**Changing paradigms: from prevention of thromboembolic events to improved survival in patients with atrial fibrillation**

Running head: AF and mortality.

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**Abstract**

Atrial fibrillation is associated with a 5-fold increase in the risk of stroke. Current guidelines recommend the use of the CHA2DS2-VASc score to stratify the risk of stroke. In addition guidelines recommend the identification of the conditions that increase the risk of hemorrhage in order to be modified and thus decrease the risk of bleeding. Nevertheless, many patients with a high thromboembolic risk are prescribed antiplatelet treatment or do not receive any antithrombotic therapy. In addition, therapeutic inertia is common in anticoagulated patients taking vitamin K antagonists, and underdosing is an emerging problem with direct oral anticoagulants, probably because many physicians consider the risk of stroke and the risk of major bleeding to be equal.

It is necessary to develop a new approach to risk stratification, an approach that moves from morbidity to mortality, that is, from stratification of the risk of stroke and major bleeding to stratification of the risk of mortality associated with stroke and the risk of mortality associated with bleeding. In this manuscript, we propose a novel risk stratification approach based on the mortality associated with stroke and bleeding, illustrated by data derived from the literature.

**Key words**: anticoagulation; atrial fibrillation; bleeding; mortality; stroke.

**Condensed abstract**

A new approach to risk stratification in AF patients that moves from morbidity to mortality is necessary in order to improve anticoagulation rates. This approach moves from stratification of stroke and major bleeding risk to stratification of mortality risk associated with stroke and the risk of mortality associated with bleeding.

**1. Introduction**

 The current prevalence of atrial fibrillation (AF) in the adult population is estimated to be 2-4%.1-9 However, the frequency of AF is expected to increase 2.5-fold by 2050 owing to ageing of the population, improved survival after cardiovascular events and enhanced surveillance after acute cardiac events.1,2,4

 Mortality is twice as high in patients with AF as in individuals without AF,10 and the risk of heart failure, dementia, cognitive impairment and hospitalisation is increased in this group. In addition, AF is associated with a 5-fold increase in the risk of stroke.4,9,11 Approximately 1 in 3 ischemic strokes are associated with AF12. Of note, AF-related stroke is associated with higher rates of mortality, greater disability among survivors, and more recurrence than with other types of stroke.11,13,14 Therefore, primary and secondary prevention of stroke through adequate antithrombotic therapy is essential for most at-risk AF patients.9,15,16

**2. Evidence for antithrombotic therapy.**

European Society of Cardiology (ESC) guidelines recommend for thromboembolic risk stratification the use of the CHA2DS2-VASc score (Congestive heart failure [1 point], Hypertension [1 point], Age ≥75 years [2 points], Diabetes mellitus [1 point], Stroke/transient systemic embolism/systemic embolism [2 points], Vascular disease that includes previous myocardial infarction, peripheral artery disease, or aortic plaque [1 point], Age 65-74 years [1 point], Female sex [1 point]).9,17 These guidelines recommend administering anticoagulation therapy when the CHA2DS2-VASc score is >1 in men and >2 in women and considering this approach when the CHA2DS2-VASc score is 1 in men and 2 in women. Importantly, the prescription of antiplatelet agents is no longer recommended.9,16,17

Many studies have demonstrated that the efficacy of antiplatelet agents for prevention of thromboembolic complications in patients with AF is limited. Thus, in the meta-analysis of Hart et al.,18 adjusted-dose warfarin reduced the risk of stroke by 64% and all-cause mortality risk by 26%, whereas antiplatelet agents reduced the risk of stroke by only 22%. This marginal efficacy of antiplatelet drugs for prevention of stroke in AF patients is particularly clear in elderly patients.19,20

Treatment with direct oral anticoagulants (DOACs) is also much superior to aspirin therapy. Thus, the results of the AVERROES trial showed that apixaban reduced the risk of stroke and systemic embolism by 55% compared with aspirin. The authors identified a trend toward lower mortality rates, albeit without significantly increasing the risk of major bleeding or intracranial hemorrhage.21 This beneficial effect of apixaban (vs aspirin) was even higher in very elderly patients.22 Despite such convincing evidence, many AF patients are not anticoagulated and receive antiplatelets or no antithrombotic therapy (table 1).23-26

