrel, or NSAIDs, but we had no information about the use of NSAID which is often intermittent and difficult to adjust for. We used information about aspirin, clopidogrel, and similar from the national prescribed drug registry. As definition of alcohol abuse, an area from which is particularly difficult to obtain reliable information, we used the same collection of diagnostic codes as the Swedish Board of Health of Welfare uses for accounts of alcohol-related deaths ('alcohol index'). Thus, we are essentially testing a 'modified HAS-BLED' and 'modified $HEMORR_2HAGES$' score, similar to other studies relying on large 'real world' administrative data set cohorts.

Statistical methods

For survival analyses, we used multivariable Cox regression. Age was used as a categorical variable when presented in the tables for the sake of comprehensiveness, but otherwise used as a continuous variable in the analyses. The negative predictive value (NPV) was calculated as the number of patients classified as 'low risk' who did not have an event during follow-up divided by the total number of patients classified as low risk. We did not calculate the positive predictive value (PPV) which would have been appropriate if the aim with the 'high risk' categorization was to identify patients truly expected to have a thromboembolism. Indeed, many patients with AF are treated with anticoagulation even if it is known that most of them would not have had a thromboembolic event, even in the absence of warfarin treatment, and hence the PPV will be (very) low for all schemes.

Our strategy for the multivariable analyses was to start with simple adjustment for age and sex. Factors that were associated with outcome after this simple adjustment were used in a conditional forward Cox procedure. The threshold for entry was 0.05 and for removal, this was 0.10. Factors that remained significantly associated with the outcome were retained for the final model to which remaining factors were added one at a time at the last step. Overlapping diagnoses, or otherwise obviously interdependent covariates, were not used simultaneously in any of the analyses.

In order to quantify the predictive validity of the different stroke and bleeding risk classification schemes, we also calculated the c-statistic which quantifies discriminant ability and is a measure of the area under the receiver–operator characteristic curve, and tested the hypothesis that these schemes performed significantly better than chance (indicated by a c-statistic ≥0.5). To this end, we also calculated the net reclassification improvement (NRI) from switching from older risk stratification schemes to CHA_2DS_2-VASc. We used categorical NRIs, whereby cut-points were 'low risk' vs. 'intermediate or high risk' for the respective schemes. This was because the aim was to achieve better identification of true 'low risk' patients.

Confidence intervals (CI) were 95%. *P*-values < 0.05 were considered significant. All tests were two-sided. All analyses were performed in PASW 18.0 (IBM SPSS Statistics, IBM Corporation, Route 100, Somers, NY 10589, USA).

Results

We studied 182 678 subjects with AF, of which 170 291 (mean age 76.2 years, 53% male) fulfilled our criteria of non-valvular AF and survival of the first 14 days after index date and were prospectively followed for an average of 1.5 years (259 798 years at risk). Of these patients, 90 490 (53%) never used warfarin, and 68 307 (40%) had warfarin at index. There were another 12 498 patients without warfarin at baseline who began to use warfarin during

follow-up and 3956 patients with warfarin at baseline who stopped taking it during follow-up. Patient demographic features are summarized in Supplementary material online, *Table S1*. All analyses, except for those related to bleeding risk schemes, only considered those without warfarin use (n=90 490).

Risk factors for ischaemic stroke

There was a clear age-related increase in the risk of ischaemic stroke, not only at ages ≥75 years [hazard ratio (HR) 5.49 (4.63–6.52)], but also for patients aged 65–74 years [HR 3.07 (2.55–3.71)] (*Table 1*). On multivariable analysis, significant associations were found with prior ischaemic stroke [HR 3.13 (2.96–3.32)], hypertension [HR 1.19 (1.12–1.25)], diabetes mellitus [HR 1.19 (1.11–1.27)], female gender [HR 1.21 (1.14–1.28)], and vascular disease [HR 1.07 (1.01–1.14)]. We also found an association between ischaemic stroke and a history of prior ICH [HR 1.51 (1.32–1.72)].

A history of heart failure, thyroid disease (or of current hyperthyroidism), obesity, and chronic lung disease were not independent stroke risk factors on multivariate analysis (*Table 1*).

Risk factors for the composite thromboembolism endpoint

The risk factors that showed a significant association with the outcome were virtually the same irrespective of whether that outcome was ischaemic stroke alone, or the composite endpoint that also included unspecified stroke, TIA and systemic embolism (*Table 1*). The only difference was that renal failure showed a significant association with the composite endpoint but not with ischaemic stroke alone.

Stroke risk assessment

In the 90 490 patients without warfarin throughout follow-up, there was a clear increase in ischaemic stroke or the composite thromboembolism endpoint with increasing $CHADS_2$ and CHA_2DS_2-VASc score (*Table 2*). The adjusted composite thromboembolism endpoint rate for subjects with a $CHADS_2$ score 1 was 4.9%, while for a CHA_2DS_2-VASc score 1, the rate was only 0.9%.

