

# Atrial fibrillation and thromboprophylaxis in heart failure: the need for patient-centered approaches to address adherence

Caleb Ferguson<sup>1</sup>  
Sally C Inglis<sup>1</sup>  
Phillip J Newton<sup>1</sup>  
Sandy Middleton<sup>2,3</sup>  
Peter S Macdonald<sup>3,4</sup>  
Patricia M Davidson<sup>1,3</sup>

<sup>1</sup>Center for Cardiovascular and Chronic Care, University of Technology, <sup>2</sup>National Center for Clinical Outcomes Research (NaCCOR), Australian Catholic University, <sup>3</sup>St Vincent's Hospital, Darlinghurst, Sydney, Australia; <sup>4</sup>Victor Chang Cardiac Research Institute, University of New South Wales, Sydney, Australia

**Abstract:** Atrial fibrillation is a common arrhythmia in heart failure and a risk factor for stroke. Risk assessment tools can assist clinicians with decision making in the allocation of thromboprophylaxis. This review provides an overview of current validated risk assessment tools for atrial fibrillation and emphasizes the importance of tailoring individual risk and the importance of weighing the benefits of treatment. Further, this review provides details of innovative and patient-centered methods for ensuring optimal adherence to prescribed therapy. Prior to initiating oral anticoagulant therapy, a comprehensive risk assessment should include evaluation of associated cardiogeriatric conditions, potential for adherence to prescribed therapy, frailty, and functional and cognitive ability.

**Keywords:** stroke risk, heart failure, atrial fibrillation, anticoagulation, risk stratification, medication adherence

## Introduction

Heart failure (HF) is a complex and primarily cardiogeriatric syndrome.<sup>1</sup> One-third of patients with HF are likely to have atrial fibrillation (AF) as a concomitant condition.<sup>2</sup> AF is a predictor of stroke in patients with HF.<sup>3</sup> Therefore, predicting and treating the risk of stroke with definitive therapies, including antithrombotics, is highly justified and recommended by best practice guidelines.<sup>4-6</sup> Yet, commonly these therapies are not applied in practice.<sup>7</sup> Under 70% of estimated eligible patients receive anticoagulation therapy.<sup>7</sup>

Although the use of anticoagulants has increased in the past 2 decades,<sup>8</sup> those individuals considered to be at an increased risk of bleeding are less likely to be prescribed anticoagulation therapy.<sup>8</sup> As a consequence, patients may not be receiving therapy based purely upon their predicted stroke risk alone. Many factors contribute to clinical decision making amongst physicians that influence prescription.<sup>9,10</sup> Factors such as cognitive impairment and frailty are common reasons for clinicians choosing not to prescribe thromboprophylaxis.<sup>11,12</sup>

This is a clinical conundrum for health professionals in prescribing evidence-based therapy and deciding if the risk of treatment outweighs the risk of nontreatment.<sup>13</sup> The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial compared dose-adjusted warfarin with 75 mg aspirin in elderly patients over 75 years. The investigators found that warfarin was associated with a significant reduction in stroke with no difference in the risk of significant hemorrhage.<sup>14</sup> However, the Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm (WARCEF) study,<sup>15</sup> although conducted in people with sinus rhythm and not AF, showed that the benefit of warfarin

Correspondence: Caleb Ferguson  
235–253 Jones St, PO Box 123, Ultimo,  
Sydney, NSW, 2007, Australia  
Tel +61 2 9514 4816  
Fax +61 2 9514 4835  
Email [caleb.ferguson@uts.edu.au](mailto:caleb.ferguson@uts.edu.au)

in reducing ischemic stroke was offset by an increased risk of major hemorrhage.<sup>15</sup> Underpinning the choice to prescribe thromboprophylaxis should be one that is individualized to the risk of the patient.

This review provides a critique of current risk assessment tools for the evaluation of stroke and bleeding risk in AF. Further, it identifies the need to extend these assessments to factors that impact treatment adherence and to consider risks for adverse events, particularly bleeding. Strategies for promoting adherence to prescribed therapy are also included.

## Stroke and bleeding risk assessment schemata in AF

Risk classification schemata are intended to guide treatment decisions in AF by defining the likelihood of future clinical events based on independent risk factors.<sup>13</sup> Risk scores can be used to estimate the absolute risk of an adverse event. This may be helpful in counseling patients and informing treatment decisions.<sup>16</sup> These metrics do not consider the balance of risk of adverse events and potential nonadherence. The CHADS<sub>2</sub> (congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism) score (Table 1) was

derived from the Atrial Fibrillation Investigators' and Stroke Prevention in Atrial Fibrillation Investigators' schemata. This was validated in a retrospective cohort of hospitalized patients with AF. A score of zero identified patients at low stroke risk. A score of one to two identified patients at moderate stroke risk. A score greater than two identified patients at high stroke risk.<sup>17,18</sup> Patients with two or more points are predicted to have an annual stroke risk of over 4%, whereas those scoring no points have a predicted annual risk of less than 1%–2%.<sup>18</sup>

The Stroke Prevention in Atrial Fibrillation (SPAF) scheme estimates risk based upon the presence of the following risk factors alone or in combination: age, female sex, diabetes, previous stroke or transient ischemic attack, hypertension, or elevated systolic blood pressure.<sup>19,20</sup> Similarly, the Framingham scheme can be used to risk assess stroke risk through the assignment of values to each of the following well-established independent risk factors: age, gender, systolic blood pressure, diabetes, and prior stroke or transient ischemic attack.<sup>16,20</sup> The CHADS<sub>2</sub>, SPAF, and Framingham schemes have demonstrated greater predictive accuracy than chance.<sup>20</sup> This predictive ability may allow clinicians to target high-risk patients for more aggressive therapeutic intervention.<sup>20</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category) score, provides the highest sensitivity of all schemes to predict thromboembolism (Table 1).<sup>21</sup>

A number of bleeding risk stratification tools exist. Amongst these are the HEMORR<sub>2</sub>HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count, rebleeding risk, anemia, genetic factors, excessive falls risk, stroke)<sup>22</sup> and the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly, drug/alcohol concomitantly)<sup>23</sup> tools, yet these are not often used in clinical practice and use is cumbersome. Many use complex scoring systems, and few have been validated in patients with AF and HF. The HAS-BLED bleeding risk tool originated in 2011 and was validated in a European cohort of 3978 participants with AF (Table 2). In a comparative validation, the HAS-BLED tool displayed an increased predictive ability than four other bleeding risk stratification methods<sup>22,24–26</sup> among patients in the combined Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V cohort.<sup>23</sup> Following validation, the HAS-BLED tool was suggested as a simple, yet easy to calculate tool

**Table 1** Stroke risk stratification with CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc assessment tools

	Score	CHADS <sub>2</sub> score	Adjusted stroke rate (%/year)
<b>CHADS<sub>2</sub> acronym</b>			
Congestive heart failure	1	0	1.9%
Hypertension	1	1	2.8%
Aged $\geq$ 75 years	1	2	4.0%
Diabetes mellitus	1	3	5.9%
Stroke/TIA	2	4	8.5%
Max score	6	5	12.5%
		6	18.2%
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc acronym</b>			
Congestive heart failure/ LV dysfunction	1	0	0%
Hypertension	1	1	0.7%
Aged $\geq$ 75 years	2	2	1.9%
Diabetes mellitus	1	3	4.7%
Stroke/TIA/TE	2	4	2.3%
Vascular disease (prior to MI, PAD, or aortic plaque)	1	5	3.9%
Aged 65–74 years	1	6	4.5%
Sex category (ie, female gender)	1	7	10.1%
Max score	10	8	14.2%
		9	100%

**Abbreviations:** LV, left ventricular; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; TIA, transient ischemic attack.

**Table 2** The HAS-BLED score

Clinical characteristic	Score	HAS-BLED score	Bleeds per 100 patient-years
Hypertension	1 point	0	1.13
Abnormal liver or kidney function	1 point each (1 or 2)	1	1.02
Stroke	1 point	2	1.88
Bleeding	1 point	3	3.74
Liabile international normalized ratios	1 point	4	8.70
Elderly	1 point		
Drugs or alcohol	1 point each (1 or 2); max 9 points		

**Notes:** Hypertension = systolic blood pressure > 160 mmHg; abnormal renal function = dialysis/renal transplantation/serum creatinine > 200 mmol/L; abnormal liver function = chronic hepatic dysfunction (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin twice the upper limit of normal in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase three times the upper limit of normal); bleeding = history of bleeding or a bleeding diathesis; drugs = concomitant use of antiplatelet or nonsteroidal antiinflammatory drugs.