Unfortunately, anticoagulation is not properly performed in many patients. Thus, approximately 40-50% of patients taking VKA have a poor anticoagulation control and this is associated with poorer outcomes (stroke, bleeding and mortality) and higher costs (i.e. morbidity, disability, etc.).27-35 In addition, the limitations of VKA, together with bleeding concerns, have led to an underuse of oral anticoagulation in clinical practice, increasing the risk of stroke.36-44 Although direct oral anticoagulants (DOACs) overcome the majority of limitations of VKAs,45,46 and are associated with a better benefit-risk profile,47-51 a significant proportion of patients remain on antiplatelet agents or do not receive antithrombotic therapy.23-26,52-55 In addition, the use of inappropriate doses of DOACs, particularly improper dose reductions, has become the main problem associated with these drugs,56-60 leading to a reduction of protection against stroke.61-68 Although this occurs with all DOACs, it seems that the frequency of underdosing differs between DOACs.65-67 As a result, the adequate prescription of DOACs according to the summary of product characteristics is mandatory in order to ensure maximum benefit from their prescription.69,70

Considering all these data (table 2)4,9,11,23-35, 56-68, a new approach is needed to improve this situation.

**3. Stratification of the risk of stroke and bleeding: current approach**

Guidelines strongly recommend stratifying the risk of stroke in order to identify patients at high risk of thromboembolic complications and patients who may benefit more from anticoagulation therapy. However, guidelines also recommend assessing the bleeding risk associated with anticoagulant therapy.9,16,17

In the 2010 ESC guidelines, as well as in the 2012 update of these guidelines,70,71 the scale used to stratify risk of stroke changed from CHADS2 to the CHA2DS2-VASc, which was better able to identify patients with a low risk of stroke.73 With regard to bleeding risk, these guidelines recommended the use of the HAS-BLED score (Hypertension [1 point], Abnormal kidney or liver function [1 point each], Stroke [1 point], Bleeding [1 point], Labile INR [1 point], Elderly ->65 years- [1 point], Drugs or alcohol [1 point each]).74 Thus, the CHA2DS2-VASc score was used to estimate the annual risk of stroke and the HAS-BLED score to estimate the annual risk of major bleeding. However, this approach led many physicians to place the risk of stroke and the risk of major bleeding on the same level, thus leading to inappropriate underuse of anticoagulation therapy in many patients at high risk of stroke.23,24

In order to improve the rate of anticoagulation therapy, the 2016 European guidelines continued to recommend the use of CHA2DS2-VASc to stratify the risk of stroke. However, with regard to the bleeding risk, these guidelines did not recommend the use of a specific scale, but rather identification of conditions that could increase the risk of hemorrhage, with the aim of modifying these conditions to lessen the risk.9 The same approach remains in the 2020 ESC Guidelines for the diagnosis and management of AF.17 In addition, in response to direct questioning patients clearly prefer to face a bleeding risk rather than having to cope with a stroke.75,76

**4. Stratification of the risk of stroke and bleeding: need for change**

A new approach is needed for stratification of the risk of stroke and bleeding, since it is highly erroneous to consider the risk of stroke and the risk of major bleeding as being equal. In fact, cardioembolic stroke in AF patients is associated with significant morbidity and mortality.25,77-79 Different studies have shown that 1 year after a stroke, mortality rates reach approximately 30-50% in AF patients (table 3).13,14 Moreover, annual recurrence rates after AF-related stroke reach 19%.80 In the RE-LY trial, among those patients with stroke taking dabigatran 110 mg, dabigatran 150 mg and warfarin, 65.3%, 65.3% and 63.7% had fatal or disabling stroke per year.47 In the ARISTOTLE trial, these numbers were 42.0% and 47.0% for apixaban or warfarin, respectively.49 In the ROCKET-AF trial, among those patients with stroke taking rivaroxaban and warfarin, 25.5% and 30.1% had fatal stroke per year.48 In the ENGAGE AF-TIMI 48 trial, these numbers were 26.6% and 28.2% for edoxaban 60 mg and warfarin, respectively.50

On the other hand, data from all pivotal phase 3 clinical trials with DOACs have shown that whereas annual major bleeding rates range from 3.09% to 3.57% with warfarin and from 2.13% to 3.6% with DOACs (intracranial bleeding from 0.74% to 0.85% and from 0.23% to 0.49%, respectively), annual bleeding-related mortality rates range from 0.33% to 0.5% and from 0.19% to 0.23%, respectively.47-50 Therefore, among those patients who experience major bleeding, the event is fatal in only 10.7-14.0% of patients taking warfarin and 5.6-7.6% of patients taking DOACs (table 4).

