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Should we judge stroke risk by static or dynamic risk scores? A focus on the dynamic nature of stroke and bleeding risks in patients with atrial fibrillation.

Magdalena Domek, MD[a,d], Jakub Gumprecht, MD[a,c], Michał Mazurek, MD[c], Tze-Fan Chao, MD[e], Gregory Y. H. Lip, MD[a,b,c]

[a]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

[b]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[c]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Medical University, Silesian Centre for Heart Diseases, Zabrze, Poland

[d]Department of Internal Diseases, Diabetology and Nephrology, Silesian Medical University, Zabrze, Poland

[e]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.

Correspondence:

Professor G. Y. H. Lip, gregory.lip@liverpool.ac.uk

Abstract

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and a major risk factor for stroke. The number of patients with AF is predicted to increase in the next few decades. AF has also negative impact on quality of life as well as it significantly increases the risk of cardiovascular disease and overall mortality.

As the stroke is a pivotal outcome of AF, its prevention with the use of anticoagulation therapy constitutes an important component of AF management. The decision on oral anticoagulants (OACs) prescription should be based on appropriate risk stratification to allow comprehensive assessment of benefit/hazard ratio of stroke and bleeding along with patients' preference.

Several risk scores for stroke and bleeding as well as for stroke and systemic embolism have been developed, mainly in patients on vitamin K antagonists (VKAs). AF guidelines stress the need for repetitive evaluation of thromboembolic and bleeding risks to tailor optimal AF management. Indeed, risk is not a static 'one off' process and it should be adjusted for dynamic nature of risk factors. However, most risk scores are calculated according to baseline characteristics of patients, but the older patients get, the more comorbidities they acquire, which influences stroke risk significantly. Hence, the default management of every patient with AF should include a regular reassessment of stroke and bleeding risk factors.

Keywords: atrial fibrillation, gastrointestinal bleeding, intracranial haemorrhage, major bleeding, non-vitamin K antagonist oral anticoagulants, oral anticoagulants, vitamin K antagonists

Introduction

Atrial fibrillation (AF) is the most frequently encountered heart rhythm disorder in clinical practice and the number of patients with AF is anticipated to increase over the next few decades.[1] AF is also associated mainly with significant risk of stroke and systemic thromboembolism but also dementia, heart failure, myocardial infarction and overall mortality. [2,3]

AF management comprises both therapies with prognostic impact (anticoagulation and treatment of cardiovascular conditions) and symptomatic benefit. However, the decision on prescription of oral anticoagulants (OACs) should be based on risk assessment in order to implement appropriate management.[4]

Stroke prevention is central to AF management. Concepts and approaches to stroke prevention have changed considerably over the last decade so as to implement optimal thromboprophylaxis.[2] Several stroke and bleeding risk scores as well as clinical risk scores for stroke and systemic embolism have been developed, mainly in patients on vitamin K antagonist (VKA).[5]

The majority of current guidelines recommend the use of CHA_2DS_2-VAS_C [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74, female] and HAS-BLED [hypertension (i.e. uncontrolled blood pressure), abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR (if on warfarin), elderly (e.g. age >65, frail condition), drugs (e.g. aspirin, NSAIDs)/alcohol concomitantly] scores to assess the risk of ischemic stroke and major bleeding of AF patients, respectively.[6,7]

Given that the default should be to offer stroke prevention unless the patient is 'low risk', guidelines have evolved to suggest that OACs should be considered for AF patients with a CHA_2DS_2-VAS_C score 1 or more (men) or 2 or more (women).[8] This is driven by the positive net clinical benefit (when balancing the risk of stroke versus the risk of bleeding) of systemic anticoagulation, by means of vitamin K antagonists (VKA, e.g. warfarin) and particularly the non-VKA oral anticoagulants (NOACs) which offer relative efficacy, safety and convenience compared with VK. [9]

This review article aims to provide an overview of the dynamic nature of stroke and bleeding risk factors and its impact on decision-making for AF stroke prevention. In this review paper, we aim to describe studies carried out over the last 10 years to inform future longitudinal studies and the need for creating new, comprehensive guidelines.

Search strategy

We investigated publications on AF risk assessment and the impact of their dynamic changes from the last 10 years using MEDLINE and EMBASE bibliography databases electronic search. Language of the papers was restricted to English. In addition, we manually checked specified references of the included publications.

Individualization of risk stratification

Net clinical benefit set a basis of the AF management and was introduced to quantify the balance between risk of ischemic stroke (IS) and risk of intracranial hemorrhage (ICH) with the use oral anticoagulant therapy (OAC).[10] The study of Banerjee at al. showed not only the superiority of NOACs over warfarin, but also stress that when the risk of stroke is truly low, the net clinical benefit of ischemic stroke prevention does outbalance the risk of intracranial hemorrhage.[10]

Eckman et al. modelled the use of warfarin for prevention of thromboembolic stroke in patients with AF, in relation to the incidence of warfarin-associated intracerebral hemorrhage, and suggested that the threshold for warfarin use should be >1.7% of the annualized risk of

stroke.[11] This threshold for NOAC use may be even lower (>0.9% stroke rate per year), predominantly due to significantly lower risk of intracranial bleeding compared to warfarin.[11].

