

# NOAC in Patients with a Single CHA2DS2-VASc Risk Factor

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## Abstract

**Introduction:** The CHA2DS2-VASc risk assessment tool helps to stratify AF patients for their risk of stroke and systemic thromboembolism. Patients who score  $\geq 2$  should be considered for anticoagulation therapy but it is not always clear how to manage patients who score 1 point.

**Considering the Items:** Not all patients who score 1 are equal and some risk factors, such as age or history of stroke, transient ischemic attacks, or thromboembolic events, may weigh more heavily than others, such as diabetes mellitus or female sex. Also, some risk factors such as smoking or sickle cell disease are not included in the assessment tool but may play a role in the evaluation of specific individual patients. The HAS-BLED score may be considered when evaluating anticoagulation therapy.

**Conclusion:** Clinicians must exercise clinical judgment in individualizing anticoagulation options for patients who score 1 point on the CHA2DS2-VASc risk assessment tool.

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**Citation:** Pergolizzi JV, Magnusson P, Varrassi G, et al. (2020) NOAC in Patients with a Single CHA2DS2-VASc Risk Factor. *Int J Integr Cardiol*, Volume 2:2. 113. DOI: <https://doi.org/10.47275/2690-862X-113>.

**Received:** October 06, 2020; **Accepted:** October 19, 2020; **Published:** October 26, 2020

## Introduction

Atrial fibrillation (AF) is a prevalent arrhythmia, particularly in the geriatric population, and is associated with stroke and systemic thromboembolism [1]. AF-associated stroke increases morbidity and mortality [2]. The CHADS2 assessment tool was designed to help identify AF patients at high risk for stroke and thromboembolic complications so that anticoagulation therapy—at that time typically warfarin—could be initiated [2]. The advancement to the CHA2DS2-VASc tool allowed clinicians to better stratify stroke risk in AF patients at both low and high risk for such complications. In 2014, the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) issued guidelines that recommended CHA2DS2-VASc as the preferred risk assessment tool to use for stroke [3]. As thromboembolism and stroke risk are better elucidated and novel or non-vitamin-K antagonists (NOAC) have become the preferred prescribing choice for non-valvular AF, risk assessment for AF patients has been both clarified and complicated [4]. While a score of 0 on the CHA2DS2-VASc does not necessarily mean that there is no risk, guidelines do not recommend anticoagulation [5,6]. For patients with a score  $\geq 2$ , anticoagulation therapy should be considered and the more risk factors, the more urgent anticoagulation is [6,7].

Those who score 2 or higher on the CHA2DS2-VASc have a risk ratio (RR) for the stroke of 5.2, 95% confidence interval (CI), 3.9-6.9,  $p < 0.00001$  and 6.0 for thromboembolism (95% CI, 5.5-6.5,  $p < 0.00001$ ) compared to patients with lower scores, independent of anticoagulation used.

Thus, CHA2DS2-VASc can discriminate high-risk from lower-risk patients, independent of anticoagulation therapy [2]. But in identifying the lower-risk patient, the European Society of Cardiology in 2012 issued a guideline that said it was important to differentiate the “truly low-risk” patient from the “low-risk” patient, as the former does not need treatment while the latter does [7]. A patient who scores 0 on the CHA2DS2-VASc may be considered at low risk and anticoagulation is considered in patients who score  $\geq 2$ , but the challenge arises in how clinicians manage a patient who scores 1.

## Considering Each Point on the CHA2DS2-VASc

**Age:** The CHA2DS2-VASc test groups patients into one of three age strata: those under 65 (score 0), those between 65 and 74 (score 1), and those  $\geq 75$  years (score 2). The risk for stroke or thromboembolism increases with AF but it increases disproportionately among age groups [8]. Geriatric patients are at elevated risk for stroke even without AF,



and in patients with AF, the risk of stroke increases markedly with advanced age such that AF patients between the ages of 80 to 89 have a 23.5% risk of stroke [9]. Thus, if the patient is >65 years, anticoagulation should be considered even if there are no other risk factors.

