

## Stroke prevention in atrial fibrillation patients with a single stroke risk factor: clinical decision-making and guideline recommendations

A case report and comparative analysis of the European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guidelines on the Management of Atrial Fibrillation

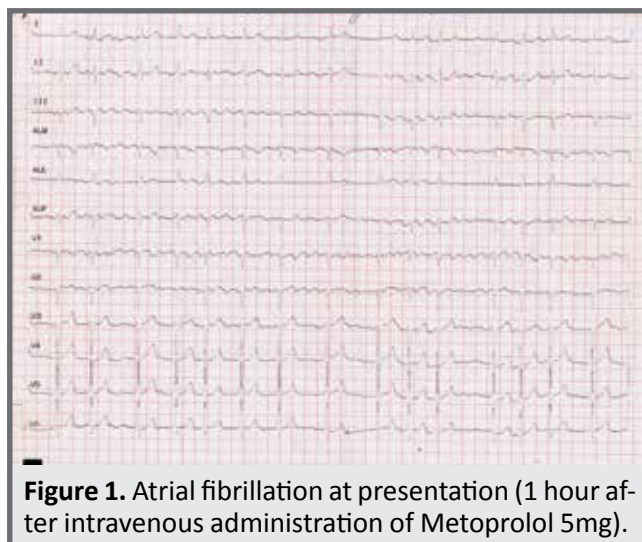
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**A** 58-year old female patient was referred to our hospital because of recurrent paroxysmal atrial fibrillation (AF) and labile International Normalised Ratio (INR) values.

Sixteen months ago, she presented to the local Emergency Room with palpitations and mild shortness of breath. Her electrocardiogram (ECG) revealed AF with rapid ventricular rate of 120 bpm (Figure 1), and her blood pressure was 150/90mmHg. Otherwise, physical examination yielded normal findings, as well as the chest radiography and routine blood testing. The patient reported cigarette smoking, but her medical record was otherwise unremarkable. There was no record of previous AF, history of hypertension, or antihypertensive treatment, but the patient reported intermittent slight elevations in her blood pressure on several recent occasions. The patient was administered metoprolol 5mg i.v. and spontaneous cardioversion to sinus rhythm occurred 4 hours after the onset of symptoms. On echocardiographic examination (performed in sinus rhythm, after spontaneous cardioversion), the left atrial (LA) anteroposterior diameter was 40mm, and left ventricular ejection fraction (LVEF) was 68%, with a normal pattern of transmitral flow. At discharge, the patient was diagnosed with first-onset lone AF and prescribed metoprolol 2x50mg. She has also been advised a closer blood pressure monitoring.

On regular follow-up visits she was in sinus rhythm, but her blood pressure ranged from 110/70mmHg to 160/95mmHg. The patient had been doing apparently well for the next eight months, when she woke up one morning with palpitations and severe neurologic deficit (right-sided hemiparesis and speech disorder). On admission to hospital her ECG showed AF with ventricular rate of 110 bpm, and a clinical diagnosis of acute ischemic stroke was subsequently confirmed by the brain computed tomography scan showing left-sided massive frontoparietal ischemia. Spontaneous cardioversion to



**Figure 1.** Atrial fibrillation at presentation (1 hour after intravenous administration of Metoprolol 5mg).

sinus rhythm occurred 3 hours after the admission. Since thrombolytic therapy was not available in the local hospital, acute ischemic stroke was treated conservatively. Four weeks later, oral anticoagulant therapy with adjusted-dose warfarin (with target INR of 2.0-3.0) was initiated, and the patient was also prescribed propafenone 450mg daily and an angiotensin-converting enzyme inhibitor (ACEi).

Six months later the patient was referred to our hospital. On admission, she was in sinus rhythm, with normal blood tests (excluding the INR of 1.8), normal chest radiogram and echocardiographic finding. Physical examination revealed a permanent neurologic deficit (disturbed walk and right-sided hemiplegia). The patient was switched to dabigatran (Pradaxa) 150mg twice daily, and propafenone dose was increased to 750mg daily, with AF catheter ablation planned in case of recurrent AF. Her hypertension was well-controlled with an ACEi and thiazide diuretic (blood pressure was below

140/90mmHg during the course of hospitalization). On the regular follow-up visit 2 months after discharge, the patient reported no AF-related symptoms (sinus rhythm was confirmed by ECG and 24-hour holter monitoring). However, she complained of pronounced gastrointestinal (GI) symptoms (dyspepsia, nausea, GI upset) despite the administration of a proton pump inhibitor (PPI), which she had been regularly taking for 6 weeks. Due to a poor tolerance to dabigatran, she was switched to rivaroxaban (Xarelto) 20mg once daily. On the next follow-up visit, the patient was in apparently stable sinus rhythm, without AF-related or GI symptoms, but with permanent, disabling neurologic deficit.