that can be used to assess bleeding risk in AF patients within everyday clinical practice.<sup>13</sup> A HAS-BLED score of at least three indicates high risk and the developers of the tool suggest the need for regular review and some caution following the initiation of oral anticoagulant or aspirin therapy.<sup>13</sup>

## Adherence

Failing to adhere to recommendations is a major reason for adverse events.<sup>27</sup> Adherence is a multidimensional phenomenon determined by the relationship of five series of factors or dimensions. There are five dimensions within the World Health Organization's multidimensional adherence model, which incorporate socioeconomic-, health care system-, condition-, treatment-, and patient-related factors;<sup>28</sup> this model assists in providing a framework for the organization of barriers to anticoagulant therapy (Table 3). Implications for practice including strategies that may be employed to improve adherence are also provided.

Once the need for oral anticoagulation is identified, several additional factors must be considered. Despite the evidence demonstrating the benefits of anticoagulation therapy in AF and HF, adherence to these recommendations is far from optimal.<sup>10,29,30</sup> The hesitation to anticoagulate patients is often based upon fear of adverse effects and poor adherence with monitoring, and this is most pronounced in the elderly.<sup>12</sup> The need for monitoring and titration as well as the adverse effect profile likely contributes to this reticence.<sup>31</sup> Although the use of newer agents such as oral direct thrombin inhibitors (eg, dabigatran) and oral factor Xa inhibitors (eg, rivaroxaban and apixaban) show particular promise in decreasing monitoring, concerns regarding adherence and adverse events remain high.<sup>13</sup> Despite data describing the barriers and facilitators to thromboprophylaxis in the elderly, there has been a lesser focus on individuals with HF who are at high risk.<sup>12</sup> New approaches, that are patient centered, are

required to enhance evidence-based use of therapy to prevent thromboembolism and identify risk of bleeding.<sup>32</sup>

## Health system-related factors

Clinical trials and meta-analyses have demonstrated the effect of anticoagulation in reducing the risk of ischemic stroke in patients with AF.<sup>33–37</sup> Yet, a large proportion of patients with AF are not treated with anticoagulant therapy. Despite the well-recognized association between AF and prevention of ischemic stroke and the benefits of therapy, anticoagulant therapy remains underused in AF patients.<sup>7</sup> There are numerous reasons why anticoagulant therapy is not initiated, but it is largely due to clinician and patient concerns about the risk of falls and hemorrhagic complications.<sup>7</sup> Clinicians may be apprehensive about initially prescribing oral anticoagulants to elderly patients given the concerns about a higher risk of oral anticoagulant-associated hemorrhage.<sup>38</sup>

**Table 3** Barriers to thromboprophylaxis

Health system-related factors	Clinician apprehension Fear of intracranial hemorrhage and falls Lack of multidisciplinary approach Urban versus rural resource barriers
Treatment-related factors	International normalized ratio monitoring Dietary restrictions Risk of hemorrhage
Socioeconomic-related factors	Cost of medication Cost of visiting clinics Ability to attend clinics
Patient-related factors	Level of cognition Medication and condition knowledge Language difficulties Inadequate patient education
Condition-related factors	Polypharmacy Frailty Cognitive and functional impairment Stress and depression

Of 4188 patients in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study with AF who were newly commenced on warfarin therapy, more than one-quarter of patients had discontinued treatment after 1 year.<sup>39</sup> The study authors hypothesized that this may have been due to difficulty in INR control or concerns from clinicians or patients about bleeding risk.<sup>39</sup> More recently, in a Swedish atrial fibrillation cohort study, in almost all patients within a large cohort of 182,678 patients with AF, the risk of ischemic stroke without anticoagulant treatment was higher than the risk of intracranial bleeding with anticoagulant treatment.<sup>40</sup>

### Solution to health system-related factors

Clinician apprehension may be reduced through providing training and education and practical clinical practice guidelines that provide support for clinical decision making.<sup>41–43</sup> The additional use of a bleeding prediction tool (eg, HAS-BLED) with the stroke risk prediction tool (eg, CHA<sub>2</sub>DS<sub>2</sub>-VASc) may also assist in clinical decision making.<sup>13</sup> Undertaking chart reviews and clinical audits and excluding patients with documented contraindications to therapy may assist in the identification of patients who are eligible for oral anticoagulant therapy; however, this is not prescribed as a method to increase uptake.<sup>44</sup> From a wider health systems perspective, having access to a state or national surveillance system or the development of a national AF and anticoagulation registry is advocated.<sup>41,45</sup> Clinician adherence to guidelines is a complex issue.<sup>46</sup> Cabana et al offer a range of barriers why clinicians don't follow guidelines. They include barriers affected by clinician knowledge (eg, lack of awareness or lack of familiarity), attitudes (lack of agreement, lack of self-efficacy, lack of outcome expectancy, or the inertia of previous practice), or behavior.<sup>47</sup> A way to improve clinician adherence to guidelines may include developing specialized anticoagulation clinics with expert nurses and doctors as a way to reduce clinician apprehension when commencing patients on oral anticoagulant therapy.<sup>48</sup> This warrants further exploration.

### Treatment-related factors

Both the efficacy and safety of warfarin therapy are strongly correlated with therapeutic dosages.<sup>49</sup> An INR of 2.0–3.0 is well established as a therapeutic target range for stroke prevention in AF;<sup>50,51</sup> therefore, time that a patient spends within their range of target INR should be maximized.<sup>50,52</sup> A major concern is intracranial hemorrhage, which is associated with high morbidity and mortality.<sup>53,54</sup> Novel anticoagulants appear to have a more favorable safety profile

than warfarin, as evident through large clinical trials.<sup>55–57</sup> One of the foremost attractions of such novel agents including oral direct thrombin inhibitors and factor Xa inhibitors over warfarin is that they have predictable pharmacokinetics, therefore reducing or eliminating the burden of routine anticoagulation monitoring. Nevertheless, reversal of such newer agents can be complex and problematic.<sup>58</sup>

### Solutions to treatment-related factors

In patients with normal kidney function and an estimated glomerular filtration rate > 30 mL/minute, thromboprophylaxis should be selected accordingly after a comprehensive clinical assessment. Dabigatran and rivaroxaban are excreted by the kidneys (dabigatran 80% and rivaroxaban 66%), therefore dosage may require adjustment according to estimated glomerular filtration rate.<sup>59</sup>

Many patients continue to be prescribed warfarin therapy, requiring them to have their INR monitored, which can be burdensome.<sup>7</sup> Health infrastructure must be supportive and enabling of this need for surveillance. Ensuring regular INR monitoring to maintain therapeutic targets and avoid adverse events is critical.<sup>38</sup> Rural outreach or metropolitan hospital liaison services and dedicated anticoagulation clinics are one such approach to achieve these goals.<sup>41</sup> INR self-check kits are an effective strategy to encourage patients with self-care.<sup>60</sup> However, patients must be able, well-informed, and be supplied with a coagulometer.<sup>60</sup> Although providing financial incentives to patients to attend clinics or visit clinicians to increase attendance rates is novel, uptake is low.<sup>61</sup>

### Socioeconomic-related factors

The annual cost of anticoagulation with warfarin is estimated to be £207.30 in comparison to £1573.50 with the novel anticoagulant dabigatran (per patient; excluding the cost of INR monitoring).<sup>62</sup> The high cost of medication can prohibit initial purchase and continuation of therapy. In some instances this may lead to doses skipped in order to save money.<sup>63</sup> Costs associated with visiting a primary care physician or other member of the multidisciplinary health care team may discourage essential follow-up visits. It is essential to monitor the effectiveness of therapy. These factors may prohibit optimal care and outcomes of oral anticoagulation therapy.

### Solutions to socioeconomic-related factors

Several suggested solutions have been offered to deal with such barriers. These include the use of innovative

technologies like self-check INR kits to undertake self-care at home. This limits the need for frequent visits to primary care, though this may be an expensive appliance which the patient may have to purchase and maintain.<sup>60</sup> A level of cognitive capacity and knowledge is required to interpret results and respond to these in an appropriate manner.<sup>64</sup> Point of care and health rebate systems as well as monitoring pharmacy refill records may assist in the uptake and maintenance of therapy.<sup>41</sup>

