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[Review article]

$CHADS_2$ risk score and rate of stroke or systemic embolism and major bleeding in patients with non-valvular atrial fibrillation receiving non-vitamin K antagonist oral anticoagulants

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Abstract Randomized trials showed non-inferior or superior results of the non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin in patients with non-valvular atrial fibrillation (AF). Despite the absence of direct head-to-head comparisons between the different NOACs, certain molecules have been proposed for subgroups of patients based mainly on the perception of different bleeding risks. The $CHADS_2$ score has been uniformly used in the inclusion criteria of these studies and shared similar risk factors as the haemorrhagic risk score HAS-BLED. The aim of the present report was to highlight the relationships between $CHADS_2$ score and the rate of stroke or systemic embolism, and the rate of major bleeding in patients with AF on treatment with NOACs. Overall, in all the available randomized studies, a fairly good continuous relationship was observed between the $CHADS_2$ risk score and the rate of stroke or systemic embolism, and the rate of major bleeding in the different studies. Larger registries are needed to confirm this hypothesis.

Keywords *Atrial fibrillation – $CHADS_2$ score – NOACs – stroke – major bleeding.*

INTRODUCTION

Atrial fibrillation (AF) is the most commonly occurring sustained cardiac arrhythmia[1]. Above age 40 nearly 1 in 4 people will develop AF[2] and the prevalence increases with age[3]. Atrial stasis, endothelial dysfunction and increased blood coagulability lead to thrombus formation resulting in a 4- to 5-fold increase in the risk of ischaemic stroke relative to the non-affected population[4]. Stroke in AF is generally more severe and associated with greater mortality and disability as compared to stroke from other causes[5]. Over the years, many strategies have been proposed for thromboprophylaxis in AF. Aspirin has been used widely for many years but has been proven inferior to warfarin and not significantly better than placebo for stroke prevention in AF[6]. Well-controlled warfarin therapy is very effective in reducing the risk of ischaemic stroke but warfarin has a narrow therapeutic window and irregular gastrointestinal absorption with many drug and dietary interactions. For this reason, achieving good control requires careful monitoring with regular dose adjustments.

Unlike warfarin, the non-vitamin K antagonist oral anticoagulants (NOACs) have more predictable pharmacokinetic profiles, wide therapeutic windows, minimal drug interactions and do not require therapeutic monitoring. Several large, international, randomized controlled trials have shown the available NOACs to be at least as good as or superior to warfarin in the prophylaxis of stroke or systemic embolism (SE) compared to warfarin, with similar or lower risk for major bleeding. In one trial, the NOAC apixaban was proven superior for the prevention of stroke or SE compared to aspirin.

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Despite the fact that there are no direct head-to-head comparisons between the different NOACs and that indirect comparison between the different trials is complicated because of baseline differences, inclusion criteria (particularly stroke risk), $CHADS_2$ score and varying dose reduction protocols, certain molecules have been proposed for subgroups of patients based mainly on the perception of different bleeding risks[7,8]. Recently, important information has become available of efficacy and bleeding risk with NOACs in routine clinical practice.

OBJECTIVES

Until now, the results of five large international randomized controlled trials have been reported. In all of them the primary efficacy end point was stroke or SE and the primary safety outcome the occurrence of major bleeding (in one trial the primary safety end point was major and non-major clinically relevant bleeding events but major bleeding was reported separately). In four of these trials, dabigatran, rivaroxaban, apixaban and edoxaban were compared to warfarin in a non-inferiority protocol. In the fifth trial apixaban was compared to aspirin in a superiority protocol.

In all these trials, the risk of stroke was assessed according to the $CHADS_2$ score system, introduced in 2001 and based upon a cumulative scoring system focusing on five major risk factors: congestive heart failure, hypertension, age ≥ 75 years, diabetes, and history of stroke or transient ischaemic attack. Each factor is scored 1, except the cerebral events scored 2 points, reflecting their increased weight. The original validation of the score classified $CHADS_2$ 1-2 as moderate, and CHADS > 2 as high risk[9].

