



## Controversies and updates in management of atrial fibrillation

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### Abstract

Atrial fibrillation (AF) is the most common arrhythmia leading to multiple comorbidities and cardiovascular (CV) mortality. Several controversies and questions always existed in the management of AF: the clinical significance of earlier detection of AF, importance of the duration and burden of AF, optimal rate control, rate and rhythm control controversies, stroke prevention strategies, cardioversion in AF less than 48 hours without prior anticoagulation, inadequate stroke risk assessment with current AF stroke risk calculators, dilemma of using class 1C antiarrhythmic drugs (AADs) in patients with AF with coronary artery disease (CAD), and when and how to perform catheter based AF ablation, etc. Recent knowledge from multiple observational, prospective and randomized control trials (RCTs) have helped us reshape our understanding in those areas to better treat those patients with tailored approaches taking into consideration of individual stroke and bleeding risk assessments.

**Key Words:** Atrial fibrillation, controversies, rate and rhythm control, antiarrhythmic drugs, catheter ablation.

Among arrhythmias, atrial fibrillation (AF) is the most common sustained form leading to multiple comorbidities, such as stroke, heart failure (HF) and dementia.<sup>1</sup> Prevalence of AF has been increasing with better detection, aging of the population, and longer survival of patients with AF.<sup>1,2</sup> Over the last decades, AF management has evolved from rate control to a more proactive rhythm control strategy to achieve and maintain in sinus rhythm. Several controversies persisted over the last decades about understanding of the mechanisms, detection and management of AF, which included rate control vs rhythm control strategies, choice of antiarrhythmic therapies, stroke prevention strategies, cardioversion and ablation therapies. With accumulation of enormous data from registries, prospective and RCTs, we have better understanding in certain areas, but some controversies still persist. The purpose of this review is to highlight some of the clinical controversies and progress in these areas.

#### Detection and burden of AF

AF is a global epidemic associated with comorbidity and mortality. Early detection of AF is essential to initiate a comprehensive approach to management, slow the progression of the disease, prevent complications like stroke and HF, and most importantly improve survival.<sup>3</sup>

AF is commonly diagnosed when the patient presents with symptomatic arrhythmia to a healthcare facility. In an asymptomatic patient, it could be detected on a routine clinical examination, by cardiac monitoring, implantable loop recorder (ILR), pacemaker interrogation, and recently, by smart wearable devices. The 12 lead ECG, once considered as the gold standard to confirm the diagnosis of AF, is only relevant in persistent AF, not in paroxysmal AF. Since 30% of strokes are cryptogenic, potentially from unrecognized AF, continuous monitoring with an ILR has shown increased detection of subclinical AF.<sup>4,5</sup> Initial data with ILR devices reported that even short episodes of AF were associated with increased risk of stroke.<sup>6</sup> Interestingly, in the randomized LOOP trial occult AF detection rate was nearly 30% in the ILR arm of this trial, but the reductions in stroke or systemic embolism risk were lower to usual care despite being on appropriate oral anticoagulation, which suggests that shorter duration subclinical AF might have less clinical importance compared to longer duration and/or clinically significant AF.<sup>7</sup> Upon further analysis the LOOP study also revealed that the subjects who had elevated levels of NT-proBNP were at higher risk of thromboembolic events or HF compared with those with lower levels,<sup>8</sup> suggesting the importance of finding those subsets of patients with AF who not only are at higher risk of stroke but also at risk of progression of HF.

However, the question remains what duration and burden of AF are clinically important to prevent stroke or systemic embolism, HF, or other adverse cardiovascular outcomes? AF burden is defined as the percentage of monitored time the person remains in AF.<sup>9</sup> Results from multiple studies have shown that the greater the burden of AF, the higher the risk of stroke and HF.<sup>10-13</sup> However, the episode duration related to increased stroke risk is variable.<sup>6,10,11,14</sup>

In the ASSERT study, subclinical AF episodes lasting at least 6 min were associated with an increased risk of stroke.<sup>6</sup> However, results from TRENDS,<sup>12</sup> the Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk (IMPACT)<sup>15</sup> study, and a time-dependent analysis for ASSERT<sup>6</sup> did not show clear temporal relationship between episodes of subclinical AF and stroke.<sup>15,16</sup> This further complicates our understanding of a connection between atrial stasis, thrombus formation, and stroke and raises the possibility that stroke mechanisms could be independent of episodes of subclinical AF.<sup>16</sup>

The recently published Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation (ATRESIA) trial showed that for patients with subclinical AF lasting 6 min to 24 hours, anticoagulation with apixaban resulted in a lower risk of stroke or systemic embolism than aspirin, but a higher risk of major bleeding.<sup>17</sup> Similarly, the NOAH-AFNET 6 trial demonstrated no reduction in CV death, stroke, or systemic embolism with edoxaban compared with placebo in a population at increased risk of stroke and with incidentally detected atrial high-rate episodes (AHRE) but without known AF, independent of AHRE duration.<sup>18</sup>

This study results suggest that the diagnosis of AF itself carries an increased stroke risk, compared to those exhibiting only AHRE. AHRE is still clinically relevant since about 1 in 5 patients was ultimately diagnosed with AF in this study. Unfortunately, the stroke risk calculators, such as CHA<sub>2</sub>DS<sub>2</sub>-VASc, (Table 1), ATRIA<sup>19-21</sup>

GRAFIELD-AF<sup>22,23</sup> were not developed taking into consideration of the burden of AF. Rather, they merely incorporated the presence or absence of AF. such as CHA<sub>2</sub>DS<sub>2</sub>-VASc, (Table 1), ATRIA<sup>19-21</sup> and GRAFIELD-AF<sup>22,23</sup> were not developed taking into consideration of the burden of AF. Rather, they merely incorporated the presence or absence of AF.

While the debate continues, based on the current strength of evidence, recently published ACC/AHA/ACCP/HRS guideline for AF recommends that for patients who have device-detected AF with high-rate episodes lasting greater than 24 hrs and CHA<sub>2</sub>DS<sub>2</sub>-VASc score <2, it is reasonable

to initiate oral anticoagulation after discussion with the patient.<sup>24</sup> For patients who have device-detected AF from 5 min to 24 hrs with CHA<sub>2</sub>DS<sub>2</sub>-VASc score

<3, with shared decision-making, it is reasonable to start oral anticoagulation for stroke prevention.<sup>24</sup> In patients with device-detected AF episodes lasting less than 5 min without another indication for anticoagulation, oral anticoagulation should be avoided.<sup>24</sup>

### Stroke prevention strategy

Stroke prevention is the most important aspect of AF management to improve survival and reduce comorbidities. Benefits of anticoagulation have been validated in all forms of AF including paroxysmal, persistent, long-standing persistent, and permanent forms of AF.<sup>25-27</sup> Anticoagulation strategy is guided by the patient's individual risk score, risk of bleeding with anticoagulation, and patient's preference. Absolute annual stroke risk score should be calculated by available AF stroke risk scores, which is considered low (≤1%), intermediate (1-2%) and high (>2%) (Table 1.).

**Table 1.** CHA<sub>2</sub>DS<sub>2</sub>-VASc Score and annual stroke risk. Adapted from Lip et al.,<sup>10</sup> and Gazova et al.<sup>28</sup>

Clinical condition		Points		CHA <sub>2</sub> DS <sub>2</sub> -VASc Score	Annual Stroke Risk (%)
Congestive heart failure	C	1		0	0
Hypertension	H	1		1	1.3
Age ≥75 years	A <sub>2</sub>	2		2	2.2
Diabetes mellitus	D	1		3	3.2
Prior stroke or TIA or Thromboembolism	S <sub>2</sub>	2		4	4.0
Vascular disease	V	1		5	6.7
Age 65 – 74 years	A	1		6	9.8
Sex category	Sc	1		7	9.6
				8	12.5
				9	15.2

CHA<sub>2</sub>DS<sub>2</sub>-VASc score = congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category

Based on the evidence current ACC<sup>24</sup> and ESC<sup>29</sup> AF guidelines recommend that AF patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2% in men and ≥3 in women should receive anticoagulation for stroke prevention.<sup>19,22,30-34</sup> Direct oral anticoagulants are better choice than warfarin, but should be avoided in patients with moderate to severe rheumatic mitral stenosis and mechanic valves.<sup>19,22,30-34</sup>

The net clinical benefit for patients with intermediate risk (non-sex CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1) is not as clear. Current ACC/AHA/ACCP/HRS AF guideline put anticoagulation of intermediate risk group with non-sex CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in class 2A indication.<sup>24</sup> A recently published population-based study focused on intermediate stroke risk group with non-sex CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1, the AFNOR (AF in Norway) trial showed that a combined outcome of ischemic stroke, major bleeding, and mortality was lower among AF patients who were on anticoagulation compared to those who were not.<sup>35</sup> These data may help guiding the shared decision making process while starting anticoagulation in this intermediate risk group.

Contrary to prior practice habits, recent studies have shown that aspirin either alone or in combination with clopidogrel is not recommended as an alternative to anticoagulation in patients with AF who are eligible for anticoagulation.<sup>36</sup> In addition, for patients with AF without risk factors for stroke, aspirin therapy has no benefit for prevention of stroke or peripheral thromboembolism.<sup>37,38</sup>

Despite commonly used, CHA<sub>2</sub>DS<sub>2</sub>-VASc score was found to be suboptimal in certain group of patients, like those with renal disease. When stroke risk is borderline or unclear with traditional CHA<sub>2</sub>DS<sub>2</sub>-VASc score, ATRIA<sup>39-41</sup> or GARFIELD-AF<sup>42,43</sup> scores could be helpful where additional risk factors, like smoking status, chronic kidney disease and dementia are included.<sup>24</sup> Individual risk assessment should be implemented to further define intervention strategies to reduce bleeding, such as stopping antiplatelet therapy or nonsteroidal anti-inflammatory drugs or consideration of left atrial appendage occlusion devices.<sup>44</sup> Recent interest in proBNP level as well as left atrium and left atrial appendage size and function could help better define stroke risk. However, these factors are not well validated and not yet incorporated into clinical decision making.<sup>45</sup>

If there is no absolute contraindication to anticoagulation, several studies have shown that stroke prevention benefits outweigh the risks of bleeding with anticoagulation, even in patients thought to be at elevated risk of bleeding.<sup>46,47</sup> It is important to note that the issue of anticoagulation should be periodically reassessed, maybe every 6 months, since a patient's risk profile may change over time, with the addition of new risk factors.<sup>24</sup>

### **Controversy about cardioversion of AF less than 48 hours without prior anticoagulation**

Not only can the duration and burden of AF be underestimated in asymptomatic AF patients, but also recent data suggest that stroke risk in patients with <48 hours of AF are not uniformly low. Multiple studies have shown that for patients with AF <48 hours, stroke risk with cardioversion increases with increase in CH<sub>2</sub>ADS<sub>2</sub>-VASc score,<sup>48,49</sup> particularly, when the score is  $\geq 2$  without prior anticoagulation. Patients with CH<sub>2</sub>ADS<sub>2</sub>-VASc score of 0 to 1 and AF duration of <12 hours represent the lowest risk of stroke post-cardioversion in the absence of prior anticoagulation.<sup>48</sup>

### **Rate Controls, Rhythm Control**

### **What is the ideal rate control?**

In the RACE II study (Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient Versus Strict Rate Control II) where 614 patients with permanent AF were randomized to either lenient rate control (resting heart rate <110 bpm) or strict rate control (resting heart rate <80 bpm), no significant difference was seen in primary composite outcome of death from cardiovascular causes, hospitalization for HF, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events.<sup>50</sup> However, specific populations that may benefit from a low heart rate target include those with rate-related cardiomyopathy,<sup>51</sup> those with implantable cardioverter-defibrillators,<sup>52</sup> those who received cardiac resynchronization therapy,<sup>53</sup> and those with tachy-brady episodes with AF.<sup>54</sup>

### **Rhythm Control**

Several studies have shown that a rhythm control strategy improves quality of life<sup>55-59</sup> and left ventricular (LV) function<sup>60-64</sup> in patients with AF. The benefit of rhythm control is likely the greatest in those with earliest restoration of sinus rhythm.<sup>65-68</sup> In the EAST-AFNET 4 randomized trial, rhythm control arm achieved a 25% reduction in the combined endpoint of mortality rate, stroke, and hospitalizations due to HF or acute coronary syndrome.<sup>69</sup> Two other observational studies, where rhythm control strategies were adopted early within the first year of onset of AF, showed a 15%<sup>70</sup> and 19%<sup>71</sup> reduction of combined endpoint of CV death, ischemic stroke, or hospitalization for ischemia or HF.

### **Class 1C drug dilemma in AF management**

As recommended by 2023 ACC/AHA/ACCP/HRS<sup>24</sup> and 2020 ESC<sup>29</sup> AF guidelines, Class 1C drugs flecainide<sup>72-74</sup> and propafenone<sup>74-80</sup> are preferred AADs for maintenance of sinus rhythm in patients with AF without any structural heart disease or prior history of myocardial infarction (MI).<sup>81,82</sup> Since the CAST (Cardiac Arrhythmia Suppression Trial)<sup>81</sup> published in 1991, class 1C drugs were not recommended in patients with CAD with or without MI. A large-scale data analysis recently published by Kiani et al.,<sup>83</sup> in 2023 further shed some light about the safety and feasibility of the treatment of AF in patients with varying degree of CAD with class 1C agents. The study included 3,445 patients with AF treated with class 1C AADs compared to 2,216 patients with AF who were treated with class III AADs, and concluded that in patients with stable and nonobstructive CAD, class 1C AAD use was independently associated with better event-free survival than with class III AAD use.<sup>83</sup> This study clearly established a negative interaction of class 1C drug with poorer survival in patients with obstructive CAD, suggesting the possibility of using class 1C AADs in patients with AF and nonobstructive CAD without prior history of MI.

## Caution with class III AADs

Dronedaronone can be used for maintenance of sinus rhythm but should be avoided in patients with recent decompensated HF or severe LV systolic dysfunction.<sup>74,84-86</sup> In RCTs, amiodarone<sup>87</sup> and dofetilide<sup>88</sup> have been shown to be effective in maintaining sinus rhythm in patients with AF and HF and these two AADs are better options in HF with reduced ejection fraction (HFrEF) where other AADs are contraindicated. It is important to note that low dose amiodarone is more effective in maintaining sinus rhythm compared to sotalol and class 1C drugs. However, amiodarone should not be the first choice and is reserved for patients for whom other AADs are not effective or contraindicated because of its potential serious side effects and drug interactions.<sup>24</sup> Unfortunately, regardless of ACC and ESC recommendations, class 1C drugs are still underused and amiodarone is still overused despite its potential long-term side effects.<sup>89</sup>

## New debate about catheter-based AF ablation (AF-ablation) strategy

Over the last decade, with accumulation of data from multiple recent trials, AF-ablation has become the major focus of AF management.<sup>90-97</sup> The new debate is when and how to perform AF-ablation. The EAST-AFNET 4<sup>69</sup> trial was the first RCT to reshape our long-held view from the AFFIRM<sup>98</sup> trial that there was no clinical benefit in rhythm control vs. rate control strategy in the management of AF. This trial clearly demonstrated the benefit of early rhythm control strategy to rate control.<sup>69</sup> It is important to note that 20% of patients in the early rhythm control strategy had AF-ablation compared to 7% in the rate control group. Trials exploring additional ablation targets apart from pulmonary vein isolation (PVI), such as VENUS (PVI with ethanol infusion of the Vein of Marshall),<sup>99</sup> ERASE-AF (PVI with posterior, inferior, septal, lateral and anterior left atrial wall segments)<sup>100</sup> and CONVERGE (PVI with LA roof line isolation or PVI with endocardial and epicardial posterior wall isolation)<sup>101</sup> trials, showed greater freedom from atrial arrhythmias compared to PVI only and no significant difference in adverse events between the treatment and control groups. Since traditional thermal ablation procedures have the potential for serious complications, such as pulmonary vein stenosis, phrenic nerve injury or esophageal injury,<sup>102</sup> the recently published PULSED AF Pivotal<sup>103</sup> trial using the newer generation pulsed field ablation technology demonstrated low procedure-related adverse events with no pulmonary vein

stenosis, phrenic nerve injury or esophageal injury, but was equally effective as thermal ablation.<sup>103</sup> AF-ablation has been shown to be more effective than AADs for both persistent and paroxysmal AF and that earlier approach of rhythm control strategies improve AF-ablation success rates.<sup>104-109</sup> It is important to note that about 30% to 40% of patients will have recurrence of AF after first ablation,<sup>104,110</sup> and about 11% of patients will have a repeat ablation in 1 year.<sup>111</sup> Though most patients have better quality of life post AF-ablation, recurrence of AF with symptoms or LV dysfunction will necessitate further treatment. Catheter ablation of typical atrial flutter has a high success rate of 90% and should be given consideration as a first-line therapy for treatment of typical atrial flutter, if not indicated for other reasons.<sup>24</sup>

## Current approach of AF with heart failure (HF) management

The relationship of AF and HF appears to be complex both pathophysiologically and clinically, and both disease entities frequently coexist.<sup>61,112,113</sup> Approximately one-third of patients with HFrEF will have AF at some point,<sup>114</sup> and the prevalence of AF is even higher in HF with preserved ejection fraction, approaching up to one-half of patients.<sup>115,116</sup> Regardless of reasonable rate control, allowing AF to persist longer, eventually will worsen LV function. Over the years, the focus has shifted in the treatment of AF with HF patients from rate control to rhythm control strategy with earlier intervention, preferably by catheter ablation. Multiple RCTs in patient with AF and HF have shown significant improvement of LV function and clinical symptoms after AF-ablation.<sup>67,114,117-120</sup> Romeo et al, 2022 recently published a large meta-analysis of eight RCTs showing a 35% relative risk reduction and 4.7% absolute risk reduction in all-cause mortality in AF-ablation arm compared to medical therapy in patents with AF and HF.<sup>121</sup> An early and aggressive approach to rhythm control by AF-ablation can reduce AF burden, resulting in favorable ventricular remodeling and halting of any occult tachycardia-induced cardiomyopathy.

## Conclusion

Apart from traditional risk calculators, new stroke risk markers should be further studied, incorporated, and validated for calculating individual risk assessment for AF-related thromboembolism to better understand the controversies that still exist. Despite significant advances in catheter-based ablation therapy, AADs will remain a cornerstone of rhythm control strategy for millions of AF patients worldwide. Unfortunately, more than two-thirds of AF recurrence happens in the first year of single or repeated ablations.<sup>105,122</sup> With recent advances in newer comprehensive ablation techniques, the AF recurrence rate is expected to improve. Ideal patient selection for AF ablation is still evolving. Though, AF-ablation is helpful to improve symptoms and halt progression of HF, a substantial number of patients will still require AADs to maintain their rhythm despite



being ablated. Recent advancement in molecular biology of AF have helped us better understand the mechanisms underlying different forms of AF and identify newer approaches to develop mechanism-based AADs, including AF-specific ion-channel blockers, targeting the abnormal Ca<sup>2+</sup>-handling such as Ca<sup>2+</sup>-calmodulin protein kinase II, ryanodine receptor type-2, and modulation of upstream signal pathways.<sup>123</sup>

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## **Declarations**

Conflict of interest: The author declares no conflict of interest.

## **Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by the author.

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