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Usefulness of the CHA_2DS_2-VASc and HAS-BLED Scores in Predicting the Risk of Stroke Versus Intracranial Bleeding in Patients with Atrial Fibrillation (From the FibStroke Study)

Short title: Risk of Stroke versus Intracranial Bleed

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Abstract

CHA_2DS_2-VASc and HAS-BLED scores stratify the risk of thromboembolic and bleeding events respectively in patients with atrial fibrillation (AF). There is only little information on how they differentiate which of the 2 clinically most important complications (ischemic stroke, IS or an intracranial bleeding, IB) the patient is more prone to suffer. We evaluated both scores in patients suffering either of these major complications. The FibStroke Study collected data on all patients with AF suffering either an ischemic stroke or an intracranial bleeding event between 2003-2012 in 4 Finnish hospital districts. Individual electronic patient records were manually reviewed to collect the study data. To assess the relative risk of IS and IB, an IS/IB-ratio was calculated by dividing the absolute number of ISs with the absolute number of IBs within each score category. A total of 3816 (82.7%) ISs and 798 (17.3%) IBs were detected in 3909 patients. In general, ISs occurred more often than IBs in patients on oral anticoagulation in each score category (ratio 1.6-5.1). The ratio decreased below one, however, only with very high HAS-BLED scores (>4). Moreover, 221 ischemic strokes and 53 intracranial bleeds occurred in patients with HAS-BLED > CHA_2DS_2-VASc, of whom only 19.7% were on anticoagulation. In conclusion, IS was the predominant intracranial event irrespective of CHA_2DS_2-VASc score, HAS-BLED score ≤4, or use of oral anticoagulation, also in patients with low estimated thromboembolic risk (CHA_2DS_2-VASc 0-1). Furthermore, the HAS-BLED score predicted the excess of IBs over ISs only at very high-risk levels.

Key words: Atrial Fibrillation, Ischemic Stroke, Intracranial Bleeding, Risk Score

Ischemic stroke is the most feared complication of atrial fibrillation (AF). Even though two thirds of AF related strokes and thromboembolisms can be prevented with anticoagulation, the increased bleeding risk associated with anticoagulation necessitates careful patient selection[1,2]. Intracranial bleeds associate with high mortality and lifelong morbidity[3]. Several risk stratification tools have been developed to aid in selecting patients with AF for anticoagulation[4-8]. In clinical practice, the most widely used are the CHA_2DS_2-VASc score for stroke prediction and HAS-BLED score for predicting major bleeds[4,6,9,10]. These scores share same risk factors and consequently patients often have high-risk status according to both scores. Therefore, it is of interest how these scores perform in differentiating patients with an ischemic stroke or an intracranial bleeding. It is of clinical importance to evaluate the distribution of major complications in each risk score category especially in high bleeding risk patients[2,10,11]. To date, there are no large-scale studies in terms of number of strokes and intracranial bleedings evaluating the scores in patients on oral anticoagulation (OAC) suffering from either an ischemic stroke or an intracranial bleeding. We sought to evaluate whether CHA_2DS_2-VASc and HAS-BLED scores could differentiate these risks in the large FibStroke study patient cohort

Methods

This study is a pre-specified analysis of the cross-sectional observational multicenter FibStroke-study (www.ClinicalTrials.gov, identifier NCT02146040)[12,13 14]. The study data was collected at 4 hospitals in Finland covering a population of roughly 1.2 million people. All patients with a diagnosis of AF / Atrial flutter (diagnosed before or at the time of the event) and either an ischemic stroke or an intracranial bleeding event between the years 2003–2012 were included. Individual electronic patient records were manually reviewed to collect study data as previously described[14]. Two study groups were defined according to the index event: an ischemic stroke (Ischemic stroke group) or an intracranial bleeding event (Intracranial bleeding

group). All patients with subdural, subarachnoidal or intracerebral bleeding were included in the Intracranial bleeding group. In the supplementary analysis of patients with HAS-BLED > CHA_2DS_2-VASc, bleeding complications were classified as major, clinically significant minor or minor according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions[15].