The aim of the present report was to highlight the relationships between $CHADS_2$ score and the rate of stroke or SE, and the rate of major bleeding in patients with AF on treatment with NOACs. We used the data from the five randomized clinical trials and in addition the rate of stroke or SE and the rate of major bleeding in one large high-quality registry with independent central adjudication of events, reflecting real-life information.

METHODS

We collected the mean CHADS2 score, rate of stroke or SE, rate of major bleeding, rate of bleeding from a gastrointestinal site and the number of patients with a fatal bleeding, when available, from each study (table 1). From these data we related the CHADS2 score of each study to the rate of stroke or SE and to the rate of major bleeding. We also evaluated the results with a high and a low dose of the study drug when this was prespecified in the protocols.

We plotted the rate of stoke or SE and the rate of major bleeding against the $CHADS_2$ risk score from each study (table 1 and table 2). In studies where the results of two dose regimens were reported, their different impact on outcomes is discussed and the rate of stroke or systemic embolism was plotted against the rate of major bleeding for each dose (figure 3).

$CHADS_2$ score, the rate of stroke or SE, and major bleeding

Dabigatran, a direct thrombin inhibitor, was evaluated in the phase III RE-LY (Randomized Evaluation of Long-term-Anticoagulation Therapy) study[10]. The RE-LY study randomized 6,076 patients with AF to a treatment with dabigatran 150 mg twice daily (b.i.d.) and 6,015 patients to a treatment with dabigatran 110 mg b.i.d. The primary efficacy outcome, stroke or SE occurred in 1.11%/y of the patients in the 150-mg group,

Table 1 Thromboembolic and major bleeding events in the studies analysed

STUDY	ROCKET AF	ENGAGE AF	ENGAGE AF	RELY	RELY	ARISTOTLE	AVERROES	XANTUS
NOACs	Rivaroxaban 20 mg o.d.	Edoxaban 60 mg o.d.	Edoxaban 30 mg o.d.	Dabigatran 150 mg b.i.d	Dabigatran 110 mg b.i.d	Apixaban 5 mg b.i.d	Apixaban 5 mg b.i.d	Rivaroxaban 20 mg o.d.
Patients (n)	7,001	7,035	7,034	6,076	6,015	9,120	2,808	6,784
CHADS2	3.5	2.8	2.8	2.2	2.1	2.1	2	2
Stroke and SE (%/y)	2.1	1.57	2.04	1.11	1.53	1.27	1.6	0.8
Major bleeding (%/y)	3.6	2.75	1.61	3.11	2.71	2.13	1.4	2.1
gastrointestinal site (%/y)	3.2	1.51	0.82	1.51	1.12	0.76	0.4	0.9
Fatal bleeding (n)	27	32	21	n.a	n.a	34	4	12

and major bleeding in 3.11%/y. The bleeding site was gastrointestinal in 1.51%/y of the patients. The $CHADS_2$ score in these patients was 2.2. The rate of stroke or SE in the 110-mg group was 1.53%/y and the rate of major bleeding 2.71%/y. The bleeding site was gastrointestinal in 1.21%/y of the patients. The $CHADS_2$ score was 2.1. Data on fatal bleeding was not available.

Rivaroxaban is a factor Xa inhibitor evaluated in the phase III ROCKET-AF (The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study[11]. This trial randomized 7,111 patients with AF to a treatment with rivaroxaban 20 mg once daily (o.d), or a protocol mandated dose of 15 mg o.d. if creatinine clearance (CrCl) was 30-49 ml/min (21% of the patients). The mean $CHADS_2$ score was 3.5. Stroke or SE occurred at a rate of 2.1%/y. The rate of major bleeding was 3.6%/y. The site of major bleeding was gastrointestinal in 3.2%/y of the patients. The bleeding was fatal in 27 patients.

