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Review

Thromboembolic risk stratification in atrial fibrillation—beyond clinical risk scores

Darryl Wan[1,†], Jason Andrade[1,2,3,†], Zachary Laksman[1,*,†]

[1] Department of Medicine, Heart Rhythm Services, University of British Columbia, Vancouver, BC V5Y, Canada

[2] Department of Medicine, Montreal Heart Institute, University of Montreal, Montréal, QC H2L, Canada

[3] Center for Cardiovascular Innovation, Vancouver, BC V5Y, Canada

*Correspondence: zlaksman@mail.ubc.ca (Zachary Laksman)

† These authors contributed equally.

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Atrial fibrillation (AF) is the most common arrhythmia in the adult general population. As populations age, the global burden of AF is expected to rise. AF is associated with stroke and thromboembolic complications, which contribute to significant morbidity and mortality. As a result, it remains paramount to identify patients at elevated risk of thromboembolism and to determine who will benefit from thromboembolic prophylaxis. Conventional practice advocates the use of clinical risk scoring criteria to identify patients at risk of thromboembolic complications. These risk scores have modest discriminatory ability in many sub-populations of patients with AF, highlighting the need for improved risk stratification tools. New insights have been gained on the utility of biomarkers and imaging modalities, and there is emerging data on the importance of the identification and treatment of subclinical AF. Finally, the advent of wearable devices to detect cardiac arrhythmias pose a new and evolving challenge in the practice of cardiology. This review aims to address strategies to enhance thromboembolic risk stratification and identify challenges with current and future practice.

Keywords

Atrial fibrillation; Stroke; Risk scores

1. Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia in the adult general population [1]. As populations age, the shifting demographic is expected to lead to rising rates of AF. Population-based studies have estimated that AF will affect over 5.6 million patients in the United States alone by the year 2050 [2]. This has a substantial implication to public health, as AF is associated with heart failure and thromboembolic complications, both of which lead to morbidity and mortality [3]. Current guidelines advocate for the use of clinical risk scoring systems to stratify thromboembolic risk in patients with non-valvular AF [4–6]. However, clinical risk scores may be problematic in specific populations where predicted thromboembolic risk may not reflect clinical experience. Advances in clinical research and implementation of novel technologies have contributed to the enhancement of risk stratification paradigms.

Problems with clinical risk stratification

Clinical risk scores have tremendous utility due to the ease of calculation, and previous validation in large populations. However, there remain challenges and pitfalls with clinical risk scores that limit their applicability to certain populations. In addition, the discriminatory ability of clinical risk scores to predict stroke risk in any given individual is moderate at best. Several studies assessing the utility of various clinical risk scores have shown moderate performance in stroke prediction with C-statistics of 0.65–0.70 [7].

2. Clinical risk scoring

2.1 Comparing clinical risk scores

Several clinical risk scores have been proposed to aid in thromboembolic risk stratification in patients with AF. The best known are the $CHADS_2$ and CHA_2DS_2-VASc scores, which are frequently recommended by national guidelines to guide thromboembolic prophylaxis. However, other risk prediction paradigms exist, such as SPAF, $CHADS_2$-R, ATRIA, Framingham, and GARFIELD-AF.

Renal dysfunction was found to be a significant independent predictor of stroke and systemic embolism in the ROCKET-AF study. As a result, the R_2CHADS_2 score was devised and validated for clinical use. In the derivation cohort, the R_2CHADS_2 score modestly outperformed the $CHADS_2$ score (C-statistic 0.587 vs. 0.575), and the CHA_2DS_2-VASc score (C-statistic 0.578) [8]. The minimal incremental predictive value is likely the reason that there has not been widespread adoption of this model.

Few studies have directly compared the accuracy of multiple risk scores in predicting thromboembolic events. One such study compared 9 well-known risk stratification schemes in a retrospective community-based cohort [9]. Of note, the proportion of patients categorized as low risk was highly variable between risk scores, ranging from 5% using the CHA_2DS_2-VASc score, up to 14% using SPAF. When the predictive ability of the risk scores were compared, all scores

performed similarly, with c-statistics ranging from 0.57–0.66. While this suggests only a moderate predictive performance at best, the most accurate risk stratification schemes were SPAF (c = 0.659), $CHADS_2$-R (c = 0.654) and $CHADS_2$ classical (c = 0.653) [9].

Despite the adoption of the CHA_2DS_2-VASc score by major societal guidelines, several large scale studies in North American, Swedish and the United Kingdom have shown improved discrimination in predicting stroke using the ATRIA risk score. In addition, the ATRIA risk score has been useful in more accurately identifying higher risk patients who would otherwise be classified as low risk by the CHA_2DS_2-VASc score [7, 10, 11].

More recently, the GARFIELD-AF tool has gained popularity as a web-based module to guide stroke prevention strategies in AF. The advantage of the GARFIELD-AF tool is its ability to stratify risk of ischemic embolism, bleeding and all-cause mortality with a single tool. The tool was derived using stepwise regression, then validated in the ORBIT-AF dataset. The GARFIELD-AF tool outperformed the CHA_2DS_2-VASc score in all patients (C-statistic 0.69 vs. 0.64), and in low risk patients (C-statistic 0.65 vs. 0.59) as well [12].

The totality of evidence suggests that clinical risk scores are useful for rapid assessment at the bedside, but have modest discriminatory ability at best. While some risk scores consistently outperform others in statistical analysis, the incremental predictive value may not warrant clinical adoption (Fig. 1).

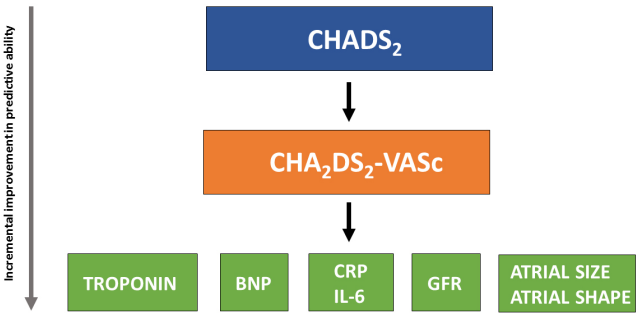

Fig. 1. Incremental improvement in predictive ability with the incorporation of additional risk factors. $CHADS_2$ (Congestive heart failure; Hypertension; Age ≥75; Diabetes; Stroke), CHA_2DS_2VASc (Congestive heart failure; Hypertension; Age ≥75 [2 points]; Diabetes; Stroke [2 points]; Vascular disease; Age 65–74 [1 point]; Female), BNP (B-type natriuretic peptide), CRP (C-reactive protein), IL-6 (Interleukin-6), GFR (Glomerular filtration rate).

2.2 Temporal trends in AF and stroke

The conventional paradigm dictates that AF leads to stasis and pooling of blood in a diseased left atrium. This in turn increases the likelihood of thrombotic clot formation, particularly in the left atrial appendage. Embolization of these clots lead to obstruction of blood flow in systemic vascular beds and are responsible for cardioembolic strokes and other systemic thromboembolic phenomena. While it has previously been proposed that the duration or burden of AF is irrelevant with regards to stroke risk, more contemporary evidence from patients with continuous intracardiac device monitoring has suggested that the burden of AF may in fact be associated with higher risk [13, 14].

The TRENDS study was a prospective observational cohort study that enrolled 2486 patients with at least one risk factor for stroke, and who were undergoing implantation of an intracardiac device capable of monitoring rhythms. While the overall thromboembolic burden was low, the data suggested that patients with longer durations of atrial tachycardia (AT) or AF were more likely to have thromboembolic complications [14]. However, the temporal relationship between AT/AF and stroke was unclear. A later sub-study of patients from TRENDS who had suffered stroke or systemic embolism revealed that only 26% of these patients had any AT or AF detected in the 30 days prior to their embolic event [15]. This suggests that the temporal relationship between atrial arrhythmia and stroke is not fully understood, and the complication of thromboembolism may not be solely due to the presence of AF.

However, it should also be emphasized that AF is not the sole cause of stroke. In another analysis of the ASSERT study, strokes were subclassified by type, and subclinical AF (SCAF) was found to be potentially causal of many caridioembolic strokes, but only acting as a risk factor in 43% of strokes [16]. However, a growing body of evidence suggests that AF is merely a manifestation of systemic or local cardiovascular dysfunction, and that thromboembolic risk begins to increase before the overt manifestation of an atrial arrhythmia. Studies on the role of biomarkers, as well as anatomic and functional characterization of the left atrium, provide some insight into the mechanisms around thromboembolic risk [17–20].

2.3 Biomarkers

Several biomarkers have been studied as adjunctive markers of thromboembolic risk assessment in patients with nonvalvular AF. This was initially proposed in 2006, when Lip *et al.* demonstrated the utility of adding von Willebrand factor plasma levels to conventional clinical risk scores. This resulted in further enhancement of prediction of vascular events, but not ischemic strokes [21].

The most widely studied and clinically applicable biomarkers are troponin and B-type natriuretic peptide (BNP) [17, 18]. Other studies have also assessed the utility of biochemical markers of hypercoaguability such as D-dimer and antithrombin-III [18]. In a sub-study from the ENGAGE AF-TIMI 28 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thorombolysis in Myocardial Infarction 28) trial, the utility of biomarkers was evaluated using a nested prospective study in a multinational randomized trial. This study analyzed high-sensitivity troponin T, NT-proBNP and growth differentiation factor-15

as potential markers to improve stroke risk prediction in patients with non-valvular AF. While the study showed a statistically significant improvement in the C-index when biomarkers were combined with clinical data (ABC stroke score; age, biomarkers, clinical history) for stroke prediction, the improvement was modest (0.67 [95% CI, 0.65–0.70] for biomarkers plus clinical features versus 0.59 [95% CI, 0.66–0.71] for CHA_2DS_2-VASc score alone; $p < 0.001$) [17].

The ABC stroke score was recently applied as a predictive model to predict other cardiovascular adverse events. The score was shown to have incremental value in predicting myocardial infarction, heart failure, cardiovascular mortality, and all-cause mortality. This highlights the point that biomarkers in this setting tend to be non-specific markers or patients who are generally unwell [22].