We analyzed the CHA_2DS_2-VASc (Congestive heart failure; Hypertension; Age ≥75(doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female)) and modified HAS-BLED ((Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly) scores. For this analysis, all patients were assigned 0 points for labile INR risk factor in the modified HAS-BLED score.

The scores were analyzed in both study groups (Ischemic stroke and Intracranial bleeding) with two-sample t-test. Equality of variances was tested with Levene's test, and equal variance for the CHA_2DS_2-VASc score was assumed. For the HAS-BLED risk score, the equality of variances was not assumed according to Levene's test result. The ratio of ischemic strokes to intracranial bleeds was calculated by dividing the absolute number of ischemic strokes with the absolute number of intracranial bleedings. This manuscript was written following STROBE guidelines for the reporting of observational studies[16]. Statistical analyses were performed with SPSS software (version 23.0, SPSS, Inc., Chicago, Illinois).

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institution for Health and Welfare. Informed consent was not required, because of the register-based nature of the study. The study complies with the Declaration of Helsinki as revised in 2002.

Results

A total of 3816 (82.7%) ischemic strokes and 798 (17.3%) intracranial bleedings were recorded in 3909 patients with AF. The use of OAC (99.5% of anticoagulated patients on warfarin, 0.5% on dabigatran) was clearly and logically influenced by both scores; the higher the CHA_2DS_2-VASc score, the more often patients were on OAC, and high HAS-BLED scores were associated with lower rates of OAC use (Figure 1). There were 1545 ischemic strokes and 604 intracranial bleeds in patients on OAC treatment at the time of the event. International normalized ratio (INR) was subtherapeutic (<2.0) in 772 (50.5%) ischemic strokes of warfarin treated patients, whereas 628 (41.0%) strokes occurred while INR was within the target range. A total of 192 (32.8%) intracranial bleeds occurred with INR above the therapeutic range and 297 (50.5%) while within the target range. INR data was missing in 96 (4.5%) events.

Mean CHA_2DS_2-VASc score was slightly higher in patients suffering an ischemic stroke than in patients with an intracranial bleeding (4.16; 95%CI 4.10-4.21 vs. 3.95; 95%CI 3.83-4.07, p=0.002). The mean HAS-BLED score was comparable in patients with an ischemic stroke or an intracranial bleeding (2.50; 95%CI 2.46-2.53 vs. 2.44; 95%CI 2.37-2.51, p=0.18).

The number of ischemic strokes was higher than the number of intracranial bleeds irrespective of CHA_2DS_2-VASc score category in patients on and off OAC. In patients with no OAC, the ratio of ischemic strokes to intracranial bleedings (IS/IB –ratio) increased in line with CHA_2DS_2-VASc score. OAC dramatically reduced the IS/IB –ratio and an increase in ratio was only observed at CHA_2DS_2-VASc score >5 in these patients (Figure 2).

Similarly, there were more ischemic strokes than intracranial bleeds in all HAS-BLED score levels in patients without anticoagulation (Figure 2). The increasing HAS-BLED score decreased the IS/IB –ratio only at very high scores (>4), but the ratio remained as high as 9.1. As expected, in patients on OAC, the IS/IB-ratio was lower (2.4-3.5), but the number of intracranial bleeds exceeded the number of ischemic strokes only at HAS-BLED score >4 (IS/IB –ratio 0.77).

HAS-BLED score was higher than the CHA_2DS_2-VASc score in 263 (6.7%) patients and only 54 (19.7%) of these patients were on OAC. The mean HAS-BLED and CHA_2DS_2-VASc scores of these patients were 2.77 (95%CI 2.62-2.92) and 1.55 (95%CI 1.41-1.69), respectively. There were 221 ischemic strokes and 53 intracranial bleeds in this group. Of the 221 strokes, 32 (14.5%) occurred during OAC and nearly half (46.9%) of these at subtherapeutic INR level. Altogether 22 (41.5%) of the 53 intracranial bleeds occurred on OAC, 16 (30.2%) on aspirin monotherapy, 3 (5.7%) cases on a combination therapy of aspirin and OAC, and 1 (1.9%) event occurred on low molecular weight heparin treatment. In 10 (45.5%) of the anticoagulated patients with an intracranial bleed in this group, INR was above the target level. The IS/IB –ratio in this subgroup was 6.1 (189/31) in patients without anticoagulation and 1.5 (32/22) in patients on warfarin anticoagulation.

In the supplementary analysis of the 263 patients with HAS-BLED > CHA_2DS_2-VASc we found a total of 100 major bleeding events (including the 53 intracranial bleeds) and 18 clinically relevant minor bleeds during the study period in 78 (28.5%) patients. Of the 100 major bleeds, 36 (36.0%) occurred on OAC, 30 (30.0%) on aspirin therapy, 5 (5.0%) on a combination of aspirin and OAC, and 3 (3.0%) patients were on low molecular weight heparin.

Discussion

The present analysis of the large FibStroke patient cohort shows that ischemic stroke is the predominant complication regardless of the CHA_2DS_2-VASc score level also in patients on anticoagulation therapy and even in those with low scores (0-1). Importantly, in the subgroup of patients with HAS-BLED > CHA_2DS_2-VASc, OAC (consisting mainly of warfarin) was seldom used and patients suffered ischemic strokes 4 times more often than intracranial bleeds. Furthermore, a significant proportion of these complications occurred while INR was out of therapeutic range. Notably, intracranial bleeds outweighed ischemic strokes only in patients with HAS-BLED scores >4.

These scores should be used to assess the risk of only 1 of the 2 types of major complications, and are discouraged to be used vice versa[11,17,18]. We decided to evaluate how these scores distinguish the risk of the 2 complications using a large patient cohort suffering either one of these major complications. As most patients fulfill anticoagulation criteria according to current guidelines, the events occurring during OAC were of particular interest. The proportion of anticoagulated patients in our current study patients was low, but comparable to that reported in the large GARFIELD-AF registry[19,20].

The CHA_2DS_2-VASc score was originally developed to perform optimally in identifying patients at low risk for cardioembolic complications i.e. to select patients who do not benefit from OAC[4,17,21]. In this study, ischemic events occurred more often than intracranial bleeds also in low risk categories (0-1). In patients on OAC the IS/IB -ratio was 2.8–fold, whereas in those without OAC it was as high as 5.8-fold. Although stroke is a very rare complication in low risk patients, this finding may imply potential benefit of anticoagulation in this patient subgroup especially in patients with other concomitant risk factors for ischemic events such as smoking, decreased renal function and dyslipidemia.

At CHA_2DS_2-VASc score points 2-5, the IS/IB-ratio was stable and stroke was the predominant complication also during anticoagulation. The risk of strokes in relation to intracranial bleedings increased only at a high (>5) CHA_2DS_2-VASc score level. The above-discussed findings may signal a need for more aggressive stroke prevention in all score levels and especially those with very high CHA_2DS_2-VASc score, even though the means for achieving that are currently scarce.

Our main findings are in line with the data derived from contemporary large randomized controlled trials where the calculated IS/IB-ratios range from 1.63 to 2.87 during anticoagulation[22-25]. However, each of these randomized studies included only < 100 intracranial bleeding events. The present study shows that this risk ratio is almost comparable

throughout the wide spectrum of the absolute risk levels predicted by these scores. Furthermore, randomized trials select patients according to strict exclusion criteria as opposed to our real-life unselected large patient cohort including all strokes and intracranial bleedings (more than 4 600 events) within a population of 1.2 million inhabitants.

The HAS-BLED score stratifies the risk of major bleeding complications during anticoagulation and an increasing score correlates with the risk of intracranial bleeds in warfarin anticoagulated patients[6,17,26]. The European Society of Cardiology 2016 Guideline on Management of Atrial Fibrillation concludes that high bleeding risk score should generally not result in withholding OAC, and the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation suggests closer patient observation (INR monitoring or dose adjustments of OACs) of patients with increased risk of bleeding [9,10]. These principles are supported by the present results, as the net clinical benefit of OAC was negative only in patients with a very high (>4) HAS-BLED score, who were more prone to suffer an intracranial bleeding than an ischemic stroke. Of note, patients with HAS-BLED score >4 have risk factors (such as alcohol consumption, liver disease, prior bleeding, concomitant medication) unique to the bleeding score that are not included in the CHA_2DS_2-VASc score.

The original HAS-BLED publication weighted the risks and benefits of OAC speculating that >10% of major bleeds could be avoided if the principle of withholding OAC therapy from patients with $CHADS_2$-score 1 and HAS-BLED >2 would be respected[6]. This conclusion, however, was based on only 4 major bleeds (out of 33 major bleeds in patients with OAC and $CHADS_2$ ≥1) in patients fulfilling these criteria. In the present study we observed a similar finding regarding intracranial bleeds, but only in patients with a very high (>4) HAS-BLED. Even though, there was a high number of major bleeds in our study patients with HAS-BLED > CHA_2DS_2-VASc, they still suffered more ischemic strokes than intracranial hemorrhages during OAC and the IS/IB –ratio (1.5) was only slightly lower than in patients included in large

randomized studies. Taking this into consideration, denying OAC from all patients with HAS-BLED > CHA_2DS_2-VASc seems not to be justified. For patients with HAS-BLED >4, in addition to correcting all modifiable bleeding risk factors and carefully monitoring INR (patients on warfarin), OAC dose adjustments or even withholding OAC therapy altogether may be justified. Non vitamin K oral anticoagulants provide a more stable and predictable anticoagulation level and carry a lower risk of intracranial bleeding as compared to warfarin[22-25]. Thus non vitamin K oral anticoagulants and left atrial appendage closure offer reasonable alternatives to warfarin anticoagulation in these patients.

Our study has the usual limitations of a retrospective study design. On the other hand, this is a large real-world data including all strokes and intracranial bleeds in a region of 1.2 million people. The data was recorded by the physicians treating the patients, and collected from the electronic patient records by the study personnel. To ensure adequate ischemic stroke diagnosis, in addition to clinical assessment, all patients underwent a head CT or MRI scan. We did not analyze all major bleeds in these patients (except for patients with HAS-BLED > CHA_2DS_2-VASc), which underestimates clinically significant bleedings in our study patients. However, intracranial bleedings have a high mortality rate and they cause the most severe and permanent disabilities of all bleeds outweighing even the effects of an ischemic stroke.

In real-life AF patients, ischemic stroke is the predominant intracranial event irrespective of CHA_2DS_2-VASc score, HAS-BLED score ≤4, or use of OAC. Risk scores predicted the type of intracranial complication only at very high risk levels.

Author contributions

All authors have contributed significantly to the submitted work. KEJA was the head of the research group, and AY, PM and JEKH principal investigators in the other participating centers. KEJA, TOK, IN, JEKH and SJ participated in the design and concept of the study. SJ analyzed

and all authors interpreted the data. SJ wrote the first draft and all other authors reviewed it and provided further contributions and suggestions. All authors have read and approved submission of the manuscript,

Disclosure of conflicts of interest

Samuli Jaakkola: received research grants from the Finnish Foundation for Cardiovascular Research; Clinical Research Fund (EVO) of Turku University Hospital, Turku, Finland, Finnish Cardiac Society. Dr. Kiviniemi has given lectures for Bayer, BMS-Pfizer, MSD, Medicines Company, Astra Zeneca and St. Jude Medical, and received research grants from the Finnish Medical Foundation, the Finnish Foundation for Cardiovascular Research and Finnish Cardiac Society. Dr. Mustonen has given lectures for Orion, Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb, Sanofi-Aventis and Leo Pharma, and has been a member in the advisory boards for Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb and Leo Pharma. Dr. Palomäki has given a lecture for Bayer and MSD. Dr. Juha Hartikainen has received research grants from the Finnish Foundation for Cardiovascular Research and the European Union Seventh Framework Program and Horizon 2020 program, has given lectures for Cardiome, St. Jude Medical and Biotronic, and has been member in the advisory boardsfor Astra Zeneca, Amgen and Bayer. Dr. Päivi Hartikainen has received honoraria from Genzyme, Novartis, Biogen Idec, TEVA, and has given lectures for Sanofi-Aventis. Dr. Airaksinen has received research grants from the Finnish Foundation for Cardiovascular Research, has given lectures for Bayer, Cardiome and Boehringer Ingelheim, and has been a member in the advisory boards for Bayer, Astra Zeneca and Boston Scientific. The other authors report no disclosures.

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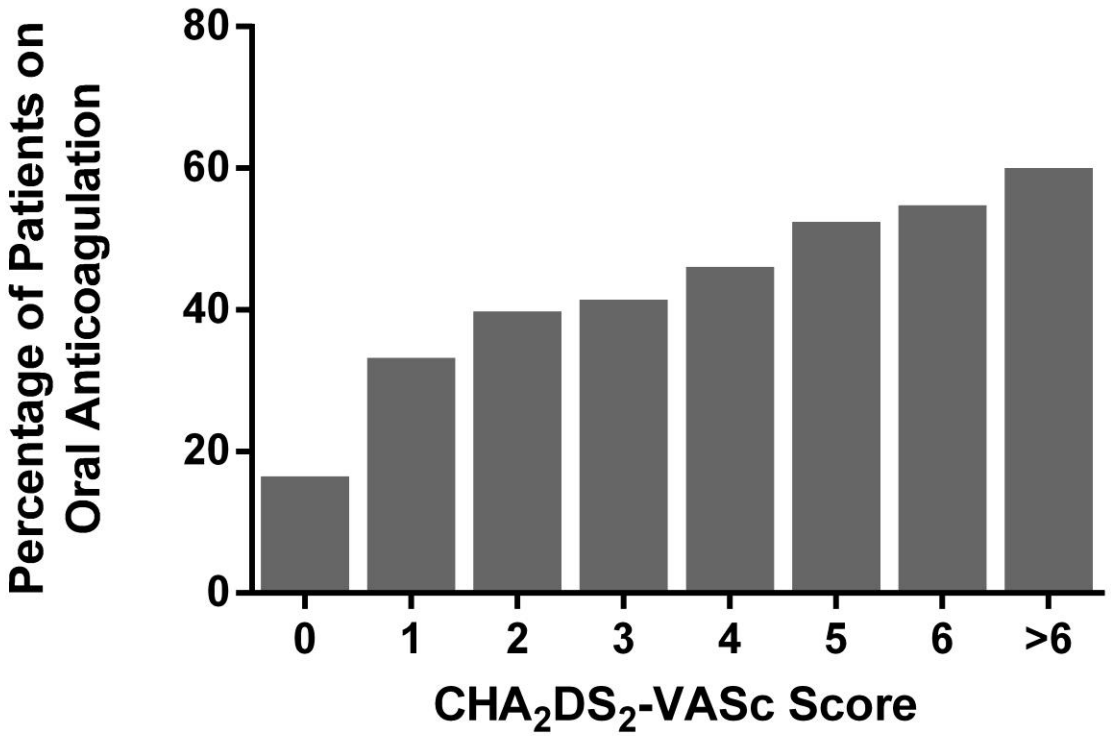
Figure captions:

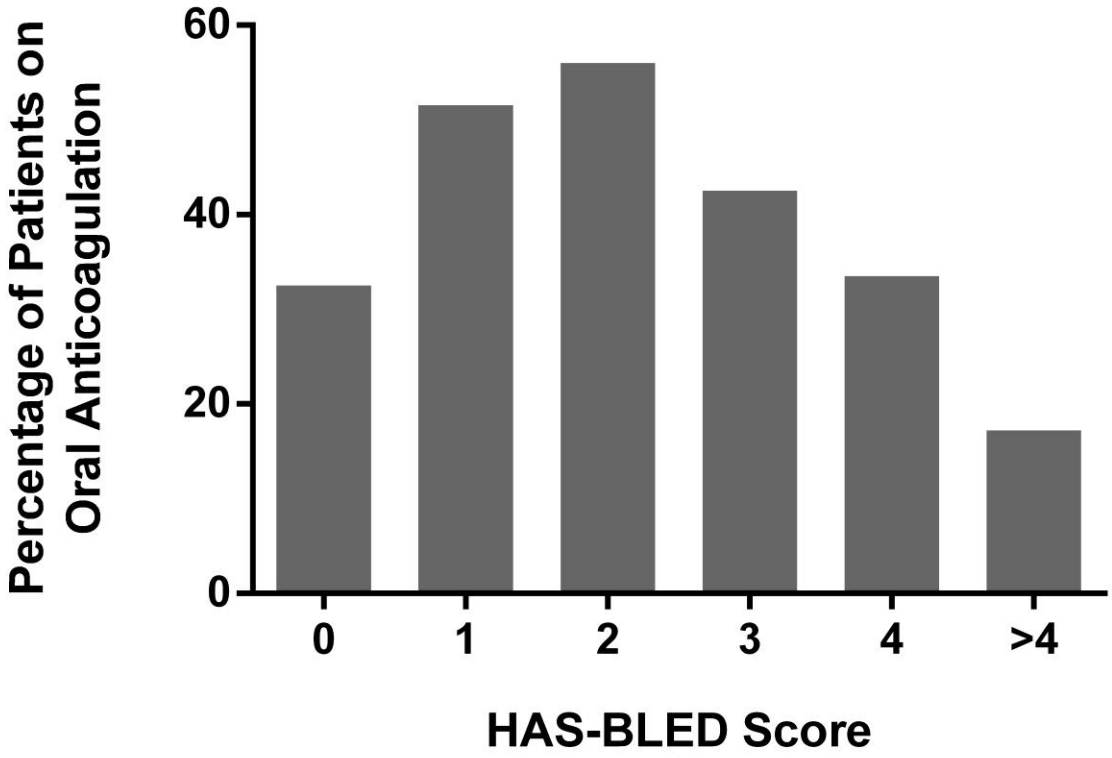
Figure 1 title: Percentage of Patients on Anticoagulation According to CHA_2DS_2-VASc and HAS-BLED Score levels

Figure 1 footnote: CHA_2DS_2-VASc: Congestive heart failure; Hypertension; Age ≥75(doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female)) and modified HAS-BLED: ((Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly). All patients were assigned 0 points for labile INR.

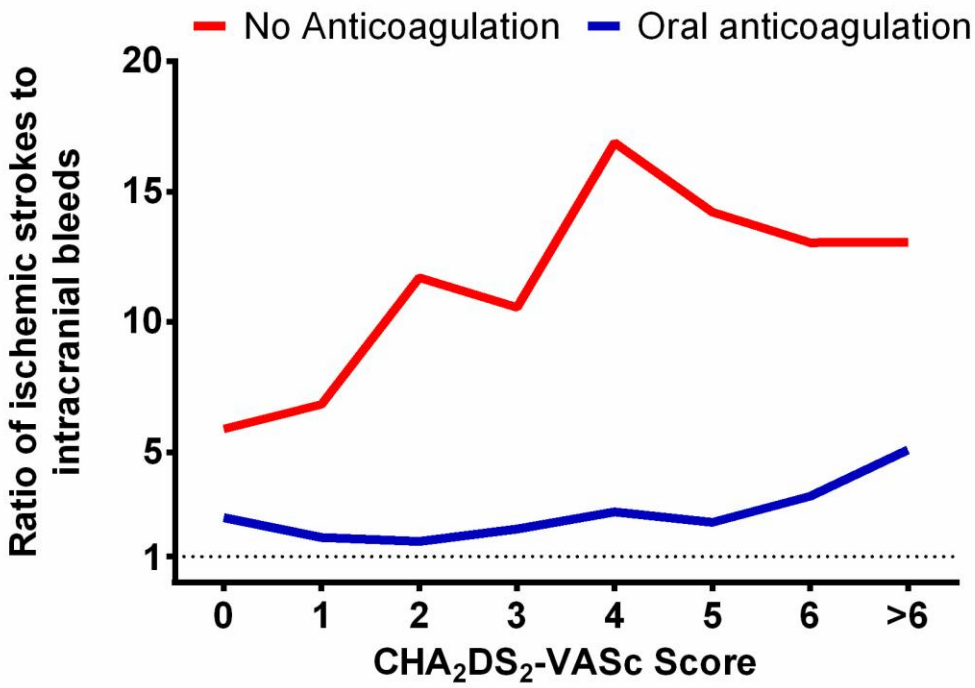
Figure 2 title: Ratio of ischemic strokes to intracranial bleedings according to CHA_2DS_2-VASc and HAS-BLED scores in patients with and without oral anticoagulation.