Event rates in relation to low, moderate, and high risk strata are shown in *Table 3*. Those classified as 'low risk' using the AF Investigators, NICE, and CHA_2DS_2-VASc were 'truly low risk' with a composite thromboembolism endpoint event rate of 0.3% per year, in comparison to $CHADS_2$ (0.9%) and SPAF (2.3%). The NPV of being classified as belonging to a 'low risk group' was very high for all schemes with NPVs around 0.99.

The ability to predict ischaemic stroke in relation to different stroke risk stratification schemes is shown in *Table 4*. Most of the schema had broadly similar c-statistics for the composite thromboembolism endpoint, ranging between 0.59 (AF Investigators) and 0.67 (CHA_2DS_2-VASc). The c-statistics for predicting the composite thromboembolic endpoint of 'stroke/TIA/systemic emboli' with the $CHADS_2$ and CHA_2DS_2-VASc scores were 0.66 (95%CI 0.65–0.66) and 0.67(0.67–0.68), respectively—with no overlap in their 95% CIs.

All schemes had high sensitivity to detect patients at risk (range 0.89–1.00), but the specificity was low in all schemes (range 0.09–0.30). Analysis of NRI from switching to CHA_2DS_2-VASc showed no significant change. When sensitivity increased, specificity decreased by approximately the same amount.

Bleeding risk factors

In the 90 490 patients without anticoagulant treatment during follow-up, there was a clear age-related increase in the risk of ICH and major bleeding, with the highest risk at age ≥75 (*Table 5*). Prior ischaemic stroke or thromboembolism, prior major bleeding events (ICH or severe bleeding), and hypertension were other significant predictors of ICH and major bleeding. Heart failure, diabetes, renal failure, liver disease, anaemia or platelet/coagulation defect, alcohol abuse, and cancer were significant predictors for major bleeding, but not for ICH (*Table 5*). Female gender, myocardial infarction, vascular disease, diabetes, obesity, thyroid disease, accidental falls (≥2 hospitalizations), and aspirin use were not significant predictors.

Bleeding risk assessment

In the whole cohort, 1600 (0.6/100 years at risk) intracranial bleeds and 5810 (2.3/100 years at risk) major bleeding events occurred. The rates were not higher when subjects were taking aspirin compared with no antithrombotic therapy. Bleeding risk increased with increasing HAS-BLED and $HEMORR_2HAGES$ scores, irrespective of background 'on treatment' therapy with aspirin, OAC, both OAC plus aspirin, or if the patient was untreated (i.e. no antithrombotic therapy) (*Table 6*). Major bleeding rates with OAC, aspirin, combination OAC plus aspirin, and 'no therapy' were 1.9, 2.7, 2.1, and 2.3/100 years at risk.

The ability for predicting ICH and major bleeding with both bleeding risk schema were similar (~0.6), although c-statistics were lower in aspirin and OAC users compared with those taking neither aspirin nor OAC (*Table 7*).

Discussion

With data on 182 678 AF patients, this is the largest published 'real world' data set of prospectively collected nation-wide cohort data on AF patients in relation to stroke and bleeding outcomes. We extend previous work[1,2] by demonstrating the importance of multivariate analysis of several independent risk factors for ischaemic stroke and/or the composite thromboembolism endpoint (ischaemic stroke, TIA, and systemic embolism) in AF that is not included in the $CHADS_2$ score (that is, prior ICH, myocardial infarction, vascular disease, and renal failure). We also show that thyroid disease was *not* an independent risk factor, despite uncertainties on its status as a stroke risk factor in previous small series. We also extend previous work[5–9,22] by presenting separate data for ischaemic stroke and the composite thromboembolism endpoint in comparing the various published stroke risk stratification schemes, with a marginally better performance for CHA_2DS_2-VASc over $CHADS_2$ for the composite thromboembolism endpoint, and confirming that a CHA_2DS_2-VASc score 0 is 'truly low risk'. Finally, we extend previous studies[10,12] by separately relating HAS-BLED and

Table 1 Associations between baseline factors and stroke and systemic embolism in patients without anticoagulant treatment ($n=90\,490$)