## Patient-related factors

Medication adherence in HF is a poorly understood yet fundamental aspect of patient care.<sup>65</sup> Medication adherence rates within the HF population vary widely.<sup>66</sup> Patients are required to balance the need for prescribed medication against any perceived adverse drug event, which may lead to nonadherence or permanent discontinuation of use of oral anticoagulant medications.<sup>67</sup> Such suboptimal drug use is associated with an increase in unplanned hospital admissions, increased mortality and morbidity rates, and accompanied by additional health care-related costs.<sup>68</sup> It has been estimated that patients who do not take their medications as prescribed costs the US health care system \$290 billion in avoidable health-related spending every year.<sup>69</sup>

## Solutions to patient-related barriers

The World Health Organization emphasizes that despite the vast amount of knowledge that exists around adherence issues, efforts to address the problems have been divided and – with a few exceptions – have failed to encapsulate the potential contributions of the diverse health disciplines.<sup>28</sup> The World Health Organization advocates that a stronger buy-in and commitment to a multidisciplinary model is required in order to make progress in the area of poor adherence.<sup>28</sup>

Poor patient education is a commonly cited problem contributing to poor adherence.<sup>43</sup> Patient knowledge is a determinant of anticoagulation control.<sup>43</sup> A lack of the perception of medication importance, risk of adverse events, irregular monitoring of serum INR, or a lack of the perception of risk-to-benefit threshold may lead to adverse events.<sup>43</sup> Inadequate self-management counseling and language difficulties also contribute to this multifaceted issue.<sup>70</sup> Bajorek et al advocate that a pharmacist-led multidisciplinary process within the hospital setting may increase overall antithrombotic therapy use.<sup>71</sup> Simplified drug regimes and improved case management comprising of patient education and discharge counseling may be of value.<sup>71</sup> This must address the behaviors and preferences of individual patients.

Interventions that target the elderly and those with poor literacy are vital.<sup>72</sup> Such strategies may include providing pamphlets and printed materials with colors, pictures, and visual aids, the enlargement of materials, compact disc read-only memory (CD-ROM) or spoken materials, structured educational programs, the mailing of educational materials, or even online resources and social media patient education interventions.<sup>41</sup> Explicit instructions to primary care providers at patient discharge from acute care, patient reminder cards, and patient forums that provide peer support may be of help.<sup>41</sup> Telemonitoring may prove an effective method to improve medication adherence for HF patients at home. It was recently reported that HF patients using structured telephone support and telemonitoring experienced improvement in the use of evidence-based pharmacotherapy.<sup>73</sup>

## Condition-related factors

### Polypharmacy and falls

Polypharmacy and comorbidity are fundamental factors that affect medication adherence. Patients with HF and AF may be using antiplatelet therapy<sup>74</sup> or are likely to have concurrent use of multiple medications with antihypertensive properties that predispose patients to symptomatic orthostatic hypotension, syncope, or falls.<sup>75</sup> Being at an increased risk of falling may inevitably lead to an increased risk of hemorrhage, particularly intracranial if a head injury is sustained during a fall due to syncope. There are many explanations for an increased risk of falling. This may only be perceived by the clinician because of age.<sup>75</sup> However, this may be attributable to gait,<sup>76</sup> cognitive impairment, or dementia.<sup>43</sup> Anticoagulant therapy should not be denied based on age alone.<sup>75</sup>

### Dietary restrictions

Patients may have dietary restrictions or preferences. This may affect pharmacokinetics and may lead to suboptimal coagulation and impact time spent in a therapeutic range.<sup>67</sup>

### Associated condition burden

Frailty,<sup>12</sup> cognitive and functional impairment,<sup>11</sup> stress,<sup>70</sup> and depression<sup>77</sup> are all conditions associated with HF and AF. These conditions may lead to failure to adhere to appropriate INR monitoring or reduced adherence through the cognitive or physical inability to self-administer oral medications. Comparable to patients with cognitive decline, there is evidence that patients with mental health conditions and AF are less likely than those without mental health conditions to have adequate AF management.<sup>78</sup> Depression has been identified as a moderately common condition in HF,<sup>79</sup> and



was associated with poor medication compliance in the Heart and Soul Study.<sup>77</sup>

## Solutions to condition-related factors

### Polypharmacy and falls

Clinicians ought to assess the risk of falls using reliable and valid methods. Planning fall minimization interventions should be in collaboration with the multidisciplinary team.<sup>44</sup> Assessment of any underlying conditions including neuropathy, frailty, and cognitive concerns should be investigated.<sup>80</sup> Cognitive ability can be evaluated using reliable and validated and readily accessible measures such as the Mini Mental State Examination or The Montreal Cognitive Assessment.<sup>81</sup>

The use of once-daily medication formulations or polypills may aid improved adherence.<sup>82</sup> Whilst this may be achievable with HF treatments where doses of many medications remain consistent once up-titrated, this may present difficulties in AF with varying dosages of certain anticoagulants and the need to regularly adjust dosage according to the INR.

### Dietary restrictions

Clinicians must ensure that a dietician consultation with specific dietary advice regarding vitamin K intake occurs. This may occur via telephone consultations or clinic visits. This is a simple yet imperative strategy that may reduce the risk of inadequate anticoagulation. Patients altering their dietary intake of green leafy vegetables should be encouraged to notify their clinician as their dosage of warfarin may require adjustment.<sup>83</sup>

### Monitoring adherence

Patient self-reporting is a useful method of assessing medication adherence. Self-reporting offers reliable predictors of a broad array of cardiovascular health outcomes – including blood pressure control, hospitalization for HF, and serum drug concentrations – that are highly applicable to this group of patients.<sup>77</sup> There are a number of tools available to measure self-reported adherence. The Morisky Scale provides good predictive ability and can be easily integrated as part of a comprehensive patient assessment prior to the commencement of any oral anticoagulant therapy.<sup>84</sup>

### Associated condition burden

Although there are numerous risk stratification tools available to assist clinicians in allocating treatments, they

do not consider frailty, which impacts adversely on health outcomes.<sup>12</sup> Cognitive and functional decline are significant consequences of both HF and AF.<sup>85</sup> Undertaking a formal frailty assessment may assist in the guidance of prescribing of oral anticoagulants and may help clinicians identify patients who are at increased risk of adverse events from anticoagulant therapy.<sup>12</sup> Further investigation is warranted to examine the causal relationship between depression and adherence particularly in the HF and AF patient population. Where depression exists, the inclusion of a mental health clinician in the multidisciplinary care model providing care to the patient may be of benefit.<sup>74</sup>

Enhanced models for stratifying bleeding risk particularly in the frail population are required.<sup>45</sup> Frailty assessment tools that currently exist could be used as an adjunct to any stroke risk prediction tool. Any new models or frailty assessment criteria should additionally be incorporated into clinical practice guidelines.<sup>45</sup> Strategies that aim to reduce or manage falls including assistance from family, relatives, informal caregivers, or the provision of home help should not be overlooked.

## Implications for clinical practice

Further research is required to examine the issue of anticoagulant therapy in patients with HF and AF. This is driven by population growth in the elderly and the increasing burden of the cardiogeriatric population.<sup>86,87</sup> Available data suggest it may be useful to include a risk assessment of other aspects of a patient's life as opposed to the restrictive tools that currently exist. Nonadherence with medication and other lifestyle recommendations is a major problem in patients with HF and has severe consequences for individual patients as well as for the health care system.<sup>88</sup> Treatment and care should take into account patients' individual needs and preferences. However, most people with AF should be considered for treatment with oral anticoagulants based on their risk of stroke, ability to tolerate anticoagulation without bleeding, and access to adequate anticoagulation monitoring.

Although there are robust stroke prediction tools, they cannot be considered external to a cardiogeriatric assessment. Extending and developing these tools to consider the risk of nonadherence to prescribed therapy and poor adherence are warranted. Currently, there is no comprehensive risk assessment tool that includes criteria that assesses or addresses the psychosocial aspects of a patient's ability to comply with anticoagulant therapy as well as the risk of stroke. Although novel agents offer promise, they still

confer risk and do not negate the importance of individual monitoring.

## Conclusion

Current stroke risk prediction tools are useful, yet limited, within the context of complex cardiogeriatric syndromes. Expanding these to consider frailty, cognitive and functional decline, or nonadherence to therapy is warranted. Although avoiding stroke is an important consideration, the potential adverse effects of treatment needs to be balanced within the context of best available evidence, clinical expertise, and the individual patient's circumstances.<sup>89</sup> Developing metrics that consider the combination of these factors are likely to shed light on the issues of adherence in this population.

## Disclosure

The authors report no conflicts of interest in this work.

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