Apixaban, a second direct factor Xa inhibitor, was evaluated in two large phase III randomized controlled trials. In the ARISTOTLE (Apixaban for reduction in Stroke and other thromboembolic events in Atrial Fibrillation) study[12], apixaban was compared with warfarin in a non-inferiority protocol. A total of 9,120 patients with AF were randomized to a treatment with apixaban 5 mg twice daily or a protocol mandated dose of 2.5 mg twice daily in patients with two or more of the following criteria: age of at least 80 years, body weight of no more than 60 kg or a serum creatinine level of 1.5 mg/dL (4.7% of the total). The mean $CHADS_2$ score was 2.1. Stroke or SE occurred in 1.27%/y of the patients. The rate of major bleeding was 2.13%/y. The site of bleeding was gastrointestinal in 0.76%/y of the patients. The bleeding was fatal in 34 patients.

In the AVERROES (Apixaban versus Acetylsalicylic Acid in Patients who have Failed or are Unsuitable for vitamin K antagonist) study[13], apixaban was compared to aspirin in a superiority protocol. A total of 2,808 patients were randomized to a dose of apixaban 5 mg b.i.d or using the same criteria as in the ARISTOTLE trial to 2.5 mg b.i.d (6% of the total). The mean $CHADS_2$ score was 2. Strokes or SE occurred in 1.6%/y, the rate of major bleeding was 1.4%/y and the site of bleeding was gastrointestinal in 0.4%/y of the patients. The bleeding was fatal in four patients.

Edobaxan, a third factor Xa inhibitor, was evaluated in the phase III ENGAGE AF-TIMI 48 (Effective anticoagulation with Factor Xa next generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 study) study[14]. In the ENGAGE AF trial, 7,035 patients with AF were randomized to a treatment with "high-dose" edobaxan 60 mg o.d., reduced to protocol mandated 30 mg o.d if Cr Cl was 30-50 ml, weight ≤ 60 kg or simultaneous use of the *P*-glycoprotein inhibitors verapamil or quinidine, and 7,034 patients to a treatment with "low-dose" edobaxan 30 mg o.d., reduced to a protocol mandated dose of 15 mg o.d. in the same circumstances as in the high-dose group. The reduced dose was given to 25.3% of the patients. The mean $CHADS_2$ score was 2.8. Stroke or SE occurred in 1.57%/y of the patients on high-dose edoxaban, and 2.04%/y of the patients on a low dose. The rate of major bleeding was 2.75/y, 1.51%/y from gastrointestinal origin in the high-dose edoxaban group. The bleeding was fatal in 32 patients. In the group treated with low-dose edoxaban, the rate of major bleeding was 1.61%/y. The origin was gastrointestinal in 1.19%/y of the patients, and in 21 patients the bleeding was fatal.

XANTUS[15] is a real-world prospective observational study of patients with AF treated with rivaroxaban. In this study, 6,784 patients newly started on rivaroxaban were followed up at 3 months intervals for 1 year or for at least 30 days after permanent discontinuation of the drug. The mean $CHADS_2$ score was 2 and all events were adjudicated by an independent central adjudication committee. The rate of stroke or SE was 0.8%/y. The rate of major bleeding was 2.1%/y. The origin of the bleeding was gastrointestinal in 0.9%/y of the patients, and the bleeding was fatal in 12 patients.

Comparison between studies

A fairly good relationship was observed between the $CHADS_2$ risk score and the rate of stroke or SE (figure 1) and the rate of major bleeding (figure 2) in the different studies, with a clear difference in outcomes between the high and low dose of dabigatran in the RELY study and between the high and low dose of edoxaban in the ENGAGE-AF study, as could be anticipated. Somewhat of a surprise were the results with apixaban in the AVERROES study, where the rate of stroke or SE was higher than expected from the $CHADS_2$ score, but with a lower than expected rate of major bleeding. In the Engage AF trial, the rate of stroke or SE was 29% higher in the "low-dose" group compared to the group of patients treated with 60 mg o.d., but in the "high-dose" group was a 70% higher rate of major bleeding.

