# Antithrombotic Therapy in Nonvalvular Atrial Fibrillation: Consensus and Challenges

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## ABSTRACT

Atrial fibrillation (AF) is associated with high risk of systemic thromboembolism leading to significant morbidity and mortality. Warfarin, previously the mainstay for stroke prevention in AF, requires close monitoring because of multiple food and drug interactions. In recent years, food and drug administration has approved several direct oral anticoagulants (DOACs) for use in patients with nonvalvular AF. These agents have not been studied in patients with valvular AF who are at an even higher risk of systemic thromboembolism. DOACs do not require frequent blood testing or changes in dosage except when renal function deteriorates, however, the lack of established antidotes for many of these agents remains a challenge. Also, currently there is no head-to-head comparison between these agents to guide clinical choice. This article discusses the advantages and disadvantages of currently approved oral antithrombotics in nonvalvular AF, with a special emphasis on the DOACs and their individual characteristics.

**Key Indexing Terms:** Direct oral anticoagulants; Atrial fibrillation; Stroke; Antithrombotics. **[Am J Med Sci 2018;355(5): 467–476.]**

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It affects roughly 33.5 million people worldwide with approximately 5 million new cases each year.[1] An individual has a lifetime risk of approximately 25% of developing AF.[2] AF is associated with frequent hospitalizations, poor quality of life and increased risk of systemic thromboembolism (STE).[3] The risk of ischemic stroke in particular increases with age, reaching 23.5% between 80 and 89 years of age.[4]

Previously, warfarin, a vitamin K antagonist (VKA) first approved in 1954, was the sole choice for chronic oral anticoagulation. Management of patients on warfarin requires dietary counseling, frequent laboratory tests and close monitoring because of multiple food and drug-drug interactions.[5] Also, patients on warfarin often remain outside of the therapeutic range, thus increasing their risk of bleeding or STE. In the last 5 years, the food and drug administration (FDA) has approved many new direct oral anticoagulants (DOACs) for STE and stroke prevention in nonvalvular AF (NVAF). These DOACs do not require frequent blood work except for periodic renal function monitoring. DOACs also do not require frequent dose adjustments unless renal function is poor or deteriorates. This article provides an overview of current evidence for antithrombotic therapy in patients with NVAF.

## RISK STRATIFICATION STRATEGIES—STROKE VERSUS BLEEDING

The risk of stroke varies widely among patients with AF, and the decision to start antithrombotic therapy must be individualized after careful consideration of the risk of stroke and potential for serious bleeding. However, many of the baseline characteristics used in bleeding risk scores overlap with those forming stroke prediction models, denoting that patients at high risk of bleeding are also at high risk of stroke, hence risk of stroke should be the primary driving force in this decision-making. Several tools are available to predict the risk of stroke and bleeding in a patient with AF.[6]

The European Society of Cardiology and the American Heart Association/American College of Cardiology recommends using the clinical prediction rule $CHA_2DS_2$-VaSc score (congestive heart failure, hypertension, age ≥ 75 years [2 points], diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism [2 points], vascular disease including prior myocardial infarction, peripheral arterial disease and aortic plaque, age 65-74

years and female sex category) for assessment of stroke risk in patients with NVAF.[3] Compared to older risk stratification models, such as $CHADS_2$, the $CHA_2DS_2$-VaSc score is better at risk stratifying patients.[7,8] $CHA_2DS_2$-VASc has a C statistic (predictive ability) of 0.845, 0.877 and 0.885 for categorizing patients into risk groups at 1, 5 and 10 years, respectively, compared to 0.711, 0.789, and 0.806 for $CHADS_2$.[9] Using $CHA_2DS_2$-VaSc score, patients with a score of 0 are categorized as low risk and do not require antithrombotic therapy. Patients with a $CHA_2DS_2$-VaSc score of 1 are categorized as moderate risk and can be treated either with aspirin or an oral anticoagulant. It is also reasonable to omit antithrombotic therapy altogether in this group. All patients with a $CHA_2DS_2$-VaSc score of 2 or greater are considered high risk and should generally receive long-term antithrombotic therapy, unless their bleeding risk is prohibitive. Table 1 presents a comparison between $CHADS_2$ and $CHA_2DS_2$-VaSc scores.

The HAS-BLED score, which incorporates hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly and drugs or alcohol score has been validated for assessment of an individual's bleeding risk and found superior to other risk stratification schemes for bleeding.[10-12] However, a recent HAS-BLED, ATRIA (anticoagulation and risk factors in atrial fibrillation), mOBRI (modified outpatient bleeding risk index), and REACH (reduction of atherothrombosis for continued health) found these tools to have poor predictive value in AF patients receiving multiple antithrombotics after percutaneous coronary intervention (PCI).[13]

## VALVULAR VERSUS NVAF

Landmark trials comparing VKA with the DOACs excluded patients at very high risk of STE, the so-called "Valvular atrial fibrillation" population, as the pathogenesis of STE complications is postulated to be different in patients with valvular heart disease compared to other forms of AF.[14] However, the definitions of valvular and NVAF in these trials are not consistent, leading to confusion when deciding which type of antithrombotic therapy to choose.[15] For example, the randomized evaluation of long-term anticoagulation therapy trial (RE-LY), excluded patients with a prosthetic valve or hemodynamically significant valve disease, without defining the latter, while the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonist for prevention of stroke and embolism trial in atrial fibrillation trial (ROCKET-AF) excluded patients with prosthetic heart valves or hemodynamically significant mitral valve stenosis. In contrast, the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation trial (ARISTOTLE) only excluded patients with clinically significant mitral stenosis or mechanical prosthetic heart valves, but otherwise included a significant number of patients with valvular heart disease. A recently published substudy of the ARISTOTLE trial comparing the effect of apixaban versus warfarin between the subgroups of

**TABLE 1.** Definitions, scoring and comparison of $CHADS_2$ and $CHA_2DS_2$-VaSc scores.[3,7,8]

| Scoring associated with $CHADS_2$ and $CHA_2DS_2$-VaSc | | | |
|---|---|---|---|
| **$CHADS_2$** | **Score** | **$CHA_2DS_2$-VaSc** | **Score** |
| **C**ongestive heart failure | 1 | **C**ongestive heart failure | 1 |
| **H**ypertension | 1 | **H**ypertension | 1 |
| **A**ge ≥ 75 | 1 | **A**ge ≥ 75 | 2 |
| **D**iabetes mellitus | 1 | **D**iabetes mellitus | 1 |
| **S**troke/TIA/thromboembolism | 2 | **S**troke/TIA/thromboembolism | 2 |
| | | **Va**scular disease[a] | 1 |
| | | **A**ge 65-74 | 1 |
| | | **S**ex **c**ategory (female) | 1 |
| Stroke rate per 100-person years associated with $CHADS_2$ and $CHA_2DS_2$-VaSc[b] | | | |
| $CHADS_2$ Score | Stroke risk | $CHA_2DS_2$-VaSc | Stroke risk (%) |
| 0 | 1.9 | 0 | 0 |
| 1 | 2.8 | 1 | 0.6 |
| 2 | 4.0 | 2 | 2.2 |
| 3 | 5.9 | 3 | 3.2 |
| 4 | 8.5 | 4 | 4.8 |
| 5 | 12.5 | 5 | 7.2 |
| 6 | 18.2 | 6 | 9.7 |
| | | 7 | 11.2 |
| | | 8 | 10.8 |
| | | 9 | 12.2 |

[a] Prior myocardial infarction, peripheral arterial disease, or aortic plaque.
[b] Stroke risk is derived from the Swedish Atrial Fibrillation Cohort Study.