Figure 2 footnote: CHA_2DS_2-VASc: Congestive heart failure; Hypertension; Age ≥75(doubled); Diabetes mellitus; prior Stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease; Age 65 to 74; Sex category (female)) and modified HAS-BLED: ((Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly). All patients were assigned 0 points for labile INR.

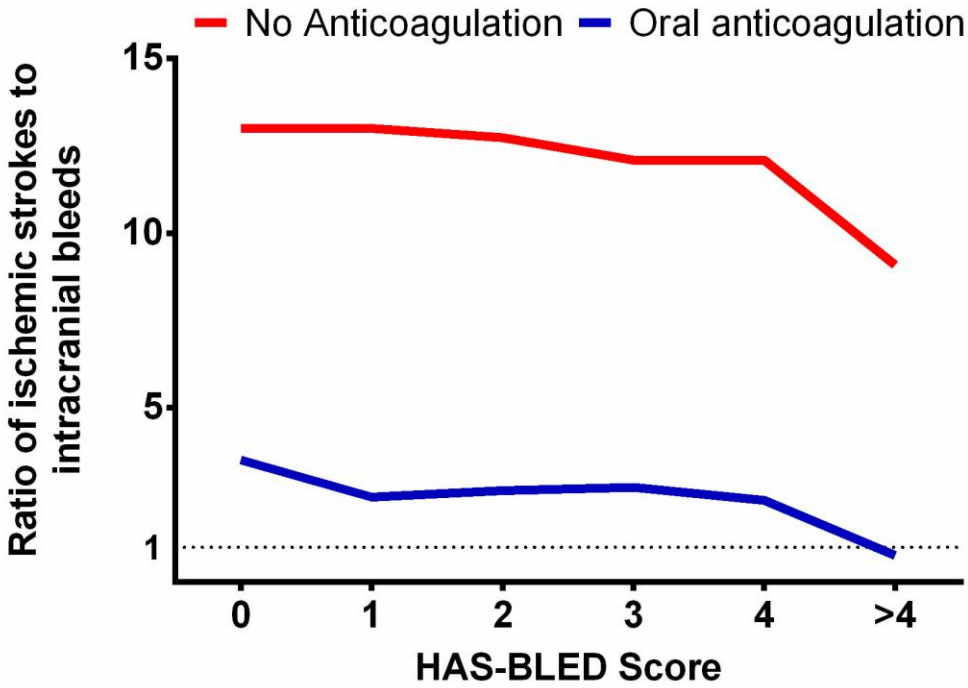




AJC_FIG1.tif



No. of strokes/ intracranial bleeds								
No anticoagulation	81/14	130/19	281/24	444/42	591/35	384/27	261/20	170/13
Oral anticoagulation	14/5	47/27	124/78	231/112	346/127	316/136	262/79	204/40



No. of strokes/ intracranial bleeds						
No anticoagulation	52/4	312/24	675/53	745/70	387/32	100/11
Oral anticoagulation	21/6	254/104	672/256	440/162	148/63	10/13

AJC_FIG2.tif