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Ischemic Stroke Risk in Patients With Nonvalvular Atrial Fibrillation

JACC Review Topic of the Week

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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) relate to the evolution of stroke risk prediction in patients with nonvalvular AF; 2) identify the advantages and limitations of the commonly used CHA_2DS_2-VASc score; and 3) discuss the emerging tools for ischemic stroke risk determination in patients with nonvalvular AF.

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ABSTRACT

The last decade has witnessed remarkable advances in pharmacological and nonpharmacological strategies for stroke prevention in patients with atrial fibrillation. However, the currently available clinical stroke risk prediction models do not account for key nonclinical factors (arrhythmia burden, left atrial physiology and anatomy, chemical and electrocardiographic markers) and other competing clinical risks. Hence, their ability to identify patients who will derive the most benefit from pharmacological and mechanical risk prevention strategies remain limited. In this paper, the authors review the current and evolving ischemic stroke risk prediction schemes in patients with nonvalvular atrial fibrillation, highlight the strengths and weaknesses of the models, and discuss the unmet needs in this field.
(J Am Coll Cardiol 2019;74:3050–65)

Atrial fibrillation (AF) is a growing epidemic, with >12 million patients projected to have AF in the United States by 2030 (1–3). Stroke is the most debilitating complication of AF, and its prevention is hence considered the cornerstone of AF management (1,4). Numerous stroke prevention strategies have been introduced, including the use of anticoagulation centers of excellence, direct oral anticoagulants, and percutaneous left atrial (LA) appendage occlusion (LAAO) devices (1,5). However, stroke risk prediction models have not kept pace with these advances. Current societal guidelines remain, for the most part, depended on a single clinical risk score (CHA_2DS_2-VASc) to determine an individual's candidacy for pharmacological or mechanical stroke prevention (6–8). Unfortunately, despite its utility and ease of calculation, the CHA_2DS_2-VASc score has demonstrated modest performance in predicting stroke or other cerebrovascular ischemic events in real-world cohorts (9). In addition, the score does not consider several key anatomic, physiological, and other factors that have been shown to impact the risk of stroke in patients with AF (10). The aim of this paper is to review current and emerging tools for ischemic stroke risk determination in patients with nonvalvular AF (NVAF), and to propose a framework for further investigation to achieve optimal stroke prevention in these patients. Data provided in this paper were gathered through a focused review of the published studies on risk prediction of ischemic stroke in patients with AF (nonsystematic review).

HISTORICAL PERSPECTIVES

William Osler characterized medicine as a science of uncertainty and an art of probability (11). This is clearly illustrated in the management of NVAF, where the prevention of AF-associated ischemic stroke is based on balancing the probability of benefit versus harm from a specific strategy using probability calculation tools that are known to have considerable limitations. Herein, we review the origin and evolution of the prior and currently utilized stroke risk prediction scores.

In 1978, Wolf et al. (12) established the association between NVAF and stroke by demonstrating a 5-fold increase in the incidence of ischemic stroke among patients with NVAF compared with patients without NVAF in the landmark Framingham study. This observation prompted several randomized clinical trials (RCTs) aiming to evaluate the efficacy of oral anticoagulation in reducing stroke risk in patients with NVAF (13). A patient-level meta-analysis of the first 5 RCTs demonstrated that warfarin was associated with a 68% relative risk (RR) reduction in stroke compared with placebo (14). This substantial benefit was confirmed in further studies and additional meta-analyses, granting warfarin a central role in the management of NVAF for several decades (1,15–18). However, the necessity of objectively estimating stroke risk in NVAF patients became quickly evident, as the risk/benefit of oral anticoagulation (OAC) varied substantially between individuals on the basis of the underlying risk of stroke (19–21). Hence,

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AI = artificial intelligence

CI = confidence interval

HR = hazard ratio

LA = left atrium

LAA = left atrial appendage

LAAO = left atrial appendage occlusion

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NVAF = nonvalvular atrial fibrillation

OAC = oral anticoagulation

RCT = randomized clinical trial

RR = relative risk

SE = systemic embolization

considerable efforts were made to devise an individualized risk classification score for ischemic stroke in patients with NVAF (22,23).

CLINICAL RISK SCORES

THE $CHADS_2$ SCORE. The AFI (Atrial Fibrillation Investigators) and the SPAF (Stroke Prevention and Atrial Fibrillation) trial classification schemes were the first to provide objective evidence of the association between clinical features and a heightened risk of stroke in patients with NVAF (14,17,24). In the AFI classification, age, hypertension, prior cerebral ischemia, and diabetes mellitus were identified as independent predictors of stroke (17). In the SPAF classification, blood pressure >160 mm Hg, prior cerebral ischemia, recent clinical or echocardiography-proven heart failure, or the combination of age ≥75 years and female sex were associated with higher odds of ischemic stroke (24). However, these classifications were viewed as ambiguous, were often conflicting, and had modest performance when validated outside of the clinical trial setting (19). Hence, Gage et al. (19) combined elements from the 2 schemes into a new risk score ($CHADS_2$: congestive heart failure, hypertension, age ≥75, diabetes, prior stroke/transient ischemic attack) and validated its predictive value in a large cohort of Medicare-age patients. Due to its C-statistic of 0.82 (95% confidence interval [CI]: 0.80 to 0.84) and ease of use, the $CHADS_2$ score emerged as the most accurate predictor of stroke, and was promulgated widely in societal guidelines and in clinical practice.

With the wide adoption of $CHADS_2$, some of its limitations have become apparent. First, the score was found to have a weak discriminatory value in identifying low-risk patients, as patients with a $CHADS_2$ score of 0 still had an annual stroke risk of ~2%. Second, the score was noninclusive of key risk factors (e.g., female sex, vascular disease) that were increasingly recognized as independently predisposing towards thromboembolism in NVAF patients (25). Third, age was treated as a binary variable in $CHADS_2$, whereas emerging data had shown that increasing age among NVAF patients >65 years of age was associated with an incremental increase in stroke risk (19). Fourth, several studies have shown modest-to-poor validity of the $CHADS_2$ score in real-world cohorts. Hence, attempts were made to further modify/supplement the $CHADS_2$ score.

HIGHLIGHTS

- Ischemic stroke risk prediction is a cornerstone in the management of patients with atrial fibrillation.
- The paper reviews the evolution of these risk scores, discusses their strengths and limitations, and appraises the emerging risk assessment tools and their incremental utility.
- There is an unmet need for a comprehensive study incorporating various clinical, anatomic, and biophysiological risk factors to optimize our stroke prevention practices in patients with atrial fibrillation.

CHA_2DS_2-VASc SCORE. To address the shortcomings of the $CHADS_2$ score, Lip et al. (25) added additional risk factors (vascular disease [coronary, peripheral arterial and venous], and female sex) and age categories (<60 years, 60 to 74 years, and ≥75 years) to create a new risk scoring system: CHA_2DS_2-VASc. In their study, the investigators found that the CHA_2DS_2-VASc score outperformed the $CHADS_2$ score in identifying NVAF patients at risk for stroke. The incremental benefit of the CHA2DS_2-VASc score documented by Lip et al. (25) was initially questioned due to its modest discriminatory power (C-statistic = 0.606), its limited follow-up (1 year), and its incomplete surveillance (no follow-up data in 31% of patients) (26). However, several subsequent validation studies confirmed the superiority of CHA_2DS_2-VASc over $CHADS_2$ in quantifying stroke risk, especially in its ability to identify low-risk patients who do not benefit from stroke prevention therapy (27–30). Hence, the European Society of Cardiology and the American College of Cardiology/American Heart Association guidelines were updated in 2012 and 2014, respectively, recommending the use of CHA_2DS_2-VASc instead of the $CHADS_2$ score to guide OAC in NVAF patients.

OTHER CLINICAL RISK SCORES. In the 2010s, the CHA_2DS_2-VASc score became the leading stroke risk prediction tool for patients with NVAF, both in the guidelines and in clinical practice. Indeed, the enthusiasm for the CHA_2DS_2-VASc score has fueled dozens of investigations demonstrating its potential role, not only for predicting ischemic stroke, but also for predicting other outcomes in patients with and without NVAF (13,31–34). However, the score is not without limitations, and its suboptimal performance

TABLE 1 Characteristics of the Main Clinical Stroke Risk Stratifications Schemes in NVAF Patients

Risk Score First Author (Ref. #)	Data Source	Score Definition	Supportive Data
$CHADS_2$ Gage et al. (19)	Medicare Database* N = 1,733	CHF, hypertension, age (≥65 yrs = 1 point, ≥75 yrs = 2 points), diabetes, and stroke/TIA (2 points)	$CHADS_2$ was superior to existing risk classification schemes AFI scheme: C-statistic = 0.68 (0.65–0.71) SPAF-III scheme: C-statistic = 0.74 (0.71–0.76) $CHADS_2$ score: C-statistic = 0.82 (0.80–0.84)
R_2CHADS_2 Piccini et al. (35)	ROCKET-AF trial, ATRIA trial N = 14,264	Added +2 points for creatinine clearance <60 ml/min	In the derivation cohort (ROCKET-AF): C-statistic was 0.587 vs. 0.575 for $CHADS_2$, NRI = 8.2% (2.5%–14%) In the validation cohort (ATRIA): C-statistic was 0.704 vs. 0.696 for $CHADS_2$, NRI = 22.6% (14.5%–30.7%)
CHA_2DS_2-VASc Lip et al. (25)	Euro Heart Survey for AF N = 1,084	CHF, hypertension, age ≥75 yrs, diabetes, stroke, or TIA, vascular disease, age 65–74 yrs, sex	C-statistic was 0.606 (0.513–0.699) for CHA_2DS_2-VASs vs. 0.561 (0.450–0.672) for $CHADS_2$. Patients were classified as low (9.2% vs. 20.4%), intermediate (15.1% vs. 61.9%), or high (75.7% vs. 17.7%) risk with CHA_2DS_2-VASs vs. $CHADS_2$.
CHA_2DS_2-VASc-R Kabra et al. (40)	Medicare Database N = 460,417	Added +1 point to African-American race	CHA_2DS_2-VASc-R superior to CHA2DS2-VASc: HR: 1.36 (1.29–1.43; p < 0.001), NRI = 7.6% (p < 0.001)
CHA_2DS_2-VA Tomita et al. (42)	J-RHYTHM registry N =997	Eliminated sex category	CHA_2DS_2-VA superior to CHA_2DS_2-VASc overall [C-statistic = 0.029; p = 0.02, NRI = 11% (1%–20%)] and in low-risk patients: [C-statistic = 0.053; p < 0.001, NRI = 11% (7%–14%)]
mCHA_2DS_2-VASc Chao et al. (37)	Taiwan National Insurance Database N = 224,866	Expanded lower threshold for age to 50 yrs (1 point for age 50–74 yrs)	mCHA_2DS_2-VASc was superior to CHA_2DS_2-VASs C-statistics = 0.708 (0.703–0.712) vs. 0.689 (0.684–0.694) NRI = 3.39% (2.16%–4.59%); p < 0.001
CHA2DS2-VAK Cha et al. (36)	Korean single-center cohort N = 12,876	Replaced sex category with kidney disease (GFR <60 ml/min/1.73 m^2)	CHA_2DS_2-VAK was superior to CHA_2DS_2-VASs C-statistics = 0.650 (0.64–0.66) vs. 0.639 (0.62–0.65)
ATRIA Singer et al. (41)	ATRIA, ATRIA-CVRN cohort N = 10,927	Age (65–74 yrs = 3 points, 75–84 yrs = 5 points, ≥85 yrs = 6 points), hypertension, diabetes, CHF, proteinuria, GFR <45 ml/min/1.73 m^2, sex	ATRIA was superior to CHA_2DS_2-VASc: C-statistics = 0.708 (0.704–0.713) vs. 694 (0.690–0.700), NRI 16% (14%–17%).
ABC Hijazi et al. (39)	ARISTOTLE trial, STABILITY trial N = 18,201	Age, biomarkers (hs-troponