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Review

# Importance of Risk Reassessment in Patients With Atrial Fibrillation in Guidelines: Assessing Risk as a Dynamic Process

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## ABSTRACT

**The appropriate use of oral anticoagulants (OACs) for prevention of stroke in atrial fibrillation (AF) relies on the convenient and accurate stroke risk-prediction scheme: namely, the $CHA_2DS_2$-VASc score. As patients with AF would become older and accumulate more comorbidities, their risks—for example, as reflected by the $CHA_2DS_2$-VASc scores—are not static and could increase over time. The available data demonstrated that follow-up and Δ $CHA_2DS_2$-VASc scores perform better than the baseline $CHA_2DS_2$-VASc score in the prediction of ischemic stroke. Approximately 90% of initially low-risk patients would have a Δ $CHA_2DS_2$-VASc score $\geq$ 1 before the occurrence of ischemic stroke. Apart from risk of stroke, the risk of bleeding for patients with AF is also highly dynamic. For example, the accuracies of the follow-up or Δ Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile INR, Elderly, Drugs or Alcohol (HAS-BLED) score in the prediction of major bleeding was significantly higher than that of the**

## RÉSUMÉ

**L'utilisation appropriée des anticoagulants oraux (ACO) pour la prévention des accidents vasculaires cérébraux (AVC) dans la fibrillation auriculaire (FA) s'appuie sur le score $CHA_2DS_2$-VASc, qui permet de prédire le risque d'AVC de façon pratique et exacte. À mesure que les patients atteints de FA vieillissent et présentent de plus en plus d'affections concomitantes, leurs risques — tel qu'indiqué, par exemple, par leur score $CHA_2DS_2$-VASc — ne sont pas statiques et peuvent augmenter au fil du temps. Il ressort des données dont on dispose que le suivi et la variation (Δ) du score $CHA_2DS_2$-VASc sont de meilleurs prédicteurs de l'AVC ischémique que le score $CHA_2DS_2$-VASc initial. Chez environ 90 % des patients à faible risque au départ, on constate une variation du score $CHA_2DS_2$-VASc $\geq$ 1 avant la survenue de l'AVC ischémique. Outre l'AVC, le risque d'hémorragie évolue également de façon très dynamique chez les patients atteints de FA. Par exemple, le suivi et le Δ du score HAS-BLED (hypertension, anomalies de la**

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with a potential for blood stasis and increased risk of formation of thrombus, resulting in a higher risk of stroke and thromboembolism. The prevalence of AF is projected to be 4% in 2050, and the lifetime risk of AF is approximately 1 in 7 for subjects aged $\geq$ 20 years.[1] In comparison with patients who do not have AF, AF increases the risk of ischemic stroke, dementia, heart failure, myocardial infarction, and mortality.[1] Most importantly, AF-related stroke is associated with a higher risk of disability and mortality than non–AF-related stroke.[2] Therefore, prevention of stroke is the cornerstone of the comprehensive and holistic management of patients with AF.[3]

Stroke-risk assessment is the first and key step in prevention of stroke in AF.[4] Although some differences exist,[5] most of the current guidelines suggest that oral anticoagulants (OACs) should be considered for patients with AF who have **C**ongestive Heart Failure, **H**ypertension, **A**ge $\geq$ 75, **D**iabetes Mellitus, **S**troke/Transient Ischemic Attack, **V**ascular Diseases, **A**ge 65 to 74 Years, **S**ex **C**ategory ($CHA_2DS_2$-VASc) scores of 1 or more for men or 2 or more for women.[6-10] The recommendations for prevention of stroke in AF in different guidelines are summarized in Table 1.[6-13]

When assessing the risk of ischemic stroke in patients with AF, the risk factors incorporated into risk scores have been conventionally calculated based on clinical features or biomarkers determined at study entry or "baseline." However, the reality is that the risk profile of patients does not remain static as patients age and accumulate more incident comorbidities.

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**baseline HAS-BLED score. Most importantly, the risks of stroke and major bleeding were higher within several months after patients had changes (increases) in their stroke- or bleeding-risk scores. Therefore, risk profiles of patients with AF should be reassessed regularly so that OACs could be prescribed in a timely manner once patients are no longer at low risk for stroke, and modifiable risk factors for bleeding could be corrected. More efforts are necessary to incorporate clear and easy-to-follow recommendations about risk reassessment into the guidelines to improve AF patient care.**

**fonction rénale et hépatique, AVC, hémorragie, INR labile, patient âgé, drogues ou alcool) ont permis de prédire la survenue d'hémorragies majeures avec une exactitude significativement supérieure à celle obtenue avec le score HAS-BLED initial. Qui plus est, les risques d'AVC et d'hémorragie majeure sont devenus plus élevés quelques mois après l'observation chez ces patients d'une variation (augmentation) de leurs scores d'évaluation du risque d'AVC ou d'hémorragie. Par conséquent, il est important de réévaluer régulièrement les profils de risque des patients atteints de FA afin de pouvoir prescrire des ACO au moment voulu, dès que le risque d'AVC cesse d'être faible, et de pouvoir corriger les facteurs de risque d'AVC modifiables. Des efforts additionnels sont nécessaires pour intégrer aux lignes directrices des recommandations claires et faciles à suivre sur la réévaluation du risque, afin d'optimiser la prise en charge des patients atteints de FA.**

This review article aims to provide an overview on the dynamic processes of risk of stroke in patients with AF. Also, the dynamic change of the bleeding risk will be discussed.

## Incident Comorbidities and the Increment in $CHA_2DS_2$-VASc Score

In a study from South Korea that included 167,262 OAC-naïve patients with nonvalvular AF (mean age 61.1 years, 50.8% male) with baseline $CHA_2DS_2$-VASc scores of 2.99, the mean $CHA_2DS_2$-VASc score of patients increased by 0.14 per year.[14] During a follow-up of 10 years, 46.6% of low-risk patients and 72.0% of intermediate-risk patients were reclassified to higher-risk group, and the increment of $CHA_2DS_2$-VASc score is mostly due to the increase of age and incident hypertension.[14]

Our study from Taiwan, which enrolled 31,039 patients with AF who had no comorbidities of the $CHA_2DS_2$-VASc score—except for age and sex at baseline—the mean $CHA_2DS_2$-VASc scores increased from 1.29 to 2.31 during a follow-up of 171,956 person-years.[15] Among these patients, approximately 51.9% of them would acquire incident comorbidities, with the most common being hypertension (37.2%), followed by heart failure (27.0%), diabetes mellitus (13.0%) and vascular disease (5.7%).[15]

These data clearly demonstrated that how patients with AF would acquire incident comorbidities and therefore an increase in their $CHA_2DS_2$-VASc scores after diagnosis of AF (Fig. 1).

## Changes of the $CHA_2DS_2$-VASc Score and the Risk of Ischemic Stroke

In addition to reporting incident comorbidities, Chao et al. proposed a new concept about assessing risk of stroke, focused on the follow-up and Δ $CHA_2DS_2$-VASc scores.[15] The follow-up $CHA_2DS_2$-VASc scores were defined as the highest recorded $CHA_2DS_2$-VASc scores of each patient during the follow-up period, before the occurrence of ischemic stroke, mortality, or the end of study. The Δ $CHA_2DS_2$-VASc score was defined as the difference between the baseline and follow-up scores (follow-up $CHA_2DS_2$-VASc minus baseline $CHA_2DS_2$-VASc scores). As expected, all baseline, follow-up, and Δ $CHA_2DS_2$-VASc scores were higher among patients who experienced ischemic stroke than those who did not. Overall, nearly 60% of patients with AF had Δ $CHA_2DS_2$-VASc scores $\geq 1$, and the percentage was higher among patients who experienced ischemic stroke than those did not (89.4% vs 54.6%).

Hence, a considerable number of patients with AF who were initially at low risk would be undertreated with OACs if we did not reassess their $CHA_2DS_2$-VASc scores. Moreover, if we looked at the temporal relationship between the changes of the $CHA_2DS_2$-VASc scores and the occurrences of ischemic stroke, a higher risk of stroke within several months of the score change was observed. Figure 2 shows the incidence rate and incidence rate ratio (IRR) of ischemic stroke in different time periods after the $CHA_2DS_2$-VASc score changed among patients who experienced ischemic stroke and had Δ-$CHA_2DS_2$-VASc $\geq 1$ reported by Chao et al.[15] The risk of ischemic stroke was particularly higher within 3 months after the score changed, with an IRR of 2.40 compared with the risk of stroke after 2 years. The finding highlights the importance of timely prescriptions of OACs for prevention of stroke for initially low-risk patients with AF once they got new risk-factor components of the $CHA_2DS_2$-VASc scheme.