	Ischaemic stroke					Stroke/TIA/systemic emboli				
	Number with event	Univariable		Multivariable		Number with event	Univariable		Multivariable	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Age										
<65 years	142	Reference		Reference		202	Reference		Reference	
65–74 years	522	3.95	3.28–4.75	3.07	2.55–3.71	711	3.80	3.25–4.44	2.97	2.54–0.348
≥75 years	4.665	8.32	7.04–9.83	5.49	4.63–6.52	6.421	8.14	7.7–9.36	5.28	4.57–6.09
Women	3.226	1.51	1.43–1.60	1.21	1.14–1.28	4.376	1.46	1.39–1.53	1.17	1.11–1.22
Embolic events										
Ischaemic stroke	2.076	4.00	3.78–4.22	3.13	2.96–3.32	2.656	3.61	3.44–3.78	2.81	2.68–2.95
Stroke, unspecified	276	2.27	2.01–2.56	1.79	1.58–2.02	430	2.65	2.41–2.92	2.08	1.88–2.29
TIA	546	2.05	1.88–2.24	1.59	1.45–1.73	825	2.34	2.18–2.52	1.80	1.68–1.94
Systemic emboli	113	2.57	2.14–3.10	1.96	1.62–2.37	176	3.01	2.59–3.49	2.18	1.87–2.54
Any embolic event	2.519	3.81	3.61–4.02	2.96	2.80–3.13	3.383	3.71	3.54–3.89	2.87	2.74–3.01
Bleeding events										
Intracranial bleeding	224	1.78	1.56–2.03	1.51	1.32–1.72	311	1.82	1.62–2.04	1.49	1.33–1.67
Gastric/duodenal bleeding	269	1.18	1.05–1.34	1.09	0.96–1.24	380	1.22	1.10–1.35	1.07	0.96–1.18
Any significant bleeding	581	1.32	1.21–1.44	1.18	1.07–1.29	817	1.36	1.26–1.46	1.14	1.06–1.23
Atherosclerotic disease										
Myocardial infarction	1.261	1.24	1.17–1.33	1.05	0.98–1.12	1.781	1.29	1.22–1.36	1.09	1.03–1.15
Ischaemic heart disease	2.002	1.17	1.11–1.23	0.96	0.90–1.01	2.844	1.23	1.18–1.29	1.00	0.96–1.05
PCI procedure	246	0.95	0.83–1.08	1.15	1.01–1.30	326	0.91	0.81–1.02	1.11	0.99–1.24
CABG procedure	217	1.12	0.98–1.28	1.16	1.01–1.34	306	1.15	1.03–1.29	1.19	1.06–1.33
Peripheral arterial disease	366	1.37	1.23–1.52	1.18	1.06–1.31	552	1.52	1.39–1.65	1.22	1.12–1.32
Vascular disease	1.489	1.27	1.20–1.35	1.07	1.01–1.14	2.127	1.35	1.28–1.42	1.14	1.06–1.23
Heart failure	1.905	1.28	1.21–1.35	0.98	0.92–1.04	2.678	1.32	1.26–1.39	0.98	0.93–1.03
Hypertension	2.724	1.51	1.43–1.59	1.19	1.12–1.25	3.720	1.49	1.43–1.56	1.17	1.11–1.22
Diabetes mellitus	1.070	1.34	1.25–1.43	1.19	1.11–1.27	1.476	1.35	1.27–1.43	1.19	1.13–1.26
Obesity	31	0.56	0.39–0.80	0.80	0.56–1.14	44	0.58	0.43–0.77	0.82	0.61–1.11
Renal failure	300	1.19	1.06–1.33	1.11	0.99–1.25	445	1.29	1.17–1.42	1.16	1.05–1.28
Thyroid										
Thyroid disease	380	1.13	1.02–1.25	0.95	0.85–1.05	553	1.21	1.11–1.31	1.00	0.92–1.09
Thyrotoxicosis	55	0.96	0.73–1.25	0.92	0.70–1.19	84	1.07	0.86–1.32	1.03	0.83–1.28
Lungs										
Chronic obstructive pulmonary disease/ emphysema	373	0.93	0.84–1.04	0.97	0.88–1.08	561	1.03	0.94–1.12	1.05	0.96–1.15
Pulmonary embolism	78	1.06	0.85–1.33	0.93	0.74–1.16	113	1.12	0.93–1.35	0.94	0.78–1.13
Acetylsalicylic acid at index	4.202	1.80	1.68–1.92	1.26	1.18–1.34	5.706	1.70	1.60–1.79	1.18	1.11–1.25

Hazard ratios compared with the absence of cofactor.

HEMORR$_2$HAGES to ICH and major bleeding events and show that the predictive ability with both bleeding risk schema were similar (and modest), although HAS-BLED clearly has the advantage of simplicity.

Stroke risk

In the present analysis, a history of heart failure did not appear to increase the risk of ischaemic stroke or the composite thromboembolism endpoint. This is consistent with the conclusions of the stroke in

Table 2 Stroke or thromboembolism/100 years at risk in relation to $CHADS_2$ and CHA_2DS_2-VASc scores in 90 490 patients without warfarin throughout follow-up

	n	Ischaemic stroke		Stroke/TIA/peripheral emboli	
		Unadjusted	Adjusted for Aspirin[a]	Unadjusted	Adjusted for aspirin[a]
$CHADS_2$ score					
0	13 258	0.6	0.6	0.9	0.9
1	23 041	3.0	3.4	4.3	4.9
2	25 813	4.2	4.7	6.1	6.8
3	15 527	7.1	8.0	9.9	11.1
4	8767	11.1	12.6	14.9	16.8
5	3315	12.5	14.1	16.7	18.9
6	769	13.0	14.6	17.2	19.4
CHA_2DS_2-VASc score					
0	5343	0.2	0.2	0.3	0.3
1	6770	0.6	0.6	0.9	1.0
2	11 240	2.2	2.5	2.9	3.3
3	17 689	3.2	3.7	4.6	5.3
4	19 091	4.8	5.5	6.7	7.8
5	14 488	7.2	8.4	10.0	11.7
6	9577	9.7	11.4	13.6	15.9
7	4465	11.2	13.1	15.7	18.4
8	1559	10.8	12.6	15.2	17.9
9	268	12.23	14.4	17.4	20.3
All	90 490	4.5	5.0	6.2	7.0

[a]Adjustment made for exposure to aspirin treatment, assuming that aspirin provides a 22% reduction in TE risk, to give an indication of 'untreated' rates. For abbreviations and details on risk schema, see text.

Table 3 Event rates/100 years at risk in 90 490 patients without warfarin throughout follow-up in relation to categorical risk score schemes

	Year	Ischaemic stroke				Stroke/TIA/systemic emboli			
		Low	Intermediate	High	Negative predictive value for low risk	Low	Intermediate	High	Negative predictive value for low risk
AFI	1994	0.2	3.0	5.8	0.996	0.3	4.1	8.2	0.994
SPAF	1999	1.6	1.6	6.8	0.990	2.3	2.4	9.5	0.967
$CHADS_2$ classic	2001	0.6	3.6	9.0	0.990	0.9	5.2	12.3	0.986
$CHADS_2$ revised		0.6	3.0	6.6	0.990	0.9	4.3	9.1	0.986
Framingham	2003	1.2	4.2	8.5	0.981	1.8	5.9	11.8	0.973
NICE	2006	0.2	2.2	6.4	0.997	0.3	0.5	9.0	0.995
ACC/AHA/ESC	2006	0.6	2.8	6.6	0.991	0.8	3.9	9.2	0.987
CHA_2DS_2-VASC	2009	0.2	0.6	6.2	0.997	0.3	1.0	8.9	0.996

AF Working Group,[1] although systolic impairment is a clear risk factor for stroke and thromboembolism.[23] Thus, the ESC guidelines emphasize 'systolic heart failure' as a stroke risk factor, as many patients labelled with a 'history of heart failure' do not actually have systolic impairment[24] and the stroke risk of heart failure with preserved ejection fraction is unclear,[25] although it does predispose to AF and is associated with many stroke risk factors, such as hypertension. Unfortunately, we did not have access to data on LV function and thus, did not include left ventricular dysfunction (EF< 35%) in our definition of heart failure (e.g. systolic heart failure).

In the present analysis, we confirm other smaller cohort studies showing that myocardial infarction and vascular disease were

Table 4 Predictive ability of different risk stratification schemes, as expressed by the c-statistic, in patients without anticoagulant treatment throughout follow-up ($n = 90\,490$)

	Ischaemic stroke					Stroke/TIA/systemic emboli				
	C-statistic	95% CI	Sensitivity	Specificity	NRI	C-statistic	95% CI	Sensitivity	Specificity	NRI
CHA_2DS_2-VASc (cont.)	0.67	0.66–0.68	–	–	–	0.67	0.67–0.68	–	–	–
CHA_2DS_2-VASc	0.56	0.56–0.57	1.00	0.06	Ref	0.56	0.56–0.57	1.00	0.07	Ref
$CHADS_2$ (cont.)	0.66	0.66–0.67	–	–	–	0.66	0.65–0.66	–	–	–
$CHADS_2$ revised	0.62	0.61–0.62	0.98	0.15	0.07	0.61	0.61–0.62	0.97	0.16	0.07
$CHADS_2$ classic	0.65	0.64–0.65	0.98	0.15	0.07	0.64	0.64–0.65	0.97	0.16	0.07
Framingham (cont.)	0.67	0.66–0.68	–	–	–	0.67	0.66–0.67	–	–	–
Framingham	0.64	0.64–0.65	0.92	0.26	0.12	0.64	0.64–0.65	0.92	0.26	0.12
SPAF 1999	0.63	0.62–0.64	0.89	0.29	0.12	0.63	0.62–0.64	0.89	0.30	0.13
ACC/AHA/ESC 2006	0.62	0.61–0.62	0.98	0.15	0.07	0.62	0.61–0.62	0.98	0.16	0.08
NICE 2006	0.61	0.60–0.62	1.00	0.09	0.00	0.61	0.61–0.62	1.00	0.09	0.03
AFI 1994	0.58	0.58–0.59	0.99	0.09	0.00	0.59	0.58–0.59	0.99	0.10	0.03

NRI, net reclassification improvement from switch to CHA_2DS_2-VASc. Cut-points were 'low risk' vs. 'intermediate or high risk'. For details on risk schema, see text. In the Framingham system, differentiated scores were given according to blood pressure levels. Lacking information about actual blood pressure readings, we assigned patients with a hospital diagnosis of hypertension 3 points in the Framingham scheme, corresponding to a systolic blood pressure between 160 and 179 mmHg.

independent predictors for the composite thromboembolism endpoint.[26,27] However, coronary artery disease was not found to be a stroke risk factor in the stroke in AF Working Group analysis,[1] perhaps given the incomplete recording of this risk factor in the historical clinical trials. However, complex aortic plaque on the descending aorta is an independent predictor of ischaemic stroke[28] and symptomatic angina was an independent predictor of ischaemic stroke in the Veterans study.[29] In the systematic review conducted as part of the NICE guidelines, myocardial infarction was found to be a predictor of thromboembolism, and 'vascular disease' (including previous myocardial infarction) is one of the stated risk factors in the NICE schema.[2,21] In a recent analysis of an anticoagulated AF cohort, coronary artery disease was an independent risk factor for stroke and systemic embolism on multivariate analysis.[8] Nonetheless, the possibility remains that some strokes in patients with vascular disease may have a different pathophysiological mechanism than intra-cardiac emboli from AF, and may respond differently to treatment.

We also found that renal failure was an independent predictor for the composite thromboembolism endpoint, consistent with some cohort studies,[30] but given that such patients are not only at high risk of stroke and thromboembolism, they are also at high risk of death, myocardial infarction, and bleeding, and—importantly—have not been studied in randomized trials.[31] One recent cohort study even reported an increased risk of stroke in AF patients with severe renal impairment who were anticoagulated with warfarin.[32] Patients with borderline renal impairment are also problematic, given that renal function may deteriorate over time in (elderly) AF patients with multiple comorbidities and polypharmacy.[31]

Interestingly, thyroid disease was not an independent predictor for ischaemic stroke or the composite thromboembolism endpoint, and is consistent with the conflicting data with thyroid disease from small series.[33] While 'thyroid disease' was listed as a 'less validated or weaker' risk factor in the 2006 ACC/AHA/ESC guidelines,[19] the inconsistency of the literature would suggest that patients with thyroid disease are at risk of stroke or thromboembolism, only in association with other stroke risk factors.[4]

While $CHADS_2$ and CHA_2DS_2-VASc have broadly similar c-statistics, CHA_2DS_2-VASc is more inclusive of 'stroke risk modifier' risk factors and would lead to a recommendation for anticoagulation rather than antiplatelet therapy.[4] Indeed, the CHA_2DS_2-VASc score is good at identifying 'truly low risk' subjects, along with the NICE and the AF Investigators risk stratification schemes.[9]

Bleeding risk

Prior ischaemic stroke or thromboembolism, prior major bleeding events (ICH or severe bleeding), and hypertension were other significant predictors of ICH and major bleeding, while heart failure, diabetes, renal failure, liver disease, anaemia or platelet/coagulation defect, alcohol abuse, and cancer were significant predictors for major bleeding, but not ICH. Many of these risk factors are incorporated into the new HAS-BLED bleeding risk score,[10] which is recommended in the ESC guidelines.[4]

In the present cohort, we report an overall major bleeding rate with warfarin at baseline of 1.9/100 years at risk and ICH rate of 0.6/100 years at risk, which are figures broadly comparable to those seen in the RE-LY trial.[34] Our analysis suggests that in subjects with a HAS-BLED score of >3, ICH and major bleeding rates rise markedly, irrespective of background antithrombotic drug usage or non-use. Any severe bleeding is a more substantial risk factor for ICH than other types of major bleeding, as this definition includes previous ICH. Of note, the ESC guidelines recommend that in those with a HAS-BLED score of ≥ 3, 'caution and/or

Table 5 Associations between baseline factors and bleeding events in 90 490 patients without anticoagulant treatment during follow-up

	Number with event	Intracranial bleeding				Number with event	Major bleeding			
		Univariable		Multivariable			Univariable		Multivariable	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Age										
<65 years	56	Reference		Reference		181	Reference		Reference	
65–74 years	122	2.30	1.68–3.16	1.97	1.43–2.71	446	2.63	2.21–3.12	2.33	1.96–2.77
≥75 years	610	2.67	2.03–3.51	2.43	1.84–3.22	2.622	3.30	3.10–4.19	3.28	2.80–3.83
Women	348	0.77	0.67–0.89	0.70	0.61–0.81	1.554	0.89	0.83–0.96	0.79	0.73–0.85
Embolic events										
Ischaemic stroke	173	1.64	1.39–1.94	1.21	1.02–1.44	621	1.39	1.27–1.52	1.14	1.04–1.24
Unspecified stroke	30	1.60	1.11–2.30	1.10	0.77–1.59	101	1.30	1.07–1.59	1.06	0.87–1.29
TIA	64	1.55	1.20–2.00	1.14	0.88–1.48	219	1.27	1.10–1.45	1.01	0.88–1.16
Peripheral systemic embolus	11	1.64	0.90–2.97	1.36	0.75–2.48	46	1.68	1.26–2.25	1.27	0.95–1.70
Any thromboembolic event	229	1.64	1.41–1.91	1.19	1.01–1.39	833	1.39	1.28–1.50	1.11	1.03–1.20
Bleeding events										
Intracranial bleeding	156	10.2	8.59–12.2	8.92	7.45–10.7	216	2.95	2.57–3.39	2.75	2.39–3.16
Gastric/duodenal bleed	34	0.99	0.70–1.40	0.88	0.62–1.24	316	2.44	2.17–2.74	1.70	1.51–1.92
Any severe bleeding	195	3.54	3.02–4.17	3.10	2.64–3.66	747	3.32	3.06–3.60	2.44	2.23–2.67
Athero-sclerotic disease										
Myocardial infarction	150	0.94	0.78–1.12	0.82	0.69–0.99	771	1.24	1.15–1.35	1.02	0.94–1.11
Ischaemic heart disease	–	0.92	0.80–1.07	0.81	0.70–0.95	1.229	1.18	1.10–1.26	0.95	0.88–1.02
PCI procedure	35	0.91	0.65–1.28	0.95	0.68–1.34	133	0.83	0.70–0.99	0.87	0.73–1.03
CABG procedure	29	1.00	0.69–1.44	0.92	0.64–1.34	127	1.06	0.89–1.26	0.92	0.77–1.10
Peripheral arterial disease	43	1.10	0.82–1.47	0.94	0.70–1.26	217	1.34	1.18–1.53	1.07	0.93–1.22
Vascular disease	180	0.96	0.82–1.14	0.84	0.71–1.00	892	1.24	1.15–1.34	1.00	0.92–1.08
Heart failure	252	1.07	0.93–1.25	0.93	0.80–1.09	1.327	1.59	1.48–1.71	1.15	1.07–1.24
Hypertension	408	1.54	1.34–1.77	1.32	1.15–1.52	1.610	1.41	1.32–1.51	1.25	1.16–1.33
Diabetes mellitus	147	1.22	1.02–1.45	1.09	0.91–1.31	595	1.19	1.09–1.30	1.01	0.92–1.11
Obesity	5	0.62	0.26–1.49	0.72	0.30–1.74	36	1.09	0.78–1.51	1.18	0.85–1.64
Renal failure	45	1.20	0.89–1.62	1.05	0.78–1.42	320	2.21	1.97–2.48	1.59	1.41–1.79
Liver disease	12	1.12	0.64–1.99	1.27	0.72–2.24	100	2.35	1.93–2.87	1.80	1.45–2.23
Anaemia	84	0.87	0.69–1.09	0.81	0.64–1.01	776	2.34	2.16–2.54	1.40	1.28–1.53
Platelet or coagulation defect	15	1.55	0.93–2.59	1.19	0.72–1.99	78	2.00	1.60–2.50	1.35	1.08–1.69
Thyroid										
Thyroid disease	48	0.95	0.71–1.28	0.99	0.73–1.33	239	1.17	1.03–1.34	1.11	0.97–1.27
Thyrotoxicosis	6	0.71	0.32–1.57	0.80	0.36–1.78	37	1.06	0.76–1.46	1.11	0.81–1.54
Alcohol abuse	29	0.95	0.65–1.37	1.08	0.74–1.58	192	1.57	1.36–1.82	1.67	1.42–1.96
Frequent falls (≥2 hospitalizations)	103	1.45	1.18–1.78	1.13	0.92–1.40	411	1.40	1.26–1.55	1.01	0.91–1.12
Cancer ≤3 years	96	1.02	0.82–1.26	0.99	0.80–1.23	501	1.35	1.23–1.48	1.15	1.04–1.27
Acetylsalicylic acid at index	556	1.14	0.98–1.33	1.06	0.90–1.24	2.257	1.08	1.01–1.17	1.00	0.92–1.08

Hazard ratios compared with the absence of cofactor.

regular review' of such patients is needed to minimize the risk of complications,[4] and to enable the clinician to think about correctable common bleeding risk factors, for example, uncontrolled blood pressure, labile INRs (if on warfarin, so as to improve time in therapeutic range), concomitant aspirin or NSAID use, etc.