Compared with warfarin, the RE-LY trial showed non-inferiority and superiority of dabigatran 110 mg BID with regard to reduction of stroke and systemic embolism and hemorrhage, respectively.[12] Alike, compared with warfarin, dabigatran 150 mg BID showed superiority and non-inferiority respectively for stroke/systemic embolism and major hemorrhage.[12] In the RELY trial, the drug dose (dabigatran 150 mg and 110 mg BID) was assigned to a patient by randomization. In the subsequent analysis form the RELY, it was suggested that an individually tailored dose of dabigatran, based on estimation of absolute benefit and harm, may be more optimal for the patients.[13] EMA (European Medicines Agency) and European experts recommend the use of both doses of dabigatran (150 mg or 110 mg BID) as per EU label.[13] In contrast, the FDA (Food and Drug Administration) did not approve the use of dabigatran 110 mg BID arguing that dabigatran 150 mg is superior to warfarin for stroke prevention (even though it may be associated with more major, but non-fatal bleeding), while AF-related thromboembolic stroke remains the most feared and devastation complication of AF and the second cause of death worldwide.[12,14,15] This highlights the importance of patients' involvement in the treatment and decision-making process, ie. shared decision- making (SDM).[16] This requires partnership between patients (and families, where appropriate) and clinicians that considers patients' values and preferences alongside medical evidence to make the best decisions for a given patient in a specific scenario.[16]

Changes in stroke and bleeding risks

Many stroke risk scores have been calculated according to various baseline characteristics of studied population. However, risk is not a static 'one off' process and should be adjusted for the dynamic nature of risk factors. Hence, risk assessment of AF patients should be updated and regularly reassessed.

There are some variables which will increase with time or even annually such as age and it concerns all patients. Others might occur incidentally e.g. incident hypertension, or the rapid onset of diabetes mellitus, vascular disease or even exacerbation of comorbidities leading to congestive heart failure, stroke or transient ischemic attack may appear in many patients.[17] Aforementioned factors have a significant impact on the CHA_2DS_2-VASc scale increasing the overall score , which reflects on changing the category of stroke risk , and total ischemic stroke rate. Nevertheless, the risk of stroke is often only assessed based on the baseline score instead of patient's current clinical condition without taking into account additional factors that change over time. Indeed, the overall risk score at baseline may include clinical incidents which happened remotely and currently have no significant effect on the patient's condition.[17]

Stroke risk

Chao *et al*[18] first proposed that the assessment of stroke risk should address the dynamic nature of these risk factors, by comparing the predictive value of CHA_2DS_2-VASc score at baseline, follow-up and the change in the score ('Delta CHA_2DS_2-VASc score'). There were investigated a total of 31,039 AF patients who were not treated with anti-platelet agents or OACs without any additional risk factors according to the CHA_2DS_2-VASc score with the exception of age and sex. Ischemic stroke occurred in 4,103 patients during 171,956 person-years follow-up.[18] Additionally, among 4,103 patients with history of ischemic stroke, a delta

CHA_2DS_2-VASc score ≥1 were observed in 89,4% of participants compared with 54.6% among patients who had not experienced ischemic stroke. Moreover 2,643 patients (64,4%) acquired >1 new-onset comorbidity and hypertension was the most common one. Delta CHA_2DS_2-VASc score turned out to be a relevant prognosis of ischemic stroke which was more reliable than baseline or even follow-up CHA_2DS_2-VASc scores.[18]

This finding was independently confirmed by Yoon *et al.* using data from the National Health Insurance Service (NHIS) database of Korea. There were studied 167,262 non-valvular AF patients aged ≥18 years, who have not been treated with anticoagulants before.[19] At the beginning, the percentage of patients classified as 'low', 'intermediate' or 'high risk' according to CHA_2DS_2-VASc score were 15.4, 10.6 and 74.0%, respectively. During 10- years of observation, a group of patients previously classified as 'low-risk' (46,6%) as well as a group of 'intermediate risk' (72%) were reassessed and recategorized into higher risk categories.[19] Among patients initially assigned as low-risk, the rate of annual ischemic strokes was higher in the group which was reclassified to 'intermediate' or even 'high-risk' compared to those whose risk strata had not changed (1.17 per 100 person-years, $p<0.001$; 1.44 per 100 person-years, p 1⁄4 0.048; 0.29 per 100 person-years respectively).[19] Hence, up-to-date CHA_2DS_2-VASc scores and their change with time in the follow-up assessment constitute a valuable predictor for ischemic stroke.[19]

Bleeding risk

Bleeding risk assessment is to address modifiable bleeding risk factors, and then to 'flag up' those at high risk for more frequent reviews and early follow-up (e.g. 4 weeks, rather than 4-6 months).[20] Of the various bleeding risk factors available, the HAS-BLED score has been shown to have the best predictive value.[21]

A strategy that simply focuses on modifiable bleeding risk factors alone is inferior for bleeding risk assessment, compared to the use of a formal bleeding risk score such as the HAS-BLED score.[22,23,24] Using a biomarker based assessment of bleeding risk for predicting remote outcomes also does not show any advantage over conventional clinical risk assessment.[25]