## Prediction of Ischemic Stroke Based on the Dynamic Assessment

In the study by Chao et al.,[15] the area under the receiver operating characteristic curve (AUC) was significantly higher for the Δ $CHA_2DS_2$-VASc score (0.742; 95% confidence interval [CI], 0.732-0.750) compared with baseline (0.578; 95% CI, 0.569-0.587) or follow-up (0.729; 95% CI, 0.721-0.737) scores (Fig. 3). The Δ $CHA_2DS_2$-VASc score also improved the net reclassification index by 16% and 15%, respectively, compared with baseline and follow-up scores. Similarly, the Korean study also showed that the most recent $CHA_2DS_2$-VASc score, and the score change with the longest follow-up, had the best prediction of ischemic stroke.[14]

Compared with the AUCs from previous reports focusing on patients with AF and comorbidities having a full range of the $CHA_2DS_2$-VASc score (AUC = 0.698),[16,17] the AUC of the baseline $CHA_2DS_2$-VASc score in predicting ischemic stroke seems to be lower among patients with AF without comorbidities at baseline (AUC = 0.58).[15,18] As approximately 90% of patients with AF and no comorbidities at baseline would develop $\geq 1$ new stroke risk factor before presentation with ischemic stroke, it could be expected that the predictive

**Table 1.** Summary of the recommendations for stroke prevention in atrial fibrillation in different guidelines

| Guidelines | Scoring scheme suggested for stroke-risk assessment | Tipping points and the recommendations for stroke prevention | Statements or recommendations about the dynamic nature of the risk of stroke |
|---|---|---|---|
| 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society[11] | $CHA_2DS_2$-VASc | Score 0: no antithrombotic therapies<br>Score 1: no antithrombotic treatment or OACs or aspirin<br>Score $\geq$ 2: OACs are recommended | None |
| 2016 European Society of Cardiology[7] | $CHA_2DS_2$-VASc | Class IIa recommendation: OACs for score 1 (men) or 2 (women)<br>Class I recommendation: OACs for score $\geq$ 2 (men) or $\geq$ 3 (women) | None |
| 2016 Canadian Cardiovascular Society[13] | CHADS65 ($CHADS_2$ risk factors and age $\geq$ 65) | OACs for patients with any 1 component of the CHADS65<br>Aspirin for patients < 65 years of age with a $CHADS_2$ score 0 with arterial vascular disease (coronary, aortic, or peripheral) | None |
| 2016 Taiwan Heart Rhythm Society[9] | $CHA_2DS_2$-VASc | OACs for patients with a score $\geq$ 1 (men) or $\geq$ 2 (women) | None |
| 2017 Asia-Pacific Heart Rhythm Society[8] | $CHA_2DS_2$-VASc | OACs for patients with a score $\geq$ 1 (men) or $\geq$ 2 (women) | None |
| 2018 National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand[12] | $CHA_2DS_2$-VA (sexless $CHA_2DS_2$-VASc) | OACs are recommended for patients with a $CHA_2DS_2$-VA score $\geq$ 2, and should be considered for those whose $CHA_2DS_2$-VA scores are 1 | The $CHA_2DS_2$-VA score should be re-evaluated yearly in low-risk patients who are not anticoagulated |
| 2018 CHEST guideline[6] | $CHA_2DS_2$-VASc | OACs should be offered for patients with a score $\geq$ 1 (men) or $\geq$ 2 (women) | Stroke risk is dynamic, and risk should be reassessed at every patient visit |
| 2018 Korean Heart Rhythm Society[10] | $CHA_2DS_2$-VASc | Class IIa recommendation: OACs for score $\geq$ 1 (men) or $\geq$ 2 (women)<br>Class I recommendation: OACs for score $\geq$ 2 (men) or $\geq$ 3 (women) | Age increases annually in all patients, and incident hypertension, diabetes mellitus, vascular disease, heart failure, and previous stroke or transient ischemic attack may become evident in some patients. |

$CHA_2DS_2$ -VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge $\geq$ 75 years, **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Diseases, **A**ge 65 to 74 years, **S**ex **C**ategory; OACs, oral anticoagulants.

accuracy of the baseline $CHA_2DS_2$-VASc score in predicting ischemic stroke is suboptimal among initially low-risk patients. Therefore, the regular assessment of the risk of stroke in patients with AF is particularly important.

## The Dynamic Nature of the Bleeding Risk of Patients With AF

Not only stroke, but risk of bleeding in patients with AF, is dynamic. When initiating antithrombotic therapies for patients, good clinical practice would initially focus on addressing any modifiable bleeding risks such as uncontrolled blood pressure, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs with anticoagulation, excessive use of alcohol, and labile international normalized ratios (INRs) if on warfarin. The next step is to identify the high-risk patients for early review and follow-up—for example, in 4 weeks rather than 4 to 6 months—to reassess risk and ensure that all modifiable bleeding risks have been addressed.[19] Although the 2016 guidelines of European Society of Cardiology (ESC) have listed a list of modifiable and nonmodifiable risk factors of bleeding rather than recommending any specific prediction scheme(s), a strategy that focuses on modifiable bleeding risk factors alone is an inferior assessment compared with a formal bleeding risk score for prediction of bleeding risk.[20-22]

Numerous bleeding scores have now been proposed of varying complexity, and some of them have incorporated biomarkers. The simple **H**ypertension, **A**bnormal Renal and Liver Function, **S**troke, **B**leeding, **L**abile INR, **E**lderly, **D**rugs or Alcohol (HAS-BLED) score is probably the most validated scoring scheme, which has been used for the prediction of bleeding events when patients are on no antithrombotic therapy, antiplatelet agents and oral anticoagulants (whether with a vitamin-K antagonist [VKA] or non-vitamin K antagonist OACs [NOACs]).[21,23,24] Moreover, in patients on VKAs, the HAS-BLED score consistently performed best, by inclusion of labile INR as one of its components.[24]

The HAS-BLED score would probably increase among anticoagulated patients with AF initially having low HAS-BLED scores ($\leq$ 2).[25] In our previous study, the AUC of the follow-up or $\Delta$ HAS-BLED score in the prediction of major bleeding was significantly higher than that of the baseline HAS-BLED score.[25] Moreover, risk of bleeding is higher within several months after the increment of the HAS-BLED score (incidence rate ratio 3.32 within 3 months compared with 2 years after the score change), and the phenomenon is similar to what we have observed for the change of the $CHA_2DS_2$-VASc score and the occurrence of ischemic stroke (Fig. 2). The AUCs of the baseline, follow-up, and $\Delta$ HAS-BLED scores in the prediction of major bleeding are shown in Figure 3.

Renal function, a component of the HAS-BLED scheme, has been demonstrated to decline in a considerable number of patients with AF during the follow up.[26-28] In the secondary

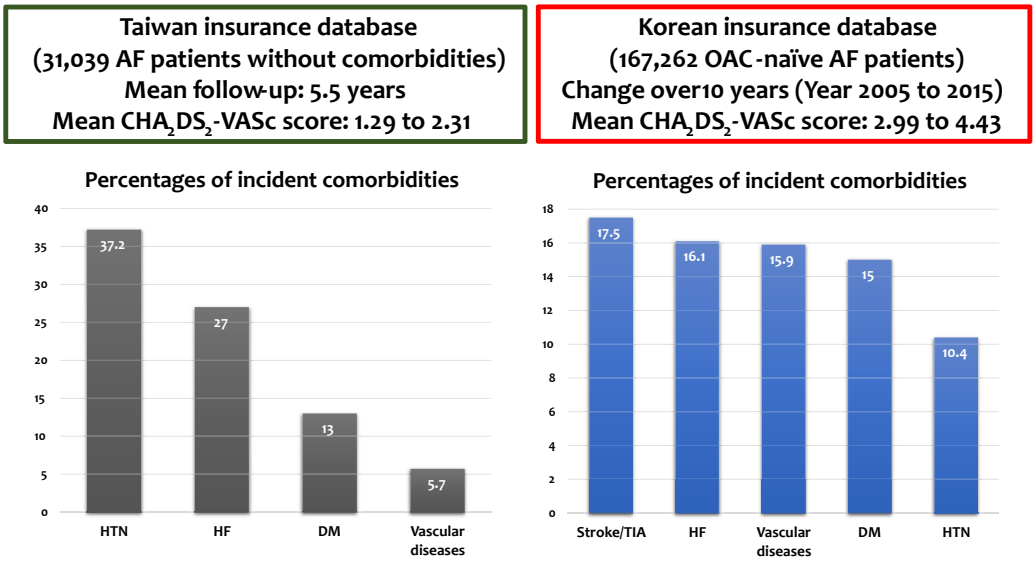


**Figure 1.** The increase of the **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Diseases, **A**ge 65 to 74 years, **S**ex **C**ategory ($CHA_2DS_2$-VASc) scores and percentages of incident comorbidities in Taiwan and Korean AF cohorts. AF, atrial fibrillation; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; TIA, transient ischemic attack. Data adapted from Yoon et al.[14] and Chao et al.[15]

analysis of the **R**andomized **E**valuation of **L**ong-Term Anticoagulation Therap**y** (RE-LY) trial, 24.2% of patients were observed to have a worsening renal function, defined as a decline in estimated glomerular filtration rate (eGFR) > 20% from baseline, and the risks of all-cause mortality and major bleeding were higher in patients with worsening renal function compared with those who had stable renal function (hazard ratio [HR] 2.17 for all-cause mortality and 1.43 for major bleeding, both $P < 0.0005$).[27]

Consistent with these trial data, Fauchier et al. demonstrated that rates of events (ischemic stroke/systemic thromboembolism, bleeding, mortality) increased with worsening

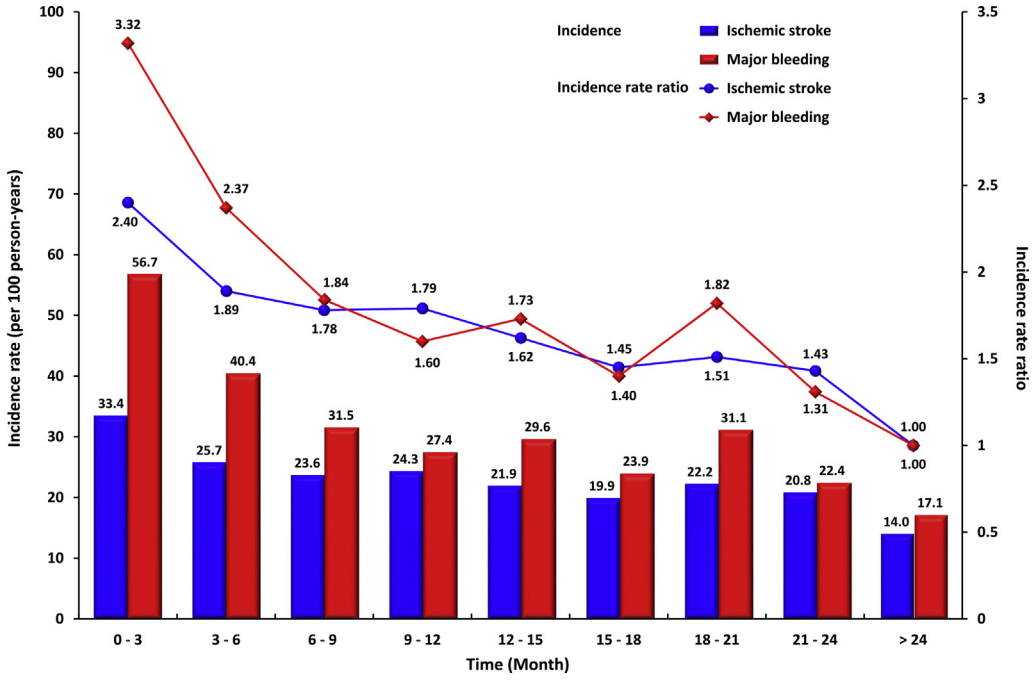


**Figure 2.** Incidence rate and incidence rate ratio of ischemic stroke and major bleeding in different time periods after the **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Diseases, **A**ge 65 to 74 years, **S**ex **C**ategory ($CHA_2DS_2$-VASc) and **H**ypertension, **A**bnormal Renal and Liver Function, **S**troke, **B**leeding, **L**abile INR, **E**lderly, **D**rugs or Alcohol (HAS-BLED) scores changed. Data adapted from Chao et al.[15,25]

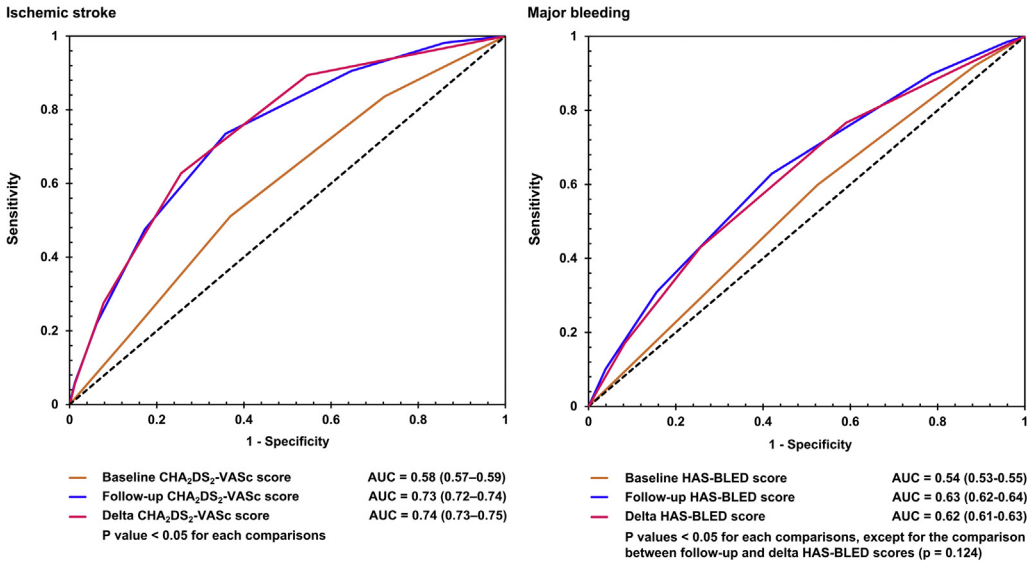


**Figure 3.** AUC, area under the receiver operating characteristic curve; $CHA_2DS_2$ -VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Diseases, **A**ge 65 to 74 years, **S**ex **C**ategory; HAS-BLED, **H**ypertension, **A**bnormal Renal and Liver Function, **S**troke, **B**leeding, **L**abile INR, **E**lderly, **D**rugs or Alcohol. Data used in the figure were adopted from Chao et al.[15,18,25]

eGFR by quartiles and was particularly increased when patients in the fourth quartile were compared with others.[28] Thus, the regular follow-up of renal function is particularly important for patients with AF taking NOACs, as renal dysfunction represents an important criterion for dosage reduction, and NOACs were even contraindicated if renal dysfunction is advanced. The 2018 European Heart Rhythm Association Practical Guide on the use of NOACs recommends that renal function should be followed up at a 6-month interval for patients aged ≥ 75 years or frail.[29] For patients with a baseline eGFR ≤ 60 mL/min, the suggested recheck interval (months) = eGFR/10.[29]

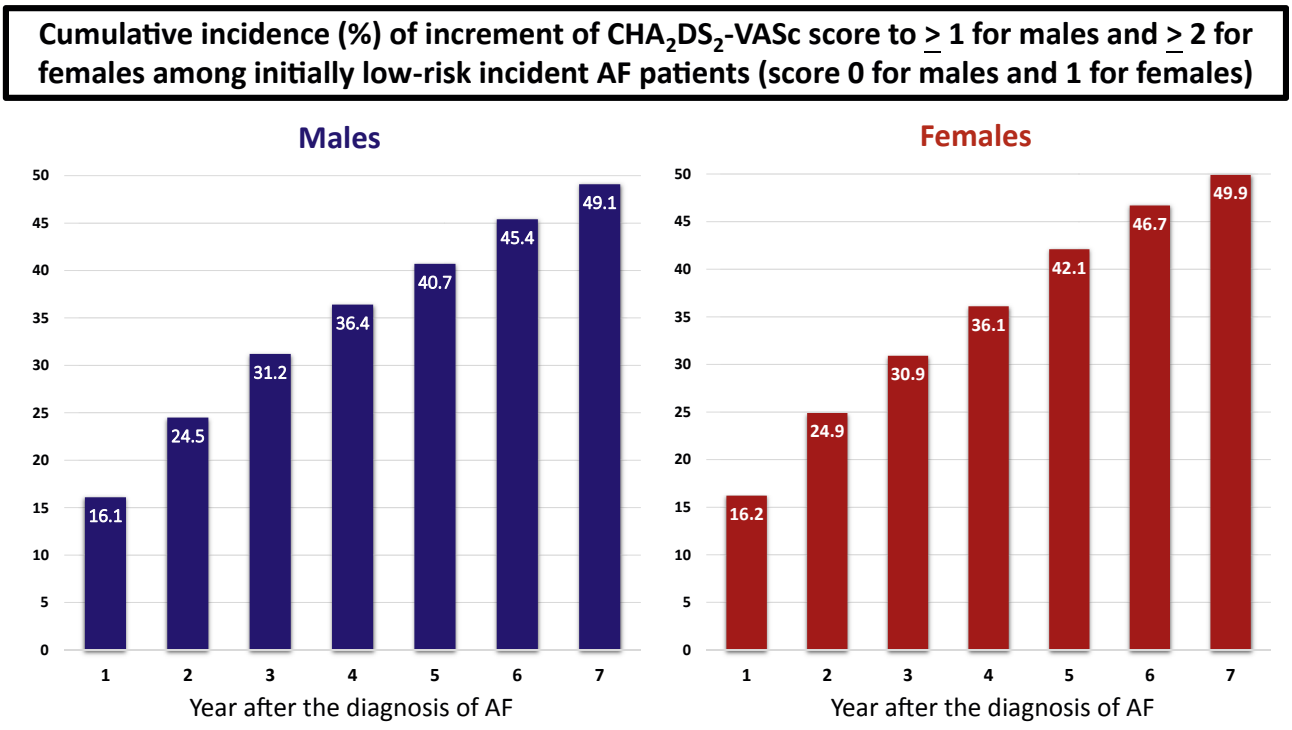


**Figure 4.** Cumulative incidences of increment of the **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Diseases, **A**ge 65 to 74 years, **S**ex **C**ategory ($CHA_2DS_2$ -VASc) scores to ≥ 1 for male patients and ≥ 2 for female patients among initially low-risk (score 0 for men and 1 for women) with AF. AF, atrial fibrillation. Data adapted from Chao et al.[31]

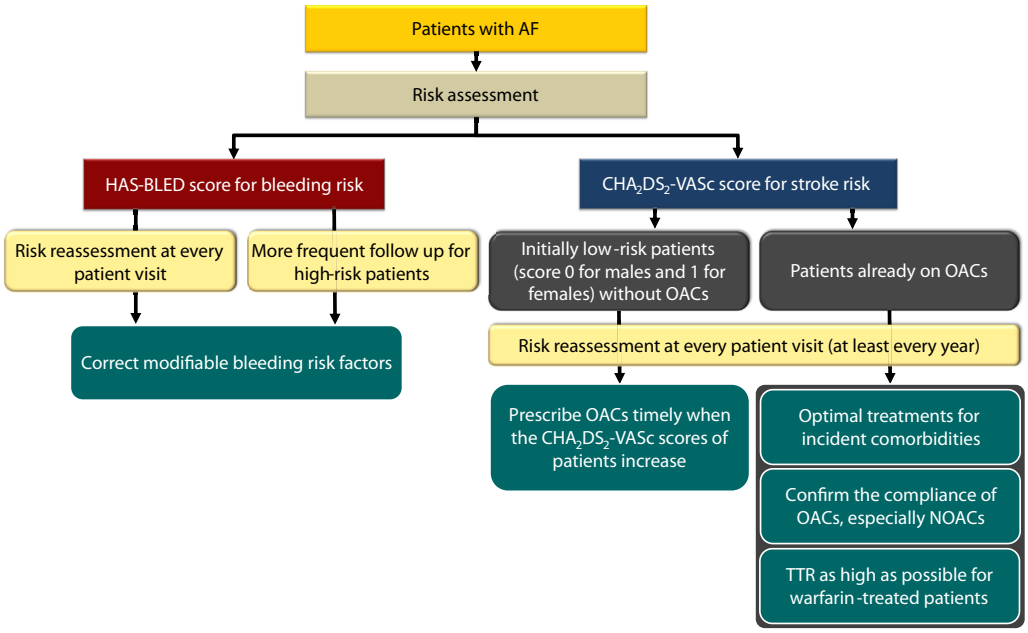


**Figure 5.** An algorithm about the use of scoring schemes in the management of patients with AF, regarding prevention of stroke. AF, atrial fibrillation; $CHA_2DS_2$ -VASc,**C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Diseases, **A**ge 65 to 74 years, **S**ex **C**ategory; HAS-BLED, HAS-BLED, **H**ypertension, **A**bnormal Renal and Liver Function, **S**troke, **B**leeding, **L**abile INR, **E**lderly, **D**rugs or Alcohol. NOACs, non-vitamin K antagonist oral anticoagulants; OACs, oral anticoagulants; TTR, time in therapeutic range.

As mentioned, the appropriate use of the HAS-BLED score should be to "flag up" patients potentially at high risk for more regular review and follow-up and to address the modifiable bleeding risk factors during follow-up visits. Further studies are necessary to investigate the benefits of reduction of bleeding risk through the correction of modifiable bleeding risk factors.

## Regular Risk Reassessment in AF: What Do the Guidelines Say?

As early as 2006, the AF guidelines of American College of Cardiology and American Heart Association have already stated that "Individual risk varies over time, so the need for anticoagulation must be re-evaluated periodically in all patients with AF."[30] Although it is a well-accepted concept that the risk of stroke in patients with AF would increase during the follow-up, no clear and concise recommendations have been incorporated into the clinical guidelines thereafter. The statements about the dynamic nature of the risk of stroke in patients with AF and the recommendations for risk reassessment in recent guidelines are summarized in Table 1.

The 2018 Australian and New Zealand guidelines stated that the stroke scores of patients with AF should be re-evaluated yearly in low-risk patients who are not anticoagulated.[12] A recent study investigated the cumulative incidences of increment of the $CHA_2DS_2$-VASc scores to ≥ 1 for men and ≥ 2 for women among 14,606 initially low-risk (score 0 for men and 1 for women) incident patients with AF, and the results are summarized in Figure 4.[31] At 1 year after the diagnosis of AF, 16.1% of male patients and 16.2% of female patients would acquire at least 1 new risk-factor components of the $CHA_2DS_2$-VASc scheme, and therefore they were not "low-risk" anymore. Of note, the prescription of OACs is a class IIa recommendation for patients with $CHA_2DS_2$-VASc scores of 1 (men) or 2 (women) and class I recommendation for those with a score ≥ 2 (male) or ≥ 3 (female) according to ESC guidelines.[7] These findings suggest that low-risk patients with AF should be reassessed for their risk of stroke at least annually to avoid the delayed use of OACs when indicated, which supports the recommendation of the Australian and New Zealand guideline.

The 2018 CHEST Guideline and Expert Panel from the American College of Chest Physicians (ACCP) states that risk of stroke is dynamic, and risk should be reassessed at every patient visit.[6] These recommendations on reassessing risk are clinically important and should be more widely adopted in other guidelines.

## Using the Scoring Schemes in the Right Way

The use of the scoring schemes in the right way to manage patients with AF regarding prevention of stroke is summarized in Figure 5. The $CHA_2DS_2$-VASc and HAS-BLED scores should be used to assess the risk of stroke and bleeding, respectively, and should be regularly reassessed. More frequent follow-up is necessary for patients with high risk of bleeding, and the identified modifiable bleeding risk factors should be corrected. The risk of stroke for each patient with AF should be reassessed at every patient visit and at least annually so OACs could be prescribed to avoid ischemic stroke once patients are no longer at low risk.

For patients who already received OACs for prevention of stroke, optimal managements of incident comorbidities should be provided, as integrated care—including optimized

management of cardiovascular comorbidity—in addition to prevention of stroke with OACs has been shown to reduce cardiovascular events.[32] In addition, physicians should confirm treatment compliance of OACs—especially for NOACs—and to keep time in therapeutic range as high as possible for warfarin. More efforts are necessary to incorporate clear and easy-to-follow recommendations about risk reassessment into management guidelines to improve patient care.

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