As expected, increasing age was associated with an increased risk for ICH and major bleeding.[35,36] Unexpectedly, aspirin use *per se* was not a predictor of ICH or major bleeding, but the main risk would perhaps be the combined prescription of aspirin plus oral anticoagulation. It is, however, important to note that

Table 6 Bleeds/year at risk in relation to treatment at baseline and risk score according to the HAS-BLED and HEMORR$_2$HAGES schemes

	n	Intracranial bleeding				Major bleeding			
		OAC only (*n*=48 599)	ASA only (*n*=61 396)	OAC+ASA (*n*=17 285)	No prophylaxis (*n*=33 486)	OAC only (*n*=48 599)	ASA only (*n*=61 396)	OAC+ASA (*n*=17 285)	No prophylaxis (*n*=33 486)
HAS-BLED									
0	8919	–	–	–	0.1	–	–	–	0.5
1	34 944	0.2	0.3	0.4	0.5	0.7	1.1	1.2	2.1
2	62 140	0.6	0.5	0.6	0.8	1.9	2.1	1.8	3.6
3	46 417	0.7	0.7	0.9	1.4	2.4	3.1	2.6	5.5
4	15 644	1.2	1.2	1.1	1.1	3.4	4.7	3.5	7.8
5	2069	1.6	1.3	2.8	1.2	5.7	7.0	7.4	9.0
6	152	–	1.8	–	–	15.5	14.5	–	357.1
7	6	–	–	–	–	–	22.8	73.5	–
HEMORR2-HAGES									
0	7922	0.2	0.3	0.3	0.1	0.6	1.0	1.1	0.4
1	52 655	0.5	0.4	0.6	0.4	1.7	1.8	1.6	1.4
2	48 013	0.7	0.7	0.8	0.6	2.2	2.6	2.3	2.8
3	25 017	0.9	0.9	1.1	1.2	3.0	3.7	3.5	4.1
4	9953	1.4	1.3	1.2	1.6	4.4	5.3	3.5	6.1
5	4324	1.8	1.2	2.2	1.1	6.0	7.3	6.7	7.1
6	1745	1.4	1.3	2.0	1.0	7.1	8.2	16.1	8.6
7	574	1.1	0.7	–	1.4	9.6	6.4	–	16.8
8	80	–	–	–	4.0	19.3	14.4	–	8.4
9	8	–	–	–	–	–	–	–	21.1
All	170 291	0.6	0.6	0.7	0.6	1.9	2.7	2.1	2.3

Table 7 Ability to predict bleeding events in two bleeding risk score schemes in relation to treatment (*n*=170 291)

	Medication at index	Intracranial bleed		Major bleed	
		C-statistic	95% CI	C-statistic	95% CI
HAS-BLED	OAC	0.60	0.58–0.62	0.61	0.59–0.62
	ASA	0.58	0.56–0.61	0.59	0.58–0.60
	OAC+ASA	0.58	0.54–0.62	0.57	0.55–0.60
	No prophylaxis	0.64	0.61–0.67	0.66	0.65–0.68
HEMORR$_2$HAGES	OAC	0.62	0.60–0.64	0.63	0.61–0.64
	ASA	0.58	0.55–0.60	0.60	0.59–0.61
	OAC+ASA	0.59	0.55–0.63	0.60	0.57–0.62
	No prophylaxis	0.66	0.63–0.69	0.69	0.67–0.70

OAC, oral anticoagulation therapy; ASA, aspirin.

patients prescribed aspirin rather than warfarin may differ from each other. The aspirin-treated group is heterogenous and consisting both of patients with lone AF, and very elderly patients at high risk both of bleeds and of embolism. Of note, Hart *et al.*[37] reported a 2.4-fold increased risk of ICH by the co-prescription of aspirin plus warfarin. The increased risk of fatal and non-fatal bleeding with combination antiplatelet therapy plus warfarin was also seen in a large Danish cohort of AF patients.[38] Falls may perhaps be an overstated cause of concern, and one decision analysis model suggested that the AF patient would need to fall 295 times per year for the risk of ICH to outweigh the potential beneficial reduction in stroke risk by anticoagulation with warfarin.[39]