In the RE-LY study, the rate of stroke or SE was 37% higher for the patients treated with dabigatran 110 mg b.i.d. compared to those treated with 150 mg b.i.d. but the rate of major bleeding was 18% higher in the group receiving dabigatran 150 mg b.i.d. In the AVERROES trial the rate of stroke was 27% higher compared to that in the ARISTOTLE trial, but in the latter the rate of major bleeding was 50% higher compared to the former trial despite an identical dosing protocol with apixaban 5 mg b.i.d. (figure 3).

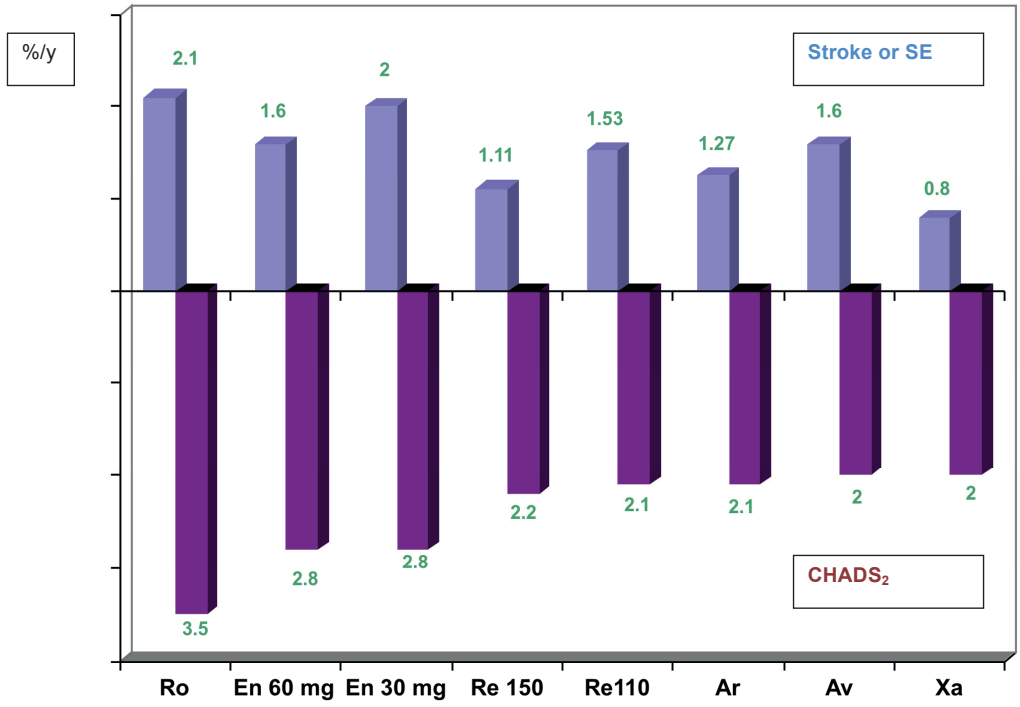

Fig. 1 Rate of stroke or SE (upper half) and $CHADS_2$ score (lower half) in the various studies
Ro (Rocket AF: rivaroxaban 20 mg o.d.), En (Engage AF: edoxaban 60 mg and 30 mg o.d.), Re (Rely: dabigatran 150 mg and 110 mg b.i.d.), Ar (Aristotle: apixaban 5 mg b.i.d.), Av (Averroes: Apixaban 5 mg b.i.d.), Xa (Xantus: rivaroxaban 20 mg o.d.).