These limitations of 'one off' bleeding risk assessment reflect the highly dynamic nature of bleeding risk. In the study by Chao et al[26] which analyzed a total of 19,566 AF patients who have been treated with warfarin and HAS-BLED score from the baseline of ≤ 2. There were observed 3,032 major bleeds during 93,783 person-years of follow-up.[26] The thorough analysis of accuracy of the baseline, delta HAS-BLED score, follow-up and the sum of modifiable risk factors in prediction of major bleeding incidents were conducted. In the baseline the mean score was 1.43 which rose up to 2.45 with an average 'delta HAS-BLED' score of 1.03. Among patients who experienced major bleeding, 76.6% had a 'delta HAS-BLED' score ≥1 ($p < 0.001$) and only in 38.2% of patients the HAS-BLED score did not change.[26] The figure 1 presents that the follow-up (0.63, 95% CI = 0.62-0.64) and or delta HAS-BLED (0.62, 95% CI = 0.61-0.63) are better predictors of major bleeding than baseline HAS-BLED score (0.54, CI = 0.53-0.55).[26] Moreover, the amount of modifiable risk factors from the baseline was not prognostic for major bleeding events (0.49, 95% CI = 0.48-0.50).[26]

Hence, stroke and bleeding risk assessment should be regularly performed, at every patient contact. The proper way to use the scoring schemes is to reassess stroke and bleeding risks and in the case of the latter, to correct the modifiable risk factors appropriately.[27]
Bleeding risk factors are summarized in Table 1.

Dynamic nature of modifiable risk factors

As patients get older, they accumulate more comorbidities. Most patients with AF who experienced ischemic stroke develop more than one new stroke risk factor before ischemic stroke occurred. [18] The patient's clinical risk profile changes over time and this change has been shown to have better prediction ability for their respective risk than simply relying on the baseline score values. Hence, neither thromboembolic nor bleeding risks are static and must be reassessed regularly.[28]

Despite ease-to-use tools, such as e.g. the GRASP-AF[29],that can help physicians to assess regularly the risk of stroke and subsequently introduce anticoagulation, the 'real-life data' from primary care practice show very low use of OAC (approximately 50%) in many AF patients. Importantly, guideline-adherent anticoagulation significantly reduces the risk of stroke and improves survival at 1 year.[29]

The duration of hypertension sets important dynamic factor. In the study of Kim et al[30]. a total of 246 459 non-valvular AF patients who have not been treated with anticoagulants before were recruited from Korea National Health Insurance Service (NHIS) database (2005–2015)[30]. The study aimed to assess the risk of ischemic stroke depending on the duration of hypertension and systolic blood pressure (SBP) levels. The study showed that the increase of hypertension duration was significantly associated with the increased risk of ischemic stroke. Nevertheless, the influence of chronic hypertension can be decreased by long-term tight SBP control during the whole time of hypertension coexistence.[30]

Another study by Chao et al[31], which aimed to provide insights into the optimal assessment of age and incident comorbidities, stressed the heterogeneity of ischemic stroke risk among patients with AF. The cohort study included 31 039 and 39 020 patients with AF and without any or having only one concomitant risk factor according to the CHA_2DS_2-VASc score

excluding sex and age, respectively[31]. The differentiated population was investigated and the risk of ischemic stroke in the certain age groups were assessed according to the following approaches: (a) the 'conventional way' which was based on baseline risk factors and age, (b) 'dynamic method' which included an evaluation of patients after the occurrence of new comorbidities, (c) an 'ideal method' which set an evaluation of patients after the occurrence of new comorbidities and adjustment the stroke risk to the proper age when stroke appeared. Finally, the study showed that the age constitutes an important and independent component of ischemic stroke risk whereas the overall score is non-homogenous and influenced by various factors[31]. Hence, in patients with AF the age thresholds for the use of NOACs differed due to individual various risk factors despite having identical number of points in CHA_2DS_2-VAS_C score (except for sex).[31] Moreover, the conventional risk assessment based on baseline risk per se may overestimate ischemic stroke risk, while use of the ideal method may provide better and more accurate assessment of the age threshold when NOAC use should be considered.[31]

Another study by Chao et al. identified 14 606 patients with newly diagnosed AF and a CHA_2DS_2-VASc score of 0 who did not receive antiplatelets or OACs. The Kaplan–Meier method were used to plot cumulative incidence curves for increases in CHA_2DS_2 -VASc scores (Figure 2)[32] Accordingly, in up to 36,6% AF patients during an average follow-up of 3,24 years at least 1 new risk factor were noted. In men, the accumulated frequency of an increment in CHA_2DS_2-VASc score to 1 or even more was 16.1%(95% CI, 15.2% to 16.9%), 24,5% CI, 23.5% to 25.5%) and 49.1%(CI, 47.8% to 50.3%) at 1 year, 2 years and 7 years, respectively.[32] In women the aforementioned increment in CHA_2DS_2-VASc score to 2 or higher amounted 16.2% (CI, 15.1% to 17.1%), 24.9% (CI, 23.7% to 26.1%) and

49.9% (CI, 48.4% to 51.4%) at 1 year, 2 years and 7 years, respectively (Figure 2).[32] Figure 2 also presents the amount of ischemic strokes and deaths in each period. [32]