Limitations

The main limitations for studying stroke prediction rules in contemporary cohorts of AF patients not on warfarin are the major selection bias for which it can only be partly adjusted, since there will be measured and unmeasured confounders why these patients were not taking warfarin in the first place, for example, more falls and dementia. Similarly, bleeding according to antithrombotic therapy is confounded, since (for example) patients not on aspirin may not be on aspirin due to perceived bleeding risk explaining the lack of higher bleeding on aspirin, and the higher rate of bleeding on aspirin alone than aspirin plus warfarin in this study. Our lack of data on anticoagulation control (e.g. time in therapeutic range, TTR) may well be a limitation but do not feel that our data on bleeding in anticoagulated patients as presented are invalid—our large cohort provides a 'real life' perspective, and in Sweden, it has been well recognized that anticoagulation control is normally very good (e.g. TTRs >75% in recent large clinical trials,[34,40] and in the AURICULA registry, which is a dosing aid for warfarin in Sweden, presently comprising data on >2 million INRs in 76 000 patients).[41] Also, we had incomplete data on NSAID use (although we had data on antiplatelet therapy) and genetic factors, so not all the components of the HAS-BLED and HEMORR$_2$HAGES scores were available. Also, there are no codes in use grading the severity of liver or renal dysfunction—these diagnoses are used in a binomial way, either present or not, and is a limitation. Nonetheless, all these limitations would be intrinsic of any huge 'real world' administrative data sets such as ours, and (for example) previous studies of the HEMORR$_2$HAGES score have not included the 'genetic factor' criterion, nor severity or liver/renal disease.[10,12,42] Indeed, mild liver/renal disease may be under-reported compared with severe forms. As mentioned above, we are also essentially testing a 'modified HAS-BLED' and 'modified HEMORR$_2$HAGES' score, which may reduce the precision of the original risk scores, should every single variable have been included.

This study is also limited by its reliance on a *hospitalizations* database, although many of the endpoints have been subject to validation, especially with respect to other diagnoses such as congestive heart failure and myocardial infarction showing a very good validity.[43,44] However, similar hospital-centred administrative data sets have been used to validate stroke and bleeding risk.[5,11,36] Clearly, our analysis cannot account of all clinical variables, changes in therapy over time, and is reliant upon the accuracy of diagnostic recording. Thus, our data are not useful for estimates of drug discontinuation and switching over time, as patients may have discontinued a drug without our knowing until the patient failed to collect a new drug prescription. In a similarly organized cohort study on AF, the hospital diagnosis for AF was well-validated, whereby evidence for AF was found in 99%.[45] Nonetheless, we were not able to include patients who were managed out of hospital during the entire study period, nor were we able to study patients with undiagnosed silent AF. Although our study comprised ~2% of the Swedish population, the prevalence of AF in Sweden is probably higher than that. It is likely that a hospital-based population may be somewhat older and have more concomitant diseases than patients with undiagnosed AF, or AF entirely managed elsewhere. Indeed, many AF patients are taken care of by the primary care physician and will thus not be included in these data, and thus, the patients in the present study may have greater illness burden than the general AF population.

Another possible limitation is the underreporting of some comorbidities, especially hypertension. Thus, residual confounding may result in potential non-comparability of baseline risk of either stroke/systemic embolism or bleeding in the various treatment groups of patients studied, and the (non-randomized) treatment is at the discretion of the physician, with treatment options altering over time in this 'real world' naturalistic cohort study. Indeed, the patients treated with aspirin at baseline did have a higher risk of ischaemic stroke than patients not treated with aspirin, which suggests either that aspirin causes stroke (possibly haemorrhagic stroke) or that patients placed on aspirin are at *a priori* higher risk of stroke, indicative of some residual confounding. The clinical question is that of risk assessment at a baseline time point for future events, and indeed, we are essentially assessing this aspect on an 'intention to treat' principle in this cohort.

When comparing the different schemes for discriminant ability, we have used the c-statistic, which is regarded as a useful method for classification (diagnostic) purposes in many validation studies,[5–12] but this method does have its limitations.[46] Other methods such as the NRI have been recommended, and we have done so in this study. In the present study, however, the central issue is not a 'reclassification' into high risk, as this merely depends on threshold of stroke risk chosen in comparison with bleeding risk (and would vary with therapeutic advances),[47] and perhaps our focus is more in adequately identifying the '*truly low risk*', and minimizing the proportion classed as a moderate risk.

Conclusion

In conclusion, we demonstrate the independent predictive value of prior ICH, myocardial infarction, vascular disease and renal failure (but not thyroid disease or heart failure) for ischaemic stroke and/or the composite thromboembolism endpoint. The CHA$_2$DS$_2$-VASc score was good at identifying 'truly low risk' subjects, and the HAS-BLED score can be correlated to ICH risk, with a similar predictive ability to older bleeding risk stratification schemes, although HAS-BLED score had the advantage of simplicity.

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Conflict of interest: L.F. is a consultant to Sanofi-Aventis, Boehringer-Ingelheim and BMS. M.R. is a consultant to Sanofi-Aventis and Nycomed, Sweden. He has also been National Coordinator for the RECORD, REALISE, and ARISTOTLE study. He is also member of the steering group for the REALISE study. He has given lectures reimbursed by Sanofi-Aventis and Boehringer Ingelheim. G.Y.H.L. has

received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis. L.F. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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