Markers of inflammation such as interleukin-6 (IL-6) and C-reactive protein (CRP) have also been hypothesized to alter thromboembolic risk. This was studied in a cohort of patients from the RE-LY (Dabigatran versus Warfarin in Patients with Atrial Fibrillation) trial. In this analysis, IL-6 was independently associated with stroke or systemic embolism ($p = 0.0041$) and CRP was associated with a composite thromboembolic outcome ($p = 0.0001$) including stroke, systemic embolism, myocardial infarction and vascular death. However, when added to the CHA_2DS_2-VASc score, the C-index for stroke or systemic embolism only increased to 0.642 from 0.615 ($p = 0.0017$) [19].

In addition, markers of elevated oxidative stress have also been suggested to contribute to adverse vascular outcomes in patients with AF. By adding serum NOX2 levels and urinary F2-IsoP in an anticoagulated population with AF, Pignatelli *et al.* [23] showed a modest improvement in prediction of vascular events over the CHA_2DS_2-VASc score, with an improved net reclassification index.

The totality of these studies suggest that while many biomarkers can be shown to have statistically significant associations with stroke or systemic embolism in patients with non-valvular AF, the discriminatory ability that these add above clinical risk scores is modest and unlikely to be clinically useful. The presence of abnormal biomarkers is nonspecific and reflects the state of an unwell patient. In addition, the pathophysiology of AF and stroke involves a complex interplay of biochemical factors, and the sole abnormality of any one marker is insufficient to justify anticoagulation [24]. Finally, many biomarkers have been studied in the context of highly selected populations, many of whom are anticoagulated [24]. To date, biomarkers have not been incorporated into guidelines from major societies, reflecting the practical clinical inapplicability.

2.4 Atrial structure and function

The concept of atrial cardiomyopathy has been sporadically used in the literature to describe histologic and anatomical disease processes that may be involved with the development and maintenance of AF. Until recently, a consensus definition and classification of atrial cardiomyopathy has not existed [20].

It has long been postulated that the mere size of the left atrium is likely related to thromboembolic potential. Studies of left atrial size and the associated impact on thromboembolic risk have been limited, but largely inconsistent. While some studies suggest that increasing left atrial size is associated with stroke and systemic embolism, other studies have failed to show the same effect. An inherent challenge of these studies is that left atrial size remains challenging to characterize on conventional 2-dimensional echocardiography. Most studies have assessed left atrial diameter according to conventional guideline-recommended measurement. However, fewer studies have assessed the relationship of left atrial volume on thromboembolic risk. Studies from a Norwegian cohort have also suggested that left atrial size appears to be independently associated with stroke risk, regardless of the presence of clinically apparent AF [25]. The totality of these studies shows no consistent association between left atrial dilation and thromboembolic risk. It remains unclear if left atrial dilation is merely a manifestation of underlying comorbidities such as chronic AF, hypertension and diastolic dysfunction, or whether it represents an independent and clinically meaningful risk factor in stroke risk assessment.

Until recently, the robust and reproducible assessment of left atrial function has been challenging. Spectral Doppler and tissue Doppler studies have previously been used to characterize atrial function. Recent studies have described the use of deformation analysis using strain and strain rate to describe abnormalities in atrial function. Speckle tracking left atrial strain provides insight into the assessment of reservoir, conduit and booster pump function. In a longitudinal study of 1361 patients with a first diagnosis of AF followed for a mean of 7.9 years, indices of left atrial strain were found to be independently associated with incident stroke. After adjusting for clinical risk factors, LA reservoir strain (HR 0.73 [95% CI 0.55–0.95] for every 10% change; $p = 0.020$) and P-wave to A' duration on tissue Doppler imaging (HR 1.08 [95% CI 1.02–1.15] for every 10 ms change; $p = 0.012$) were independently associated with risk of stroke. The C-statistic for this model was 0.7587 [26]. This suggests that assessment of left atrial function can provide incremental information in stroke risk characterization, but has yet to be validated in a prospective longitudinal study.

The left atrial appendage (LAA) is thought to be an area of increased blood stasis and a nidus for thrombus formation responsible for systemic embolic events. This has led to several studies investigating the effect that LAA morphology may have on thromboembolic stroke risk. A multi-center retrospective study of 932 patients with drug-refractory AF showed that patients with a "chicken wing" morphology were much less likely to have had a history of stroke (OR 0.21, 95% CI 0.05–0.91; $p = 0.003$) when compared to other distinct morphologies, even after adjusting for clinical risk factors in a logistic model [27].

These studies point towards an emerging role of structural assessment in thromboembolic potential in patients with AF, but none have been studied in robust prospective clinical trials.

3. Defining thromboembolic risk in the individual

Thromboembolic risk scores are most useful at estimating population-based risk, but often fail when applied to the individual. This is especially true in low risk patients.

The primary utility of clinical risk scoring is to identify patients at high risk of thromboembolism, and who would therefore benefit from oral anticoagulation. However, patients stratified as "low risk" by clinical risk scores have traditionally been a challenging population when attempting to predict stroke risk. The $CHADS_2$ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke) score was previously popularized as a convenient and practical clinical risk stratification tool. However, patients with low risk scores of 0 and 1 have variable rates of stroke and thromboembolism, which has led to the development of the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age $\geq$75, Diabetes, Stroke, Vascular disease, Age 65 to 74, Sex), which has improved utility in this population.