**Sex:** While the lifetime risk for developing AF is greater in men than women after age 40 (26% vs. 23%, respectively), [10] women with AF are at greater risk for stroke and thromboembolism. Since the female sex scores one point, a woman cannot ever score 0 on the CHA2DS2-VASc assessment. In a study of 83,513 AF patients (44,115 women), the crude incidence of stroke was 2.02 per 100 person-years in women (95% CI, 1.95-2.01) and 1.61 per 100 person-years in men (95% CI, 1.54-1.69), a significant difference ( $p < 0.001$ ). This sex difference is largely the result of differences in patients >75 years [11]. Thus, a younger woman may be at less risk than an older woman, but older women should be considered for anticoagulation treatment. The reasons for this sex-specific difference are not clear, although women's use of certain oral contraceptives and hormone replacement therapy as well as the smaller size of blood vessels have been implicated [12].

### History of Congestive Heart Failure

Congestive heart failure (CHF) is comorbid with AF and the presence of both in one patient confers an elevated risk of mortality [10]. It is thought that this strong comorbid relationship is because the conditions share certain mechanistic similarities. However, AF and CHF are also associated with arrhythmic deaths and cardiac decompensation and not solely stroke risk [10]. Thus, a history of CHF alone may not be enough to initiate anticoagulation.

### History of Hypertension

Hypertension is present in 77% of patients who experience their first stroke and is often comorbid with AF [13,14]. For AF patients, hypertension may increase the risk of two- or three-fold [15]. While treatment of hypertension using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) can significantly lower the chances for developing AF, in patients with AF the treatment of hypertension with these medicines can reduce the risk of stroke [13]. Thus, hypertension in an AF patient should be treated but if it is the sole risk factor, it may not warrant anticoagulation therapy providing it can be adequately controlled pharmacologically.

### History of Stroke, Transient Ischemic Attack, or Thromboembolism

A prior history of stroke, transient ischemic attack (TIA), or thromboembolism counts as 2 points on the CHA2DS2-VASc assessment tool are very important risk factors and would automatically necessitate considering the AF patient for anticoagulation treatment.

### History of Vascular Disease (Myocardial Infarction, Peripheral Artery Disease, Aortic Plaque)

Prior cardiac events, such as myocardial infarction (MI), valvular heart disease, cardiac tumors, peripheral artery disease, aortic atherosclerosis, and patent foramen ovale increase the risk of stroke, particularly in the AF patients [16].

### Diabetes

Type 2 diabetes mellitus (T2DM) and obesity are prevalent and frequently comorbid and abdominal fat distribution remain a more robust predictor of stroke than body mass index (BMI) taken in

isolation [17,18]. Data from a meta-analysis (22 studies, >2.2 million patients) reported that an obese patient has a relative risk for a stroke of 1.64 (95% CI, 1.36-1.99) [19]. Weight loss with or without bariatric surgery has been associated with reduced stroke risk [20]. However, with effective medical management, diabetes can often be well controlled, and this lowers stroke risk [16,21].

### Other Risk Factors Not Included in the CHA2DS2-VASc Assessment

Some other risk factors are not encompassed in the assessment tool but can help guide a clinical decision in borderline cases.

### Nonmodifiable Risk Factors

There are some nonmodifiable risk factors. For example, stroke is more prevalent in Black and Latino populations in the United States than whites [22-24]. Genetic factors may play a role, although much remains to be elucidated [16]. Babies with a low birth weight (<2,500 g) are at increased risk of stroke later in life [25].

The adjusted odds ratio for stroke in women who suffer migraines with aura and without aura is 2.41 (95% CI, 1.72-2.43) and 1.29 (95% CI, 0.81-2.06), respectively, and the risk does not seem to be as great among men who typically are not migraineurs [26]. Sleep apnea has been shown to be an independent risk factor for stroke [27]. Sickle cell disease, an autosomal-recessive disorder, is associated with a high risk for stroke [28], and such strokes may occur in childhood. At least 11% of strokes in patients with sickle cell disease occur before the age of 20 although these may be silent strokes [29].

### Modifiable Risk Factors

Other risk factors may be modified by compliant patients, including lifestyle factors such as a healthful diet and exercise [16]. Hyperlipidemia is a controllable risk factor for ischemic stroke but the relationship between high lipid levels and stroke is complex and not entirely understood [30]. For instance, there is an inverse relationship between cholesterol level and the risk of hemorrhagic stroke [31], and the risk of stroke in patients with high triglyceride levels has not been established [32]. However, it is known that statin treatment for dyslipidemia reduces the risk of stroke in patients at risk of atherosclerosis [33].

Cigarette smoking may approximately double the patient's risk of ischemic stroke and passive or "second-hand" smoking is a risk factor as well [34]. Even occasional smoking can be dangerous; smoking one cigarette can increase blood pressure, decrease arterial distensibility, and ramp up heart rate [35,36] all of which can be dangerous in people with other risk factors. Consumption of large amounts of alcohol (>4 drinks or >3 drinks a day for men or women, respectively, or >14 or >7 drinks per week for men and women, respectively) is a stroke risk factor [37] and the risk of ischemic stroke has a linear relationship to the amount of alcohol consumed [38-40]. Drug use disorder has been linked to an increased risk of stroke [41,42] with such drugs as cocaine, opioids, and methamphetamines, but marijuana use has been implicated with a higher incidence of stroke [43,44]. A retrospective analysis found that patients with cocaine-associated intracerebral hemorrhage had a three-fold increased risk of death during hospitalization compared to similar stroke patients who did not use cocaine [45].

### Bleeding Risk

The HAS-BLED score was developed to help stratify patients at risk for bleeding due to anticoagulation therapy. Anticoagulation therapy is effective for AF patients but is not without risks. Most



**Table 1:** When considering the “one-point” patient with AF at possible risk for stroke.

Reason	To be considered
Age 65-74 years	Anticoagulation should be considered Note that age $\geq 75$ years is considered a strong risk factor (2 points) and anticoagulation treatment should be considered
Sex	Lowest possible total score for a female is 1, but if a female scores 1 for sex only, anticoagulation may not be necessary
CHF	May not be a strong consideration for anticoagulation
Hypertension	May not be a strong consideration for anticoagulation particularly if it can be pharmacologically managed (controlled hypertension reduces stroke risk)
Stroke, TIA, thromboembolism	Strong risk factor (2 points) and anticoagulation treatment must be taken into consideration
Vascular disease	Some types of cardiovascular disease can be managed, so this risk factor depends on the condition and the patient
Type 2 diabetes mellitus	Obesity, type 2 diabetes mellitus, and metabolic syndrome are all risk factors for stroke but in some cases may be managed pharmacologically. Weight reduction may ameliorate this risk.
HAS-BLED scores	If HAS-BLED scores indicate a high bleeding risk, this weighs against anticoagulation

AF patients are at risk for both strokes and bleeding, so the need for anticoagulation therapy must be balanced. The purpose of HAS-BLED is to stratify patients at greater risk for bleeding to put on the brakes for anticoagulation therapy. The HAS-BLED test has nine items and patients at low risk for bleeding may be better candidates for anticoagulation than those who have higher scores.

## Commentary

Anticoagulation therapy reduces the risk of stroke in AF patients and reduces all-cause mortality [6,46] Ischemic strokes associated with AF are often fatal and, for survivors, more likely to recur than strokes of other causes [6]. AF seems to exist as a preclinical condition described as “an arrhythmia in waiting” which in most patients progresses inevitably toward a permanent cardiac arrhythmia with serious adverse events [6]. There has been only limited success in delaying the progression of AF and curative attempts have been thwarted by the fact that leaving AF untreated seems to confer no undue risk to patients. These points are summarized in (Table 1).

## Considerations

Patients who score just 1 on the CHA2DS2-VASc assessment tool are not all equal. A young female with AF in otherwise good health with no other comorbidities may be at less risk than a man between the ages of 65 and 74 although both patients would score a 1 on the test metric. It is crucial to evaluate the various points on the scale to individualize care. Other risk factors for stroke have been documented but are not incorporated in the CHA2DS2-VASc assessment; nevertheless, clinicians need to exercise their judgment in individualized patient care. In other cases, recognized risk factors for stroke and thromboembolism, such as hypertension or diabetes, may be effectively medically managed in such a way that it reduces stroke risk. Other risk factors such as age  $\geq 75$  years or history of stroke are so serious that the patient should be immediately considered for anticoagulation.

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