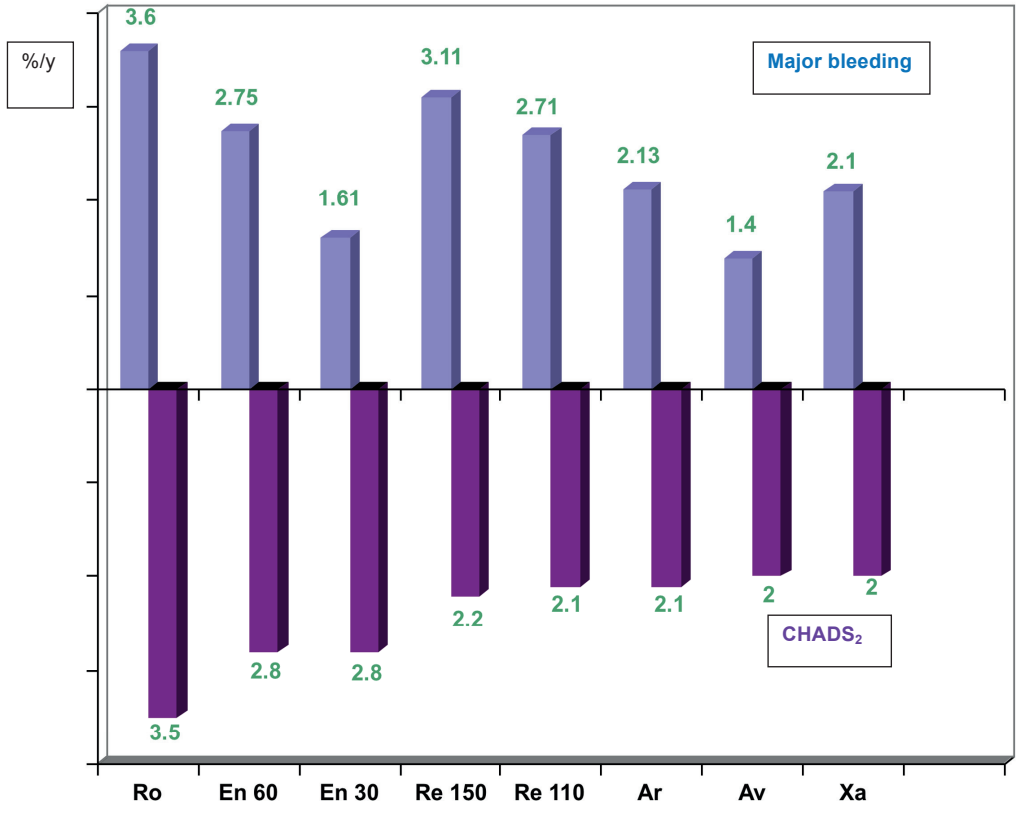

Fig. 2 Rate of major bleeding, %/year (upper half) and $CHADS_2$) score (lower half) in the different studies
Ro (Rocket AF: rivaroxaban 20 mg o.d.), En (Engage AF: edoxaban 60 mg and 30 mg o.d.), Re (Rely: dabigatran 150 mg and 110 mg b.i.d.), Ar (Aristotle: apixaban 5 mg b.i.d.), Av (Averroes: apixaban 5 mg b.i.d.), Xa (Xantus: rivaroxaban 20 mg o.d.).