The aforementioned study conducted by Chao et al. was extended with the aim of estimating of reasonable timing interval at which stroke risk should be reassessed for such AF patients.[33] They studied 14,606 AF patients without prior anti-platelet or OACS treatment whose baseline CHA_2DS_2-VASc score were 0 for male or 1 for female group, who were monitored and adjusted to the incident of ischemic stroke or death by the end of 31 December 2011.[33] The results showed that the CHA_2DS_2-VASc score rises yearly in approximately 12% of AF patients originally categorized in the 'low- risk' group, with most showing a risk change occurring in approximately 4 months. Also, of those who sustained an ischaemic stroke, approximately 80% of these had a change in their stroke risk profile on average 4 months prior to the stroke. Consequently, the authors suggested that amongst low risk patients, a reassessment of stroke risk at approximately four months was a reasonable timing period, to enable stroke prevention therapy with OACs to be appropriately prescribed.[33]

Pritchett et al. published a systematic review of studies published till July 2017 about interferences made to improve appropriate OAC prescription for stroke prevention in patients with AF.[34] The study confirms that interventions such as education of health care professionals, implementation of local guidelines, interdisciplinary medical care programs educating both Health Care Practitioners and patients and persuasive interventions utilizing peer- group experts, can be effective in improving prescription of OACs.[34] It was also state that real prescription of anticoagulants in order to prevent stroke in patients with AF is often not consistent with up-to-date guidelines which means that in some cases it is overused while in others it is not used sufficiently.[34]

The GARFIELD-AF registry reported that in newly diagnosed atrial fibrillation, the rates of all major clinical events, which is death, stroke/systemic embolism and major bleeding, were significantly higher during the first month than in subsequent periods of follow-up at 2-4, 5-8 and 9-12 months[35]. Cardiovascular events were mainly responsible for the increased all-cause mortality rate in the first month (3.5, 95% CI 3.0-4.1 per 100-person years), particularly congestive heart failure, acute coronary syndrome and sudden death while the rate of death of ischemic stroke was relatively low compared with other causes of death (0.3, 95% CI 0.2-0.6 per 100-person years)[35]. It also confirms the dynamic nature of events given that ischemic stroke did not constitute the most common cause of early mortality.[35]

Guidelines on risk re-assessment

The 2014 American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines recommend the CHA_2DS_2-VASc score to assess stroke risk and indicate that the need for anticoagulation should be re-evaluated at periodic intervals, but they do not specify their frequnecy.[36] Moreover, the 2019 update of the AHA guidelines do not provide any additional time frames in terms of stroke and bleeding risk reassessment.[37]

The 2016 ESC guidelines recommend estimating stroke risk in AF patients based on CHA_2DS_2-VASc score. Because stroke and bleeding risk factors commonly overlap, many patients may be at increased risk of both, stroke and bleeding.[38] The 2016 ESC guidelines emphasize the importance of comprehensive and structured approach to AF care with potential to improve outcomes. However, they do not provide broad-based and thorough instructions about the conditions and time frames when the follow-up should be conducted.[38]

In terms of management, it should be focused on identification and correction of individual bleeding risk factors rather than withholding OAC.[38]

The 2018 Australia New Zealand clinical guidelines for the diagnosis and management of atrial fibrillation 2018 indicate that "the CHA_2DS_2-VASc score should be re- evaluated yearly in low-risk patients who are not anticoagulated." [39]

Finally, 2018 CHEST Guideline and Expert Panel Report recommends for patients with AF, especially those at high risk (HAS-BLED score ≥3), use of the HAS-BLED score during every patient contact or review due to the highly dynamic bleeding risk.[40]

Anticoagulation for all?

The reason why OAC is not a default therapy for all AF patients lies in the perception that anticoagulation may cause harm in those at low risk, that is women with CHA_2DS_2-VASc score of 1 (perhaps 2) and men with the score of 0; however, there are no large randomized controlled trial to confirm this. Similarly, we do not have such high-quality data to evidently conclude that patients with the CHA_2DS_2-VASc score of 1 in women and zero in men are at truly low risk of stroke, given that risk changes with study setting, ethnicity, etc. Nonetheless, if the individualized annual stroke risk is assumed to be low (the threshold for the outcome will always be relative, subjective and may be argued), the net clinical benefit when balancing the stroke versus bleeding risk reduction may be negative.[41] Importantly however, bleeding events are commonly less severe than a stroke is, and the use of OAC for stroke prevention aims at "event-free outcome", in contrast to a bleeding event, which may/will appear in most of the patients over time. Moreover, the overall survival benefit with the use of OAC exceeds the benefit that may be expected from an impact on stroke-related deaths only, emphasizing

the need for a holistic approach to AF care. Due to the potential risk of OAC use in truly low risk patients, other risk factors for stroke and bleeding may be considered, such as left atrial appendage morphology, biomarkers, genetics, intracranial vascular malformations etc.[40] However, this raises the issue about balancing improved risk prediction against simplicity and practical use in busy clinical settings.

Conclusions

Due to dynamic nature of the cardiovascular risk factors which may influence treatment of AF patients, the assessment and management of these risk factors should also be dynamic. A summary of evidence discussed in this review is given in Table 2. Hence, the decision-making pathway should be simplified and clear, involving bivariate analysis what allows to achieve best possible balance between stroke and bleeding risk. Indeed, stroke and bleeding risk factors certainly ought to be reassessed at every patient contact. Moreover, optimal management of incident comorbidities should be provided due to the proven reduction of cardiovascular events via integrated care and optimized cardiovascular comorbidity treatment. Oral anticoagulants in the prevention of stroke in AF often are not adhered to current guidelines for under-use in patients at high risk of stroke and there is often over-prescription of them in low-risk individuals. Whether we need new or better guidelines or more extensive and successful implementation of current recommendations into clinical practice is an important debate to come.