Patient age and co-morbidity increase mortality and account for reluctance to use anticoagulants in clinical practice.37,43 In addition, history of and risk of bleeding has been cited for failure to anticoagulate a significant proportion of patients,81 despite in many cases this has a high subjective component.82 However, data from PREFER in AF strongly suggest that the risk of bleeding among anticoagulated patients does not depend mainly on anticoagulation, but on the underlying conditions that promote hemorrhage, and that anticoagulation therapy exposes this situation.83 Furthermore, various studies have shown that whereas there is an increase in the risk of bleeding among elderly or frail patients, the risk of stroke increases much more markedly in this population.84,85 Additionally, DOACs provide further benefits over VKAs, as DOACs halve the risk of fatal intracranial hemorrhage in AF patients compared with VKAs,86 and DOAC-related intracranial hemorrhage is associated with smaller baseline hematoma volume and lower neurologic deficit than VKA-related intracranial bleeding.87 Therefore, age and comorbidities should not avoid anticoagulation by themselves, and DOACs provide an additional benefit in this context.

**5. Stroke and bleeding risk stratification: focus on mortality.**

In view of the unsatisfactory approach to anticoagulation of patients with atrial fibrillation, a new approach is proposed for risk stratification, namely, moving from morbidity to mortality and from stratification of stroke and major bleeding risk to stratification of stroke and bleeding mortality risk. In fact, the GARFIELD-AF risk model estimates all-cause mortality, stroke, and bleeding. However, the scheme does not distinguish mortality related to stroke and to bleeding, but does compute mortality rates, in addition to the rates of stroke and major bleeding with and without treatment with different forms of anticoagulation.88

Thus, as CHA2DS2-VASc is used to estimate the annual risk of stroke73 and mortality rates range from 30% to 50% after the first year of stroke,13,14,48,50 mortality rates during the first year after a stroke can be estimated using this score (table 3). Those studies performed among non-anticoagulated patients or with low anticoagulation levels showed approximately a 50% annual mortality rate, whereas the most recent clinical trials with DOACs vs warfarin decreased this number to around 25-30%.13,14,48,50 As a result, considering both, the annual risk of stroke according to the CHA2DS2-VASc score and the estimated annual mortality-related stroke according to anticoagulant use, the annual mortality-related stroke according to the CHA2DS2-VASc score can be calculated.

On the other hand, 1-year stroke mortality rates should not be compared with major bleeding rates (mortality vs morbidity), but with annual fatal bleeding rates (mortality vs mortality). However, bleeding-related mortality rates vary considerably between real-life studies.89 In addition, there is no clear control of bias and confounders. As a result, although it is a limitation, the estimations of annual bleeding-related mortality rates were taken from the pivotal phase 3 clinical trials. 47-50 For this purpose, the probability of death after a major bleeding was calculated dividing the annual fatal bleeding rate by the annual major bleeding rate (per 100 person years). This was calculated for warfarin and DOACs (table 4). Then, in a similar way than with the CHA2DS2-VASc score, the annual mortality-related bleeding according to the HAS-BLED score was estimated according to the use of warfarin and DOACs (table 3).

As a result, table 3 summarizes the new proposed approach, which directly compares 1-year stroke mortality rates according to CHA2DS2-VASc score with annual bleeding-related mortality rates according to HAS-BLED score.

**6. Limitations of the new approach.**

This new approach is subject to limitations. One-year stroke-related mortality rates can vary according to the population or health care system. However, this also occurs with stroke risk stratification based on the CHA2DS2-VASc score may vary depending on the specific population.90-92 Nevertheless, CHA2DS2-VASc is easily applied in clinical practice and provides an acceptable estimate of stroke risk.

The stroke-related mortality risk is simply derived from the risk of stroke in AF patients (calculated using the CHA2DS2-VASc scores) multiplied by the average risk of mortality following stroke. Similarly, derived from the risk of major bleeding in AF patients (calculated using the HAS-BLED scores) multiplied by the average risk of mortality following major bleeding for patients anticoagulated with warfarin or DOACs. These are obviously crude estimates but they are sufficient to illustrate the principle of moving from risk stratification based on morbidity to a risk assessment based on mortality. However, to be acceptable as a clinical scoring scheme that could be implemented in practice, accurate risks of stoke and consequent mortality and major bleeding and subsequent mortality related to the CHA2DS2-VASc and HAS-BLED (or other scoring schemes) must be derived from reasonably contemporary cohorts, which is not an easy task.

A mortality net-benefit scheme such as that proposed for selecting patients who should receive anticoagulation may not be accurate or efficient for selecting patients with a truly low risk of stroke who should not be further considered for anticoagulation, and may, for that reason, have to be used in tandem with a scheme such as CHA2DS2-VASc. However, if the stroke-related mortality is also based on CHA2DS2-VASc this should not present any further complexity. On the other hand, with regard to very elderly patients, despite the CHA2DS2-VASc gives heavier weight to those subjects over 75 years, it is generally agreed that bleeding increases with age but there is little evidence that the subsequent mortality rate due to bleeding is higher than accounted for by age. On the other hand, stroke complications, including dementia, limited mobility, etc. is of major concern and also should be considered by physicians when analysing thromboembolic and bleeding risk. Although it would be very interesting to include this information, the main problem is that there is not enough evidence to estimate a specific number for this, as severity for dementia or limited mobility has a wide range and this has not been well validated.

Regardless of these current limitations, comparing 1-year stroke-related mortality with bleeding-related mortality in patients with AF could be a better approach than comparing stroke and bleeding risk in order to increase the awareness of the importance of anticoagulation therapy, since, with the classic approach, many patients are not anticoagulated or are taking inappropriate doses, mainly owing to concerns about bleeding. Although the proposed risk stratification approach, based on mortality associated with stroke and bleeding, is illustrated using data derived from the literature, it could be much improved by systematic analysis of large registries and will require prospective testing before it can be implemented in clinical practice.

**7. Conclusions**

Many physicians place the risk of stroke and the risk of major bleeding due to anticoagulation at the same level, leading to an under-anticoagulation of patients with AF. Such an approach is inadequate, as the consequences of each condition are markedly different. Therefore, a new approach for risk stratification in patients with AF is needed if we are to increase awareness of the importance of anticoagulation therapy. It is suggested to move from morbidity (stroke vs major bleeding) to mortality (1-year stroke-related mortality vs bleeding-related mortality).

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**Table 1. Use of antithrombotic therapy in patients with atrial fibrillation in clinical practice.**

|  |  |  |
| --- | --- | --- |
| **Study** | **CHA2DS2-VASc** | **Antithrombotic therapy use** |
| Barrios23 | * 0: 1.9%
* 1: 12.4%
* ≥2: 85.7%
 | Patients with a CHA2DS2-VASc score ≥2: * Oral anticoagulation: 56.2%.
* Oral anticoagulation + antiplatelets: 10.3%.
* Antiplatelets only: 20.2%.
* No antithrombotic therapy: 13.3%.
 |
| PINNACLE24 | * 0: 2.9%
* 1: 8.6%
* ≥2: 88.5%
 | * Oral anticoagulation: 44.9%.
* Aspirin alone: 25.9%.
* Aspirin plus a thienopyridine: 5.5%.
* No antithrombotic therapy: 23.8%.
 |
| GARFIELD-AF25 | * 0: 2.5%
* 1: 12.0%
* ≥2: 85.5%
 | * VKA: 35.2%.
* VKA and antiplatelets: 11.1%.
* Factor Xa inhibitors: 8.1%.
* Factor Xa inhibitors + antiplatelets: 2.3%.
* Direct thrombin inhibitors: 5.3%.
* Direct thrombin inhibitors + antiplatelets: 1.3%
* Antiplatelets only: 24.5%.
* No antithrombotic therapy: 12.2%.
 |
| GLORIA-AF26 | * 0: 2.2%
* 1: 11.7%
* ≥2: 86.1%
 | * DOACs: 47.6%.
* VKA: 32.3%.
* Antiplatelets: 11.3%.
* No antithrombotic therapy: 7.8%.
 |

VKA: vitamin K antagonists; DOACs: direct oral anticoagulants.

Table performed with data from references #23-26.

**Table 2. Current status of antithrombotic therapy**

|  |  |
| --- | --- |
| **No anticoagulation** | * No antithrombotic therapy or antiplatelets only: 7-25% and 10-30% of AF patients, respectively.
* No antithrombotic therapy is associated with:
	+ Stroke/systemic embolism: 5-fold increased risk.
	+ All-cause mortality: 2-fold increased risk.
 |
| **VKA** | * Inadequate INR control: 40-50% of VKA users.
* Inadequate anticoagulation control is associated with:
	+ Stroke/systemic embolism: 2.1-2.6-fold increased risk.
	+ Major bleeding: 1.5-2.2-fold increased risk.
	+ All-cause mortality: 1.7-2.4-fold increased risk.
 |
| **DOACs** | * Use of inappropriate doses: 10-60% of DOACs users.
* Inadequate dosage is associated with:
	+ Stroke/systemic embolism: 1.6-7.3-fold increased risk.
	+ Major bleeding: 0.8-1.6-fold increased risk.
	+ All-cause mortality: 0.9-2.1-fold increased risk.
 |

VKA: vitamin K antagonists; DOACs: direct oral anticoagulants.

Table performed with data from references #4,9,11,23-35, 56-68.

**Table 3. Estimated annual stroke and mortality rates according to the CHA2DS2-VASc score in nonanticoagulated patients with nonvalvular atrial fibrillation.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **CHA2DS2-VASc score** | **Annual stroke rate** | **One-year stroke-associated mortality rates among anticoagulated patients\*** | **One-year stroke-associated mortality rates among non-anticoagulated patients\*** | **HAS-BLED** | **Annual major bleeding rate** | **Annual mortality bleeding rates (patients taking warfarin)\*\*** | **Annual mortality bleeding rates (patients taking DOACs)\*\*** |
| 0 | 0% | 0% | 0% | 0 | 1.13% | 0.1-0.2% | 0.06-0.08% |
| 1 | 1.3% | 0.4% | 0.7% | 1 | 1.02% | 0.1-0.2% | 0.06-0.08% |
| 2 | 2.2% | 0.7% | 1.1% | 2 | 1.88% | 0.2-0.3% | 0.1-0.1% |
| 3 | 3.2% | 1.0% | 1.6% | 3 | 3.74% | 0.4-0.5% | 0.2-0.3% |
| 4 | 4.0% | 1.2% | 2.0% | 4 | 8.70% | 0.9-1.2% | 0.5-0.7% |
| 5 | 6.7% | 2.0% | 3.4% | ≥5 | ≥12.5% | 1.3-1.8% | 0.7-0.95% |
| 6 | 9.8% | 2.9% | 4.9% |  |
| 7 | 9.6% | 2.9% | 4.8% |
| 8 | 6.7% | 2.0% | 3.4% |
| 9 | 15.2% | 4.6% | 7.6% |

DOACs: direct oral anticoagulants.

\*It has been estimated that stroke associated mortality rates ranged from 30% (anticoagulated patients) to 50% (non-anticoagulated patients or low anticoagulation levels) 1 year after a stroke according to different studies.

\*\* Data derived from pivotal clinical trials with direct oral anticoagulants vs warfarin.

Table based on references #9,13,14,25,47-50.

**Table 4. Annual major bleeding and fatal bleeding rates and probability of death after major bleeding: data from phase 3 clinical trials comparing direct oral anticoagulants with warfarin.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Annual major bleeding rate\*** | **Annual fatal bleeding rate\*** | **Probability of death after a major bleeding** |
| **Warfarin** | 3.09-3.57 | 0.33-0.5 | 10.7-14.0% |
| **Dabigatran 150 mg****Dabigatran 110 mg** | 3.312.87 | 0.230.19 | 6.9%6.6% |
| **Rivaroxaban** | 3.6 | 0.2 | 5.6% |
| **Apixaban** | 2.13 | NR | -- |
| **Edoxaban 60 mg** | 2.75 | 0.21 | 7.6% |

NR: not reported

\*Per 100 person years

Table based on references #47-50.