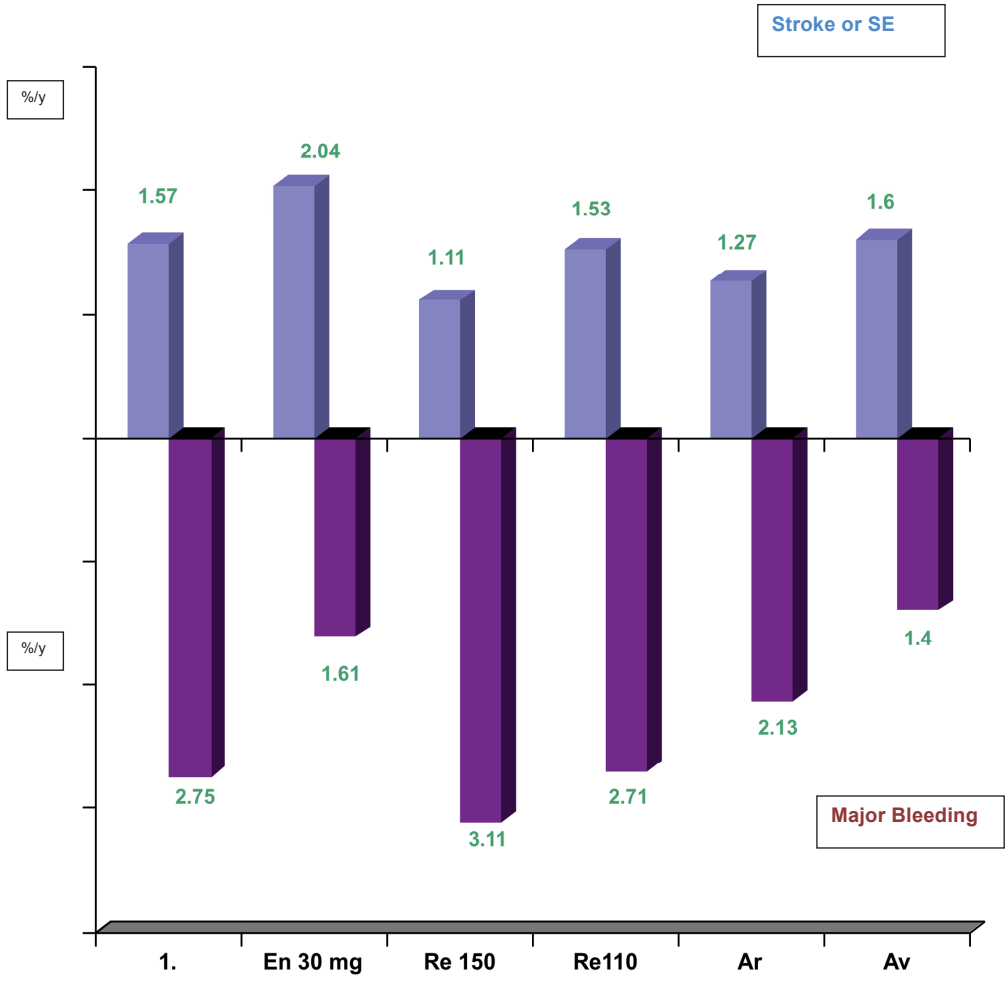

Fig. 3 Rate of stroke or SE (upper half) and major bleeding (lower half) in Engage AF, RE-LY, Aristotle and Averroes En (Engage AF – edobaxan 60 mg and 30 mg o.d.), Re (RE-LY – dabigatran 150 mg and 110 mg b.i.d), Ar (Aristotle – apixaban 5 mg b.i.d), Av (Averroes – apixaban 5 mg b.i.d).

The site of major bleeding was gastrointestinal in 35% to 55% of the bleedings in the different studies, with the exception of the ROCKET AF study with a gastrointestinal origin of the major bleeding in 90% of the events. The mortality of the major bleedings was uniformly very low in all studies.

DISCUSSION

The CHADS$_2$ risk score appears to be a reliable tool to predict the residual risk of stroke or SE for patients with AF treated with NOACs. These findings were consistent in the trials analysed except for the AVERROES study. The difference in the rate of stroke or SE between the high and low dose of the drugs for the patients in the ENGAGE AF and RE-LY trials is consistent with a greater anticoagulant activity of the higher doses. The higher rate of stroke in the AVERROES trial compared to the ARISTOTLE (or XANTUS) trial is hard to explain (figure 3).

A good continuous relationship was also found between the CHADS$_2$ score and the rate of major bleeding in most studies. The lower bleeding rate with low-dose edoxaban in the ENGAGE AF trial and the lower dose of dabigatran in the RE-LY trial, compared to the higher doses, is expected, and a reflection of the lesser anticoagulant activity at a lower dose. This clear impact on the rate of stroke and SE and the rate of major bleeding in the same risk category (CHADS$_2$ score) of a higher or lower dose of the NOAC prescribed, allows the doctor and the patient to discuss the relative benefit (prevention of stroke or SE) and risk (major bleeding) of each treatment option related to the patient's CHADS$_2$ score, particularly relevant in cases with a higher CHADS$_2$ score, where a choice can be made for a substantially higher risk of stroke or SE with a lower risk of major bleeding, or the opposite. Again, the difference in the rate of major bleeding between the ARISTOTLE and AVERROES trials is also hard to elucidate (figure 3).

The good relationship of the CHADS$_2$ score and the rate of major bleeding in AF patients treated with NOACs is not unexpected. HAS-BLED[16], the bleeding risk score derived from the EUROHEART survey, is an acronym for its constituting components: hypertension,

abnormal liver/renal function, stroke, bleeding, history of predisposition, labile INR, elderly (>65 y), drugs/alcohol concomitantly. Per definition, the HAS-BLED score contains several components (hypertension, stroke, age) present in the $CHADS_2$ score as well. Furthermore, labile INR is not relevant in patients treated with NOACs.

A similar relationship, as in the aforementioned studies reporting the relationship between the $CHADS_2$ risk score and the rate of major bleeding, was also described in a recent analysis of the large database of the United States Department of Defense concerning electronic medical records of 27,467 patients with AF treated with rivaroxaban between February 1, 2013 and March 31, 2014 [17]. The mean $CHADS_2$ score was 2.2 and 496 major bleeding events were recorded in 478 patients, a rate of 2.86% per person years. In the group of patients with major bleeding, the mean $CHADS_2$ score was 3.

The site of major bleeding was most commonly gastrointestinal (88.5%) and the bleeding mortality was very low (14 patients or 0.08% per 100 person years). Similar results were also observed in real-world and daily practice analysis concerning dabigatran with a rate of stroke or SE associated with the mean $CHADS_2$ score values[18,19].

The constantly good predictive value of the $CHADS_2$ score for the rate of major bleeding is, on the other hand, somewhat of a surprise since the definition and the site of major bleeding was not the same in the various studies. The number of patients who died because of bleeding was low in every study despite the great variability in bleeding sites. The major bleedings were gastrointestinal in 35 to 55% of the bleedings, with an exception in the ROCKET AF trial, where 90% of the major bleedings were gastrointestinal, and in the U.S. army database with a gastrointestinal origin of the bleeding in 88% of the bleeding events. This also makes the low mortality of the bleeding episodes unusual since there was no specific antidote for the NOACs available at that time and even without anticoagulant therapy is an acute gastric bleeding associated with an expected mortality of 7%[20].

LIMITATIONS

This paper is certainly not a comparison between the different studies with the NOACs but an evaluation of the possible association between the $CHADS_2$ risk score and the rate of stroke or SE, and the rate of major bleeding in patients with AF treated with one of the NOACs. The inclusion of a large high-quality prospective registry, reflecting daily clinical practice, would certainly give additional values to the present hypothesis.

CONCLUSION

The $CHADS_2$ risk score might be used to predict the risk of stroke or SE and the risk of major bleeding in patients with AF treated with a NOAC. Good adherence to the therapy is essential and the dose of NOAC has a large impact, with a lower rate of stroke or SE on a higher dose at the price of a higher rate of major bleeding. The mortality of major bleeding episodes was consistently low in the different studies despite the wide variety in bleeding sites. In patients with AF treated with NOACs, the $CHADS_2$ risk score and the dose prescribed are thus likely more important to predict the occurrence of stroke or SE and the rate of major bleeding than possible differences in the molecule of the different NOACs.

CONFLICT OF INTEREST: none.

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