It should also be recognized that the individual components of these risk scores confer differing levels of risk, such that not all patients with a score of 1 may be truly at low risk of stroke or systemic embolism. This may relate to variable levels of risk associated with specific risk factors. Female sex, for example, is associated with a 0.7% annual rate of thromboembolism, whereas having an age over 65 is associated with an annual risk of 1.9% [28]. Similar findings of significant heterogeneity in stroke rates were found when investigators assessed patients with an ATRIA clinical risk score of 0 to 5 (low risk). In this study, the rate of stroke or systemic embolism ranged from 1.13 to 36.94 per 100 patient-years in 1-year follow-up, and 0.78 to 13.79 per 100 patient-years in 13-year follow-up [29]. This highlights the heterogeneity of patients classified as low risk by clinical risk scores and indicates that further granularity and individualization of risk is necessary in this population to identify those truly at low risk. The inherent risk is variable depending on which individual risk factor the point is assigned to. This may account for some of the variability in patients traditionally stratified into low risk categories.

The interaction between clinical risk factors also remains unclear. It has been suggested that certain combinations of risk factors may impart higher risk when considered together, compared to other combinations. The online Calculator of Absolute Stroke Risk (CARS) was conceived to define the 1-year absolute stroke risk using large Danish registries. This showed a significant variability in the 1-year stroke risk amongst patients who were clinically stratified into each CHA_2DS_2-VASc score. The presence of a prior stroke, and advancing age were found to be the most potent determinants of individualized stroke risk [30]. This is supported by studies showing age as a powerful driver of stroke risk and there may be a threshold at which absolute age should be considered more strongly when deciding to anticoagulate patients at intermediate risk [31].

An additional consideration that is not included in clinical risk scoring paradigms is the impact of ethnicity. Several studies of East Asian patients have shown higher thromboembolic event rates when compared to Caucasians with identical clinical risk scores [32, 33]. A study of a Taiwanese cohort has advocated for the reduction of the age threshold of 65 years in the CHA_2DS_2-VASc paradigm, to 50 years in Taiwanese patients due to a finding of higher event rates of 1.78% per year in patients $>$50 years, and 0.53% per year in patients $<$50 years [34]. Similarly, an analysis of a Danish cohort showed higher risks of stroke compared to US cohorts [11, 35, 36] (Fig. 2).

Part of the difficulty in estimating individual stroke risk lies in the variability in reported rates of stroke across various populations who are not receiving anticoagulation. When data was analyzed from 4 prominent AF cohorts, the CHA_2DS_2-VASc score threshold above which anticoagulation showed a net clinical benefit ranged from 0 to 3 based on a Markov decision model [37]. This variability is inherent to the population being studied, and the pre-determined definition of stroke or embolic outcome.

An additional consideration is that of bleeding risk. Indeed, many risk factors associated with bleeding when considering therapeutic anticoagulation overlap with risk factors that predict thromboembolic potential. Hence, the risk of bleeding must be compared with that of stroke and systemic embolism. This balance must be continually reassessed as patient comorbidities change, and as advancing age remains a powerful predictor of both thromboembolic and bleeding events.

While some individuals may have an elevated thromboembolic risk when compared to their counterparts, the benefit of lifelong anticoagulation is not necessarily always justified. This must be balanced appropriately with a lifelong elevated risk of hemorrhagic events. A study by Eckman *et al.* [38] determined that the benefits of anticoagulation begin to outweigh risks when there is an annual ischemic stroke risk of 1.7% for warfarin, and 0.9% for dabigatran based on a Markov state transition model. However, the threshold above which anticoagulation is indicated remains a subject of debate. Accordingly, American, European and Canadian guidelines have adopted different approaches in defining low risk patients [4–6]. The Canadian guidelines use a threshold of about 1.5% per year to justify anticoagulation. Therefore, female sex and the presence of vascular disease are not considered [6]. In contrast, while the European guidelines have also excluded female sex from risk stratification [4], vascular disease is included. Finally, the American guideline does not ignore any individual risk score, but rather allows the treating clinician to use judgement across the spectrum of patients

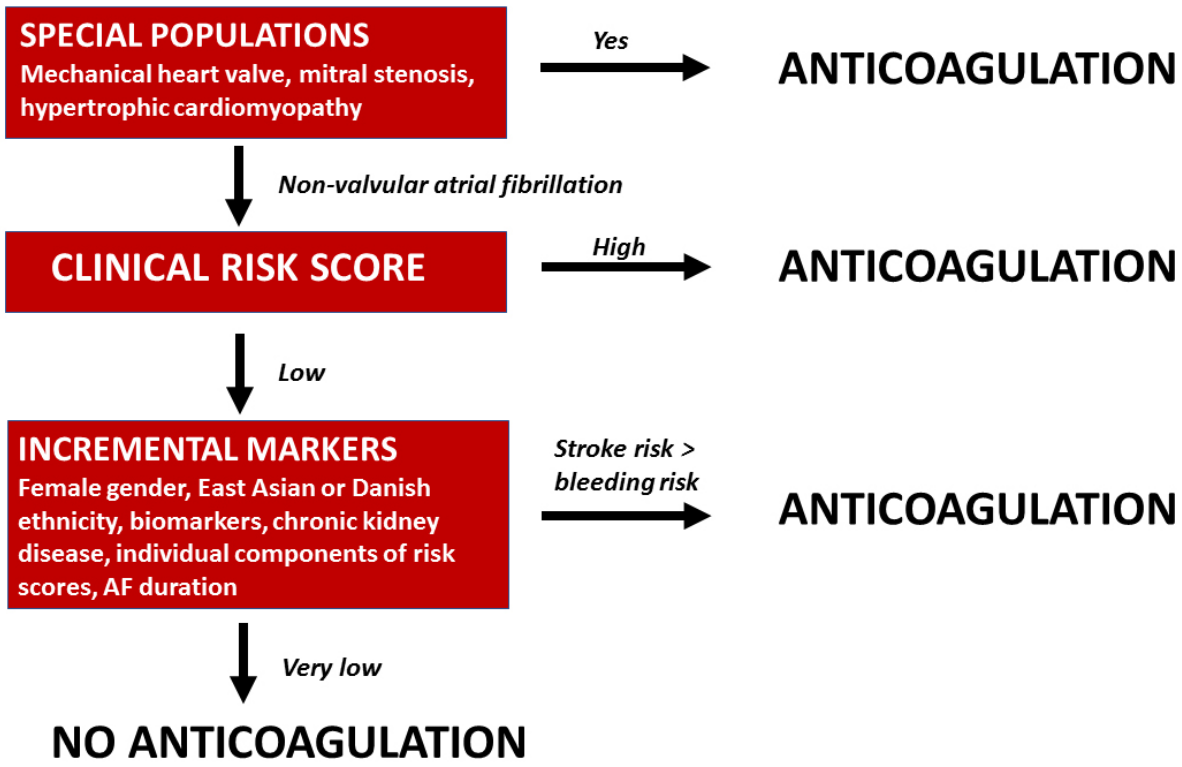

Fig. 2. Individualization of stroke risk stratification in patients who are classified as low risk by clinical risk scoring criteria. AF, atrial fibrillation.

with a single point in clinical risk scoring [5]. Such uncertainty in defining the benefit of anticoagulation in low risk patients is a result of the quality of evidence that characterizes this population. Study results are conflicting but are based on observed rates of stroke in registries or unanticoagulated cohorts, rather than large clinical trials [36, 39, 40].

4. Special populations

Several populations require special assessment when considering individualized thromboembolic risk stratification. These populations are frequently encountered but are poorly represented in original derivation cohorts for clinical risk scores, and the applicability of such scores are therefore limited.

4.1 Hypertrophic cardiomyopathy

Patients with hypertrophic cardiomyopathy (HCM) are inherently at elevated risk from thromboembolic complications. It is well recognized that AF is the most common arrhythmia in patients with HCM. This is due to a number of factors including left atrial dilation, increased filling pressures, and predisposition based on certain pathogenic genetic mutations. The thromboembolic event rate in patients with AF and HCM has been estimated at 3.75% per year [41]. In a landmark study of 900 unselected HCM patients, the cumulative incidence of stroke in non-anticoagulated patients with concurrent AF was as high as 31%. This was reduced to 18% in patients taking warfarin [42].

As a result, European and American guidelines on hypertrophic cardiomyopathy have advocated for the use of anticoagulation in patients with HCM and AF [43, 44]. Clinical risk scores have not been validated in this population, and are therefore not recommended. All patients with HCM who develop AF are therefore recommended to start anticoagulation with either a vitamin K antagonist or direct oral anticoagulant (DOAC) [45].

4.2 Valvular disease

The presence of valvular heart disease is associated with incident AF [46]. However, the nature of the specific valvular lesion greatly affects the thromboembolic potential of the individual when considered in combination with AF. The definition of valvular AF is variable depending on major societies. The most recent Canadian guidelines define valvular AF as that which occurs in the setting of any mechanical heart valve, or moderate to severe mitral stenosis (rheumatic or nonrheumatic) [6]. The 2019 American Heart Association/American College of Cariology/Heart Rhythm Society guidelines have defined valvular AF as moderate-severe mitral stenosis, or the presence of a mechanical valve [47]. The 2020 European Society of Cardiology guidelines similarly define valvular AF as patients with moderate/severe mitral stenosis and those with mechanical prosthetic valves, but also recommend that the terminology is confusing and should be abandoned altogether [48].

Rheumatic mitral stenosis results in pressure overload of the left atrium, which leads to adverse structural and electrical remodelling. This in turn leads to increased burden and severity of AF, and a risk of left atrial thrombus development. In patients not receiving anticoagulation, the thromboembolic complication rate has been estimated as high as 5.7% per year in patients with concurrent mitral stenosis and AF [49]. Studies have also shown that thromboembolism can be safely reduced using vitamin K antagonists [50]. Current guidelines have recommended that patients with mitral stenosis be anticoagulated with a vitamin K antagonist if they have concurrent AF, prior embolism, or left atrial appendage clot, as these patients were excluded from contemporary trials of DOACs [51].

Individuals with prosthetic valve implantation have independent recommendations for antiplatelet and anticoagulant therapy depending on the method and type of valve implanted [51, 52]. However, despite the need for lifelong anticoagulation in patients with mechanical valve prostheses, the use of DOACs in this population is contra-indicated. The RE-ALIGN study was designed to assess the utility of dabigatran in patients with mechanical prostheses, but was stopped prematurely due to excessive bleeding and thromboembolic complications in the treatment arm [53]. Small observational studies have indicated that the use of DOACs in the chronic setting of bioprosthetic valvular prosthesis is safe [54].