In summary, our apparently healthy 58-year old female patient presented with first-onset paroxysmal AF approximately one and a half year ago. She was considered as a low-risk patient (a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0) at that point and hence she was not given OAC, but later in her clinical course she experienced recurrent AF and a massive ischemic stroke with residual permanent neurologic deficit. Thereafter, she was treated with warfarin but, due to suboptimal quality of anticoagulation with warfarin, she was switched to dabigatran, and subsequently (due to intolerable side effects she experienced with dabigatran) she was switched from dabigatran to rivaroxaban.

## Key points for discussion

- Stroke and bleeding risk assessment,
- The use of oral anticoagulant therapy (OAC) for stroke prevention in AF patients with a single stroke risk factor.

## Comment

On average, patients with AF have a 5-fold greater risk of stroke than their counterparts in normal sinus rhythm<sup>1,2</sup>. Compared with other strokes, AF-related strokes are more often fatal or associated with more severe permanent disability<sup>3</sup>, and can be most effectively prevented using OAC therapy with either VKAs or NOACs (that is, dabigatran, rivaroxaban, apixaban or edoxaban)<sup>4-8</sup>.

However, the individual risk of stroke widely varies among AF patients, depending on the presence (or absence) of various stroke risk factors, and many stroke risk factors also increase the risk of bleeding associated with the use of OAC therapy<sup>9</sup>. Indeed, individual stroke and bleeding risks often track each other, thus posing a challenge to the physician considering the use of OAC for stroke prevention in a given patient with AF. Balancing the benefit of stroke prevention against the risk of bleeding with OAC therapy is a mandatory step in the management of stroke risk in patients with AF, since the ultimate goal is to achieve a positive net clinical benefit of treatment in all our patients.

### Stroke and bleeding risk assessment in AF patients

The annual stroke rate estimate for individual untreated AF patient can be appreciated using several stroke risk assessment scores (e.g., the CHA<sub>2</sub>DS<sub>2</sub>-VASc, CHADS<sub>2</sub>, or ATRIA score), which have been derived from various AF cohorts<sup>10</sup>. Due to its relative simplicity (the score can be easily calculated at bedside using readily identifiable clinical variables) and greater accuracy in identifying AF patients at truly low risk of stroke in comparison to other stroke risk assessment tools, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Table 1) has been recommended by the European Society of Cardiology (ESC) AF Guidelines<sup>1</sup>, the American Heart Association/American College of Cardiology/Heart Rhythm Society AF Guidelines<sup>11</sup> and several other major guidelines (e.g., the National Institute for Health and Clinical Excellence [NICE] AF Guidelines, Canadian Cardiology Society AF Guidelines, etc.)<sup>12</sup>.

Bleeding events are a downside of OAC therapy. By virtue of the principal mechanism of their action (i.e., interference with one or more components of the coagulation cascade), all anticoagulant drugs increase the risk of bleeding to some extent. Due to its high fatality<sup>13,14</sup>, intracranial bleeding (ICH) is the most feared OAC-related bleeding complication. Of note, with increasing use of VKAs for stroke prevention in AF during 1990s, the rate of ICH also increased from 0.8 to 4.4 per 100 000 patients taking warfarin<sup>15</sup>, and a meta-analysis

**Table 1.** The CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

CHA <sub>2</sub> DS <sub>2</sub> -VASc score Point score Adjusted stroke rate (%/year) <sup>40</sup>			Annual stroke rates with increasing score	
	Risk factor		0	0.0 %
<b>C</b>	Congestive heart failure/LV dysfunction	<b>1</b>	<b>1</b>	1.3 %
<b>H</b>	Hypertension	<b>1</b>	<b>2</b>	2.2 %
<b>A<sub>2</sub></b>	Age >75	<b>2</b>	<b>3</b>	3.2 %
<b>D</b>	Diabetes mellitus	<b>1</b>	<b>4</b>	4.0 %
<b>S<sub>2</sub></b>	Stroke/TIA/thromboembolism	<b>2</b>	<b>5</b>	6.7 %
<b>V</b>	Vascular disease*	<b>1</b>	<b>6</b>	9.8 %
<b>A</b>	Age 65–74	<b>1</b>	<b>7</b>	9.6 %
<b>Sc</b>	Sex category (i.e. female sex)	<b>1</b>	<b>8</b>	6.7 %
	<b>Maximum score</b>	<b>9</b>	<b>9</b>	5.2 %

\*Prior myocardial infarction, peripheral artery disease, complex aortic plaque.  
LV: left ventricular; TIA: transient ischemic attack.

of 16 randomised trials and 31 observational studies reported a 2% annual rate of major bleeding in patients taking OAC<sup>16</sup>.