Limitations

Majority of analyzed studies were carried out in the Asian population, hence it is difficult to assess whether race and ethnic origin affect the risk score(s).

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Table 1. Modifable and non-modifable risk factors for bleeding in anticoagulated patients based on bleeding risk scores.

Hypertension (especially when systolic blood pressure is >160 mmHg)[a,b,c]
Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs[a,d]
Excess alcohol (≥ 8 drinks/week)[a,b]
Potentially modifiable bleeding risk factors
Anaemia[b,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]
Age (>65 years)[a] (≥75 years)[b,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent kidney disease or renal transplant[a,c]
Cirrhotic liver disease[a]
Malignancy[b]
Genetic factors[b]
High-sensitivity troponin[e]
Growth differentiation factor-15[e]
Serum creatinine/estimated CrCl[e]

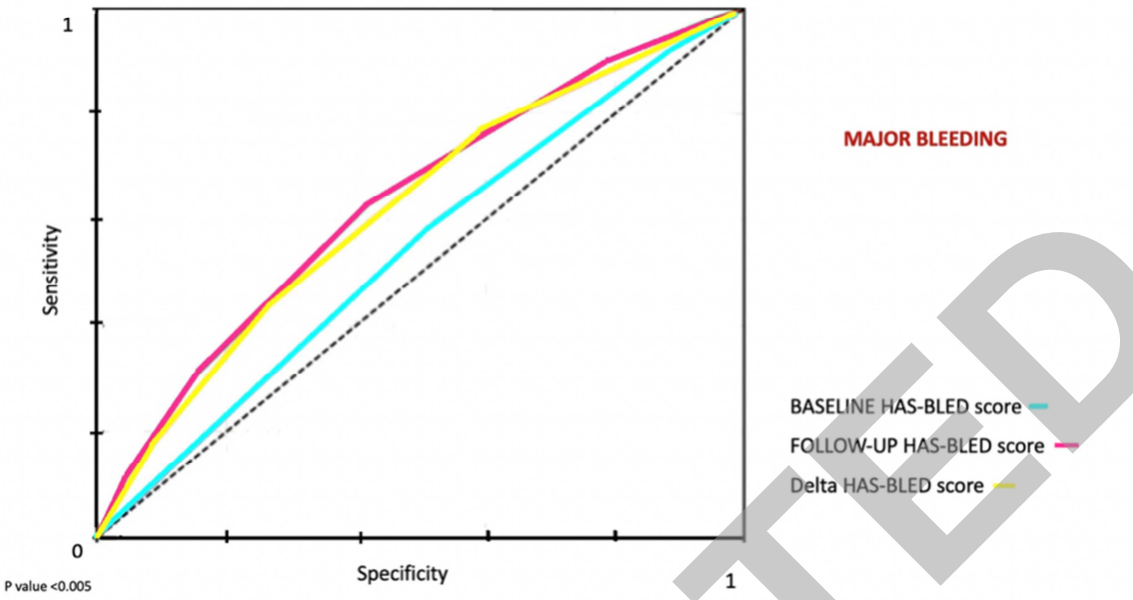
[a]Derived from the HAS-BLED score.[7]
[b]Derived from the HEMORR2HAGES score[42]
[c]Derived from the ATRIA score.[43]
[d]Derived from the ORBIT score.[44]
[e]Derived from the ABC bleeding score.[45]

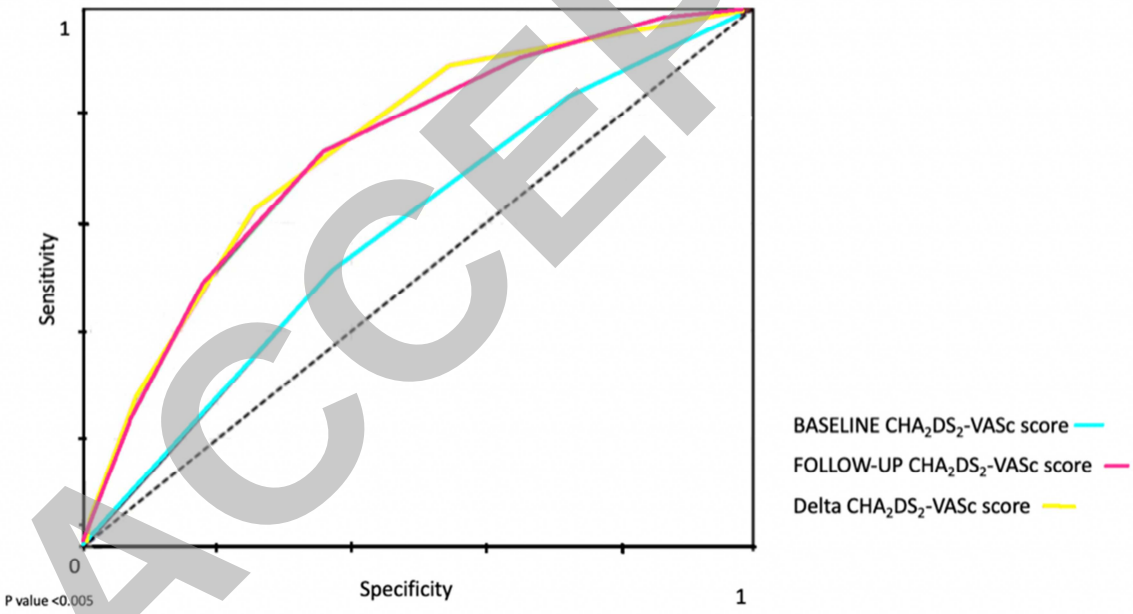
Table 2. Summary of the presented studies.

Author	Study population (number of patients)	Baseline CHA_2DS_2-VASc score	Duration	Follow-up CHA_2DS_2-VASc score	Delta CHA_2DS_2-VASc score	CHA_2DS_2-VASc score during the course of the study	Conclusions
Chao et al.[18]	31,039 AF patients without antiplatelet agents or oral anticoagulant treatment,	1.25 (without Ischemic Stroke) 1.53 (with Ischemic Stroke)	171,956 person-years	2.14 3.38	+0.89 (without Ischemic Stroke) +1.86 (with Ischemic Stroke)	Increase in 52.2% patients	Among 4,103 patients with ischemic stroke 2,643 (64.4%) patients had ≥1 new-onset comorbidity
Yoon et al[19]	167,262 oral anticoagulant-naive non-valvular AF patients	2.99 ± 1.92	10 years	4.43 ± 2.29	+1.44	Increase in 46.6% patients I 'low risk' group Increase in 71.0% patients in 'intermediate risk group'	Rates of ischaemic stroke increased when patients accumulated risk factors, and were re-classified into higher CHA2DS2-VASc score categories
Chao et al.[32]	14 606 patients with AF who did not receive antiplatelets or OACs	0 (men) or 1 (women)	7 years (47 275 total person-years)	Men: an increase in CHA_2DS_2-VASc to 1 or higher was 16.1% at 1 year, 24.5% at 2 years and 49.1% at 7 years Woman: an increase in CHA_2DS_2-VASc score to 2 or higher was 16.2% at 1 year, 24.9% at 2 years and 49.9% at 7 years			During a follow - up patients with AF acquired at least 1 new risk factor

Chao et al.[31]	All patients: 70 059	2.01 ± 1.19					Age thresholds for the use of NOACs were different for AF patients with different single risk factors (beyond sex) despite the same CHA2DS2-VASc score point (1 for males and 2 for females)
	31 039 Patients with no other comorbidities except for age and gender	1.29 ± 1.00					
	39 020 with one additional comorbidity (age and gender excluded)	2.59 ± 1.00					

Author	Study population (number of patients)	Baseline HAS-BLED score	Duration	Follow-up HAS-BLED score	Delta HAS-BLED score	HAS-BLED score during the course of the study	Conclusions
Chao et al. [26]	19.566 AF patients receiving warfarin	1.43 ± 0.68	93,783 person-years	2.45 ± 1.18	1.03 ± 1.05	The HAS-BLED score remained unchanged in 38.2% of patients	follow-up HAS-BLED or 'delta HAS-BLED score' was more predictive of major bleeding compared with baseline HAS-BLED
	3.032 with major bleeding	1.52 ± 0.64		2.94 ± 1.21	1.42 ± 1.13		
	16.534 without major bleeding	1.41 ± 0.69		2.36 ± 1.16	1.02 ± 1.04		





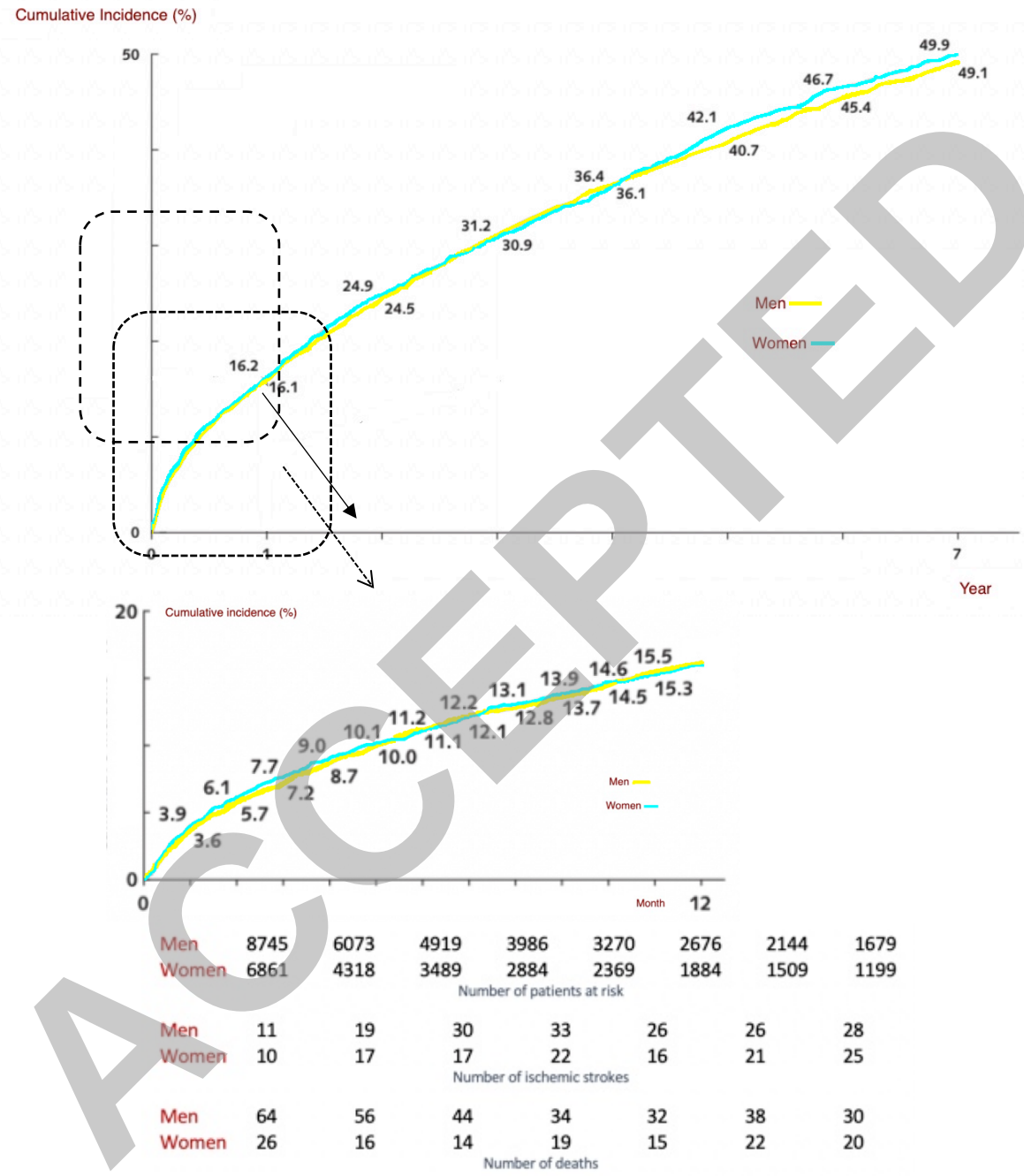


Figure 2. Cumulative incidence curves for increases in CHA2DS2-VASc score to ≥1 (men) or ≥2 (women).[32]

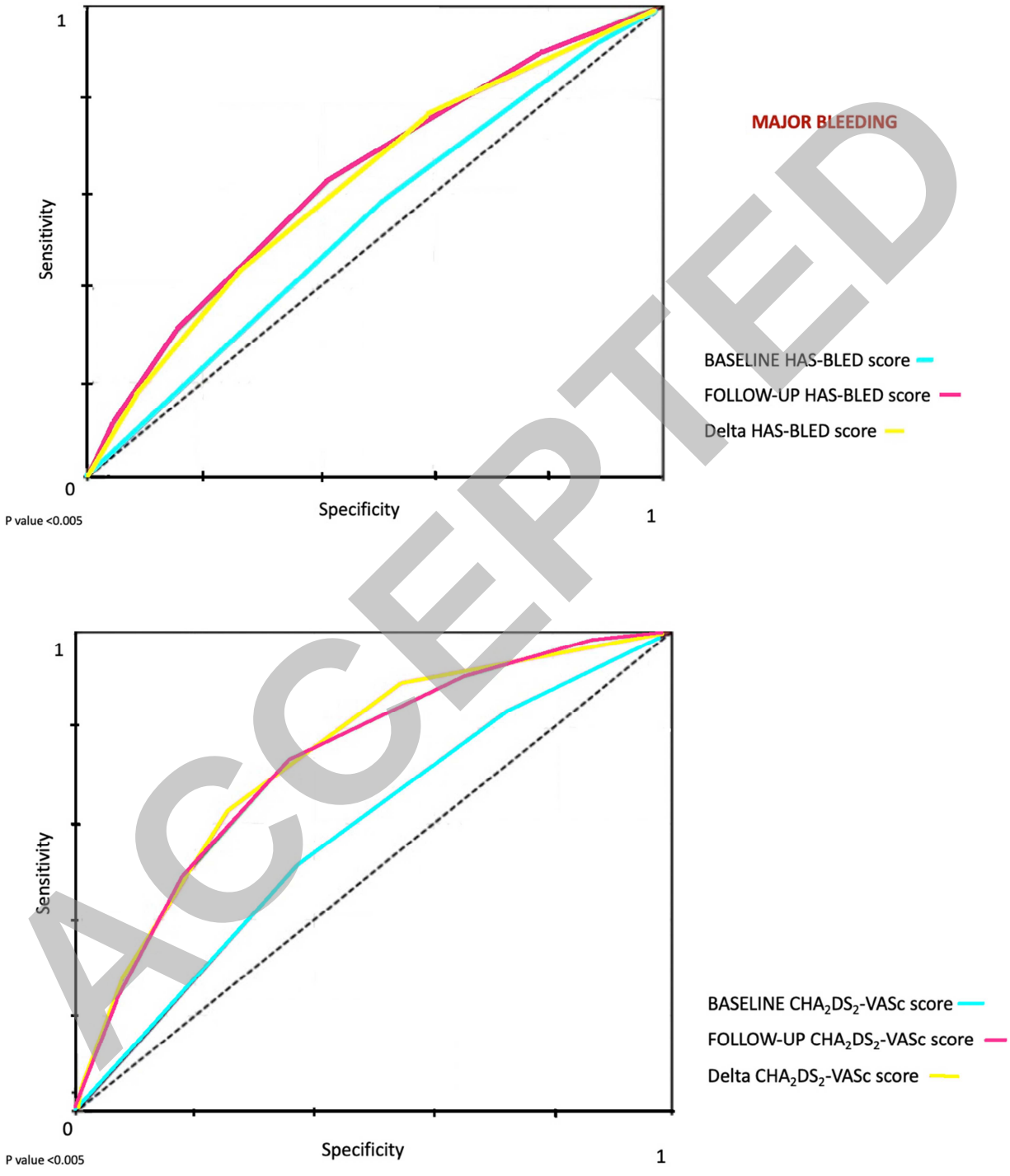


Figure 1. The AUCs of baseline, follow-up and delta scores in the prediction of ischemic stroke and major bleeding. The data used in the figure were from the papers by Chao et al.[18,26] AUC, area under the receiver operating characteristic curve.

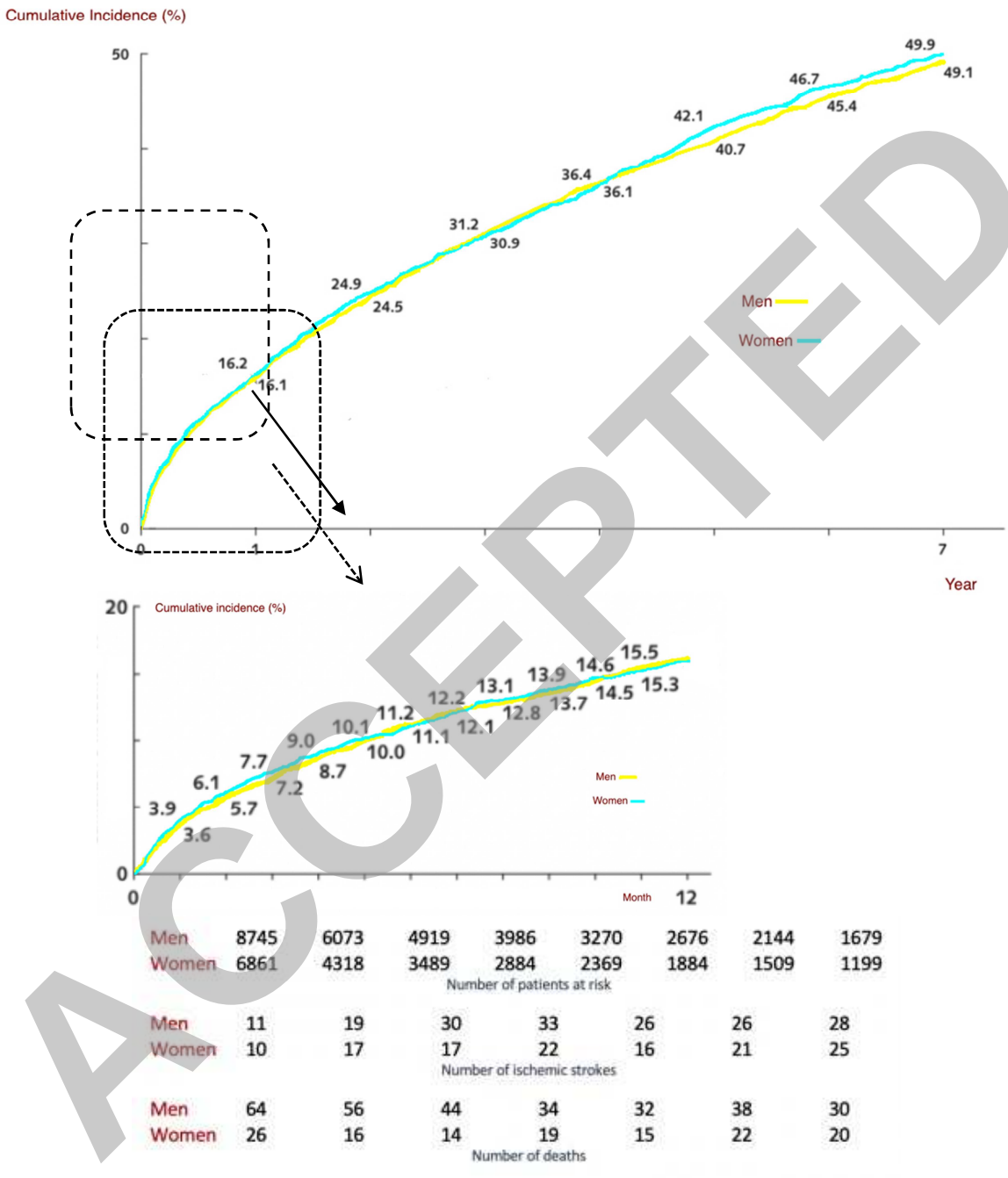


Figure 2. Cumulative incidence curves for increases in CHA2DS2-VASc score to ≥1 (men) or ≥2 (women).[32]