As many patients with rheumatic valvular disease or mechanical valve prostheses were considered to require anticoagulation regardless of AF, these patients were excluded from contemporary trials of anticoagulation in AF. In a pooled analysis of randomized clinical trials of DOACs in AF, 13,574 patients with native valvular heart disease (excluding moderate-severe mitral stenosis and mechanical prosthetic valves) were analyzed. This showed that DOACs may be superior to warfarin for prevention of stroke and systemic embolism without a significant difference in the rates of major bleeding [55]. In an expert opinion survey of Canadian cardiologists, the use of DOACs was felt to be contraindicated due to valvular AF in mechanical valve prosthesis (100% agreement), moderate-severe mitral stenosis (88% agreement), and moderate-severe non-rheumatic mitral stenosis (69% agreement) [56]. American guidelines have similar recommendations to avoid the use of DOACs in patients with moderate-severe mitral stenosis or mechanical valve prosthesis, based on exclusion criteria of contemporary anticoagulation trials [5].

4.3 Other special populations

Several other populations warrant mention when considering thromboembolic risk. These populations require individualized stratification of stroke risk, as there are no large scale nor well-established data to guide practice.

Adults with congenital heart disease have several potential risk factors for thromboembolism. Atrial arrhythmias are a common cause of morbidity and mortality in this population [57]. However, other factors such as intracardiac shunting, pulmonary hypertension, Fontan circulation and coagulopathy also affect thromboembolic risk and are not well represented in clinical risk scores [58].

Patients with chronic kidney disease also pose a clinical challenge. The coexistence of AF and renal disease seem to perpetuate each other. As a result, this leads to an elevated thromboembolic risk, which is juxtaposed by a paradoxical elevation in hemorrhagic risk. Similarly, pregnancy induces physiologic changes which alter thromboembolic risk. This needs to be balanced with the hemorrhagic risk when planning around delivery. The evidence and literature surrounding pregnancy-related thromboembolism is beyond the scope of this review.

Finally, AF has been associated with some inherited cardiomyopathies such as arrhythmogenic right ventricular dysplasia, familial dilated cardiomyopathy, and left ventricular non-compaction (LVNC). However, while some populations such as LVNC are well known to have elevated thromboembolic potential, there remains no consensus regarding indications to initiate anticoagulation for primary thromboprophylaxis [59].

5. Device detected AF

5.1 Subclinical AF

The effect of duration of AF in patients with subclinical paroxysmal AF remains controversial. Recent studies of device detected subclinical atrial fibrillation (SCAF) provide some insights into the thromboembolic risk associated with SCAF.

The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) trial enrolled 2580 patients who were 65 years of age or older and had a recent intra-cardiac device implanted. Patients were monitored for 3 months to detect any evidence of atrial tachyarrhythmia, then followed for a further 2.5 years to detect a primary outcome of stroke or systemic embolism. 10.1% of patients had subclinical atrial tachyarrhythmias detected, which was associated with an increased risk of developing clinical AF (HR 5.56; 95% CI 3.78–8.17; $p < 0.001$), as well as ischemic stroke or systemic embolism (HR 2.49; 95% CI 1.28–4.85; $p = 0.007$) [60]. While this provided evidence that atrial tachyarrhythmias could be precursors to clinical AF, the annual thromboembolic event rate of 1.69% per year in patients with subclinical tachyarrhythmias detected was lower than what would be expected in a comparable cohort of patients with clinical AF. A later analysis of the ASSERT data stratified patients into cohorts based on the longest duration of AF. This found that patients with SCAF >24 hours are at highest risk of thromboembolic complications (adjusted HR 3.24; 95% CI 1.51–6.95; $p = 0.003$). Patients with no SCAF, SCAF lasting 6 minutes to 6 hours, and SCAF lasting 6 hours to 24 hours had comparable event rates [13].

Despite evidence of increased stroke risk in this population, the benefit of prophylactic anticoagulation is uncertain.

A retrospective cohort study of data from Veterans Health Administration revealed significant practice variation in the management and prescription of anticoagulation for patients with device-detected SCAF. Even for patients with AF >24 hours, prescription for oral anticoagulation was completed for 31% of patients, but this ranged from 0 to 60% across 52 sites. In multivariate regression, prescription of oral anticoagulation was associated with a reduction in stroke (HR 0.28; 95% CI 0.1–0.81; $p = 0.02$) [61].

The IMPACT study tested a strategy of initiation and termination of anticoagulant therapy based on detection of atrial tachyarrhythmia. The study was ultimately terminated due to futility and minimal differences in the primary composite outcome of stroke, systemic embolism and major bleeding between the intervention arm (63 events in 1357 patients) and the control arm (61 events in 1361 patients) [62]. However, as the primary outcome was a composite of thromboembolic and bleeding events, the therapeutic strategy of introducing anticoagulation would be expected to reduce thromboembolism and increase bleeding. This may have contributed to the overall neutrality of the study.

Despite the rising recognition that increasing frequency and duration of AF may be associated with elevated thromboembolic risk, the benefit of anticoagulation in subclinical AF is not clear. The Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial (NCT01938248) is currently enrolling patients with SCAF between 6 minutes to 24 hours, and randomizing to receive apixaban or aspirin. This event driven trial will assess a primary outcome of ischemic stroke or systemic embolism, and perhaps provide guidance for therapeutic strategies in this cohort.

5.2 Wearable-detected AF

The evolution of technology has significantly reduced the size and cost of cardiac rhythm monitoring devices, making some devices freely available to the mass market. These devices use two main forms of technology to assess underlying rhythm disturbances. Photoplethysmography (PPG) involves using an illuminator on skin surface, which is then transmitted or reflected onto a photodiode. This information is received and can track pulsatile blood flow, akin to a standard pulse oximeter. Patterns of heart rate variability based on R-to-R intervals are fed through proprietary algorithms to determine if the detected pattern is consistent with sinus activity. Direct electrocardiography uses a minimum of two poles on various parts of the body to create a circuit, thereby allowing the measurement of cardiac electrical activity. This is similar to measurement of a single lead on an ECG recording.

The Apple Heart Study was a pragmatic real-world large-scale study that allowed 419,297 participants to self enroll over a period of 8 months [63]. This study, sponsored by Apple, aimed to assess the proportion of patients with AF shown on an ECG patch using a PPG-based technology in combination with an irregular pulse notification algorithm. Variability between R-R intervals were recorded as tachograms, which were collected and generated a notification if five out of six irregular tachograms were detected within a 48-hour period. Participants who were sent a notification were prompted to arrange a telemedicine visit and were subsequently sent an ECG patch to be worn for up to 7 days. During a median of 117 days, 0.52% of participants received a notification of irregular pulse. 20.8% of these patients were sent and returned an ECG patch. AF was detected in 153 (34%, 97.5% CI 29–39) of these patients. The positive predictive value of the individual tachogram was 0.71 (97.5% CI 0.69–0.74), and of the irregular pulse notification was 0.84 (95% CI 0.76–0.92) [63]. While this study was not designed to assess the specificity or sensitivity of the technology in diagnosing AF, it is reassuring that the detection rate was relatively low in this self-enrolled population.

Similarly, the Huawei Heart Study using the Huawei phone and compatible wrist band or watch yielded a device alert of "suspected AF" in 0.23% of patients in a general population using PPG-based technology. Of the patients who were effectively followed-up the positive predictive value was 91.6% (95% CI 91.5–91.8) [64]. While these devices require a dedicated wrist band or watch to implement the technology, others have assessed the more accessible option of using a smartphone camera. In the DETECT AF PRO study, a PPG-based algorithm was shown to be 89.9% sensitive and 99.1% specific for detecting AF based on a 1 minute analysis using the camera on a smartphone [65]. This has been shown to be a feasible way of screening a general population using hardware that is widely available and software that is easily accessible [66].

The AliveCor Kardia device has been studied as a tool to enable screening for AF in the community. The REHEARSE-AF study randomized 1001 patients without a previous history of AF to routine care versus the intervention arm [67]. Patients randomized to the intervention arm were given an AliveCor Kardia device and instructed to transmit recordings at least twice a week for a period of 12 months. 19 patients in the intervention arm versus 5 patients in the routine care arm were diagnosed with AF (HR 3.9; 95% CI 1.4–10.4; $p = 0.007$). While numerically different, there was a non-statistically significant difference in the number of strokes and systemic embolisms between the groups (6 in the intervention arm versus 10 in the control arm; HR 0.61; 95% CI 0.22–1.69; $p = 0.34$) [67]. A Canadian study in primary care clinics showed similar feasibility using the AliveCor KardiaMobile ECG device [68]. 184 primary care physicians screened a total of 7585 patients 65 years of age or older with no previous history of AF. AF was detected in 471 (6.2%) of patients, and clinicians reported a high perceived clinical value on a Likert scale-based questionnaire. Interestingly, 270 (57%) patients were initiated on anticoagulation based on screening findings alone, while the remainder awaited other confirmatory testing, specialist referral, or had contra-indications [68]. Similar findings were seen in a larger study including 612 community-based pri-

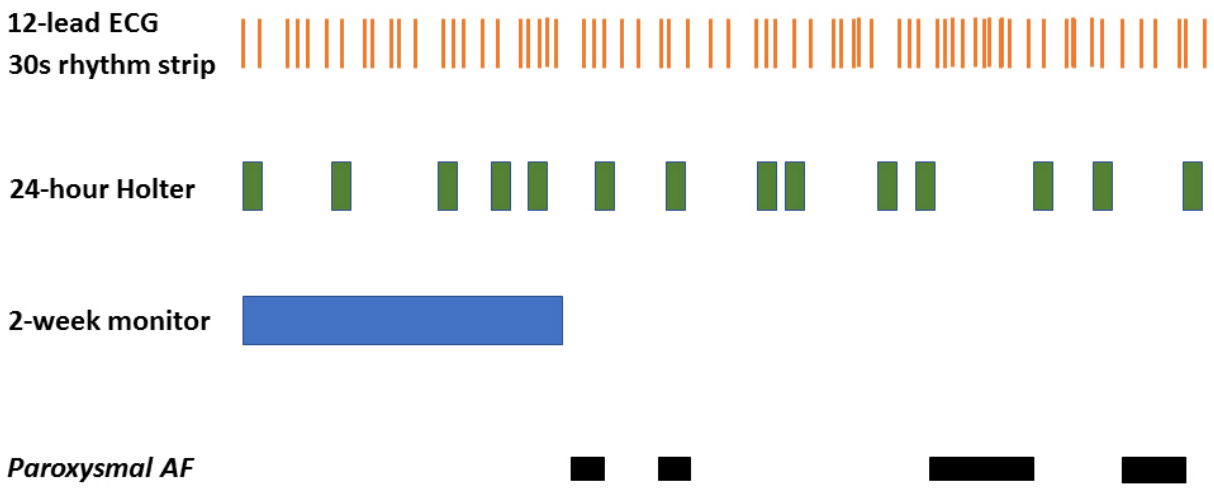

Fig. 3. Increased frequency of monitoring improves detection rate of paroxysmal AF, despite equivalent total durations of monitoring. AF, atrial fibrillation.

mary care physicians screening a total of 16,817 patients using a smartphone-enabled single-lead ECG device for a period of 6 months, yielding an AF detection rate of 7.0% [69].

Non-invasive rhythm monitoring devices have also been used to assess AF burden as a means of thromboembolic risk stratification. In the KP-RHYTHM study, patients who had paroxysmal AF detected by a 14-day ZIO Patch were further assessed for thromboembolic events stratified by AF burden. Patients in the highest tertile of cumulative burden of AF had a significantly higher rate of stroke or systemic embolism, whereas the longest continuous episode of AF did not predict thromboembolic events [70].

Finally, a novel application of wearable devices in the detection of cardiac dysrhythmias is emerging in the era of global pandemics. In late 2019, a novel coronavirus originating in the Hubei Province of China (designated COVID-19) rapidly spread, resulting in a worldwide pandemic [71]. This has led to prompt implementation of public health policy and strategies to curb the spread of disease which has multiplied exponentially in densely populated areas. As a result, telehealth and technology-enhanced remote diagnosis has experienced rapid uptake and acceleration [72]. In this context, a new role for wearable-facilitated diagnosis may evolve to minimize direct patient contact. If the resolution and diagnostic accuracy of these devices gains the faith of clinicians, the application can conceivably be extended to provide specialized consultative services to patients in remote areas. Clinicians will need to be familiar with the application and limitations of various devices, especially when critical decisions such as the need for lifelong anticoagulation are being considered.

An added benefit of wearable-based diagnosis is the ability to increase overall duration and dispersion of rhythm monitoring. Intuitively, longer duration of monitoring leads to improved diagnostic yield. However, a recent analysis from the LOOP study (Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals) provided insight into the utility of increased total monitoring duration dispersed across time [73]. In this study, 590 patients with clinical risk factors for stroke but without AF were recruited to undergo screening for AF with an implantable loop recorder. Random sampling was used to simulate and compare various screening strategies. Longer durations of monitoring were associated with an increased detection of AF; however, detection was further improved when the same monitoring duration was dispersed over multiple recordings (i.e., Annual 24-hour Holters for 3 years had a higher detection rate than a single 72-hour Holter) [73]. Similar findings from other cohorts have shown that prolonged durations of intermittent monitoring remain unreliable in detecting paroxysms of AF [74–76] (Fig. 3).

Despite the feasibility and ease of recording rhythm using these devices, their role in contemporary practice remains to be seen. There are several limitations to be cognizant of when advocating for wearable devices. While PPG-based algorithms are continuous, intermittent ECG monitoring applications are largely patient-triggered devices, and the sampling volume is highly dependent on the individual. In addition, both the Apple Watch Series 4 and the AliveCor Kardia devices depend on patients to manually record a 30-second rhythm strip. This is in contrast to traditional medical devices such as Holter monitors and event recorders that continuously monitor for rhythm disturbances for days to weeks, and even years in the case of implanted loop recorders. The utility of current wearables is therefore limited in patients with arrhythmias causing changes in the level of consciousness, or abrupt and short-lived rhythm disturbances. A persistent difficulty in interpreting studies of wearable devices is the variability in the populations studied. While many com-

mercial devices are studied in a healthy general population, implanted devices and medical-grade extended rhythm monitoring devices are typically assessed in selected populations who may be at higher baseline risk. Finally, the role of anticoagulation in brief episodes of AF is unclear. Despite accumulating evidence of the importance of frequency and duration of arrhythmia in studies of device-detected AF, there is no evidence to support the use of prophylactic anticoagulation for brief periods of AF under 30 seconds.

6. Conclusions

Thromboembolic risk stratification for AF is rapidly evolving, and new data continues to emerge. While clinical risk scores are likely to remain a cornerstone of practice due to their ease of calculation, the contemporary cardiovascular professional should be aware of additional risk factors that modify stroke risk. These are particularly useful in contexts where clinical risk scoring may not apply. Further, the astute clinician also needs to balance the totality of evidence regarding thromboembolic risk, with other factors that predict bleeding risk when deciding to prescribe therapeutic anticoagulation. Newer technologies are on the horizon and will drastically change the way atrial arrhythmias are detected in a contemporary cardiology practice.

Author contributions

Conceptualization, DW and ZL; Methodology, DW; Writing, DW and ZL and JA; Supervision, ZL and JA. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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