Individual risk of bleeding in AF patients taking OAC therapy depends on the presence and combination of the bleeding risk factors<sup>17</sup>. Importantly, the risk of haemorrhage complications can be decreased by optimal risk factor management addressing several bleeding risk factors which are modifiable (Table 2). Both ESC and U.S. AF Guidelines (as well as most other major guidelines) recommend the HAS-BLED score (Figure 2) as bleeding risk assessment tool in patients with AF considered for OAC therapy (or taking OAC)<sup>1,11</sup>. There are several other bleeding risk assessment tools (e.g., the HEMORR2HAGES score or ATRIA score) but those scores have been less validated in AF patients, or performed less well in comparison to the HAS-BLED score<sup>9,10,18</sup>. A HAS-BLED score of 3 or more indicates increased risk of OAC-related bleeding. However, no specific value of the HAS-BLED score should itself be considered prohibitive for OAC use, but should serve to flag up patients at increased risk of bleeding in whom modifiable bleeding risk factors should be addressed, and closer clinical follow-up planned<sup>17</sup>.

At her initial presentation, our patient was apparently healthy and younger than 65 years. Thus, her CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 1 (female gender), and her HAS-BLED score was 0. However, she should have been diagnosed with arterial hypertension early in the course of her clinical follow-up, with an increase in her CHA<sub>2</sub>DS<sub>2</sub>-VASc score for 1 point. Should our patient have been given OAC therapy at that point?

#### *The use of OAC in AF patients with a single stroke risk factor*

Recent reports on various real-world AF cohorts consistently show increasing use of OAC therapy for stroke

prevention in patients with non-valvular AF<sup>19-21</sup>, but OAC use seems to be in relation with the patients' stroke (and bleeding) risk in only a few of those reports. A recent combined national survey of randomly selected physicians and AF patients in Canada, for example, revealed that physicians often misestimate stroke and bleeding risk in their AF patients, over- or underestimating the risks in considerable proportions of patients<sup>22</sup>. In addition, physicians ranked the fear of bleeding the highest in the list of their concerns with respect to the use of OAC, whilst patients were far less concerned about OAC-related risk of bleeding<sup>23</sup>. Of note, another study showed that most AF patients are willing to sustain 4 major bleeding events in exchange for preventing one AF-related stroke<sup>24</sup>. However, efforts are needed to improve patients' knowledge and understanding of AF and its complications<sup>25,26</sup>, as well as the decision-making on OAC use in routine clinical practice.

Whilst various AF Guidelines consistently recommend no therapy in patients with AF and no additional stroke risk factors (that is, a CHA<sub>2</sub>DS<sub>2</sub>-VASc of 0 in males and 1 in females), and OAC therapy for all AF patients with 2 or more additional stroke risk factors (in the absence of contraindications to OAC therapy, of course), there is some inconsistency among Guidelines regarding AF patients with a single additional stroke risk factor (that is, a CHA<sub>2</sub>DS<sub>2</sub>-VASc of 1 in males and 2 in females)<sup>27</sup>. In brief, the ESC Guidelines favour a simplified approach to stroke prevention in patients with non-valvular AF, whereby the first step would be to identify AF patients with no additional stroke risk factors using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, which outperforms other stroke risk assessment tools in identification of AF patients at truly low risk of stroke<sup>28</sup>. Such patients would not need any anti-thrombotic therapy, whilst all other AF patients should be considered for OAC therapy in the absence of contra-

**Table 2.** The HAS-BLED score. Modifiable bleeding risk factors are highlighted in grey.

HAS-BLED score Point score Bleeds per 100 Patient-Years <sup>41</sup>			Annual stroke rates with increasing score	
	<b>Clinical characteristic</b>		<b>0</b>	1.13
<b>H</b>	Hypertension (uncontrolled)	<b>1</b>	<b>1</b>	1.02
<b>A</b>	Abnormal renal and liver function (1 point each)	<b>1 or 2</b>	<b>2</b>	1.88
<b>S</b>	Stroke	<b>1</b>	<b>3</b>	3.74
<b>B</b>	Bleeding	<b>1</b>	<b>4</b>	8.70
<b>L</b>	Labile INR	<b>1</b>	<b>5</b>	12.50
<b>E</b>	Elderly (e.g. age >65 years)	<b>1</b>	<b>6</b>	0.0
<b>D</b>	Drugs or alcohol (1 point each)	<b>1 or 2</b>	<b>7</b>	...
<b>Maximum score</b>		<b>9</b>	<b>8</b>	...
		<b>9</b>	...	
		<b>Any score</b>	1.56	

Hypertension is defined as systolic blood pressure of >160 mmHg. Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine  $\geq 200$  mmol/L. Abnormal liver function is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). Bleeding refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. Labile INRs refers to unstable/high INRs or poor time in therapeutic range (e.g., <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.

INR: international normalized ratio.

indications to OAC use (again, a HAS-BLED of  $\geq 3$  itself is not a contraindication for OAC)<sup>1</sup>. Many other AF guidelines (e.g., the Canadian Cardiovascular Society guidelines<sup>12</sup>, Asia Pacific Heart Rhythm Society guidelines<sup>29</sup>, etc.)<sup>27</sup> also recommended OAC in AF patients with a single stroke risk factor. The AHA/ACC/HRS Guidelines, however, recommended no therapy, or OAC or aspirin in such patients<sup>11</sup>.

What would be the rationale for OAC use (or non-use) in AF patients with a single additional stroke risk factor? As recently reported, the threshold for OAC use at  $\geq 1.7\%$  annual stroke risk (which justified the use of VKAs considering the net clinical benefit of those drugs) should be decreased to the cut-off at  $\geq 0.9\%$  annual stroke risk with increasing availability of the safer oral anticoagulant drugs (that is, NOACs)<sup>30</sup>. Indeed, several reports on the nationwide cohorts of AF patients have clearly shown a positive net clinical benefit of OAC in almost all AF patients (excluding those with no additional stroke risk factors)<sup>31,32</sup>. The two recent observational analyses focusing on the large cohorts of patients with AF and one additional stroke risk factors reported the annual stroke rates ranging from 1.55%<sup>33</sup> to 2.75%<sup>34</sup>, which is well above the threshold for NOACs use. The net clinical benefit of OAC in comparison to aspirin or no therapy was clearly shown in these and other studies<sup>33-35</sup>. Another real-world observational study of untreated AF patients with a single additional stroke risk factor reported considerably lower annual rates of stroke ( $< 0.9\%$ ) and the authors concluded that the use of OAC in such patients might not be justified<sup>36</sup>. However, the study has several major limitations, including a strong selection bias. Namely, all AF patients with a single additional stroke risk factor who were subsequently prescribed OAC at any time point during the follow-up were excluded from the final analysis, which may have resulted in the selection of the very low-risk patients. Thus, the results of the aforementioned study cannot be translated to all patients presenting with AF and a single additional stroke risk factor<sup>37,38</sup>.

Another key message from the observational real-world studies on AF patients with a single additional stroke risk factor would be that various conventional stroke risk factors (Table 1) may not have the same 'weight' with respect to the risk of stroke. A history of prior stroke has been repeatedly shown to be the single most powerful predictor of recurrent stroke, even in patients taking OAC<sup>39</sup>. In the aforementioned cohorts with first-diagnosed AF and no prior history of stroke, age was the strongest stroke risk factor in both male and female AF patients, followed by diabetes mellitus, hypertension, heart failure and other components of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>33,34</sup>. Clearly, individual patient risk profile may significantly differ depending on the presence or absence of a 'stronger' or 'weaker' risk factor but, again, the overall net clinical benefit has been shown to be positive in the AF cohorts with a single additional stroke risk factor. Therefore, instead of attempting to weight a single stroke risk factor (that is, to quantify its impact on the patient's overall risk of stroke), physicians should focus on identification of the pres-

ence of any of the stroke risk factors and should always consider the use of OAC as the most effective means of stroke prevention in patients with AF and one or more additional stroke risk factors.

Importantly, various AF guidelines (including the ESC and AHA/ACC/HRS Guidelines on AF management), increasingly emphasize the need for individualized approach to stroke prevention in patients with AF, taking into account individual patient's values and preferences and reaching the final decision on OAC use through an informed, shared decision-making process. Finally, we should also remember how deleterious consequences AF-related strokes may be associated with and how strong is the AF patients' fear from thromboembolic complications of their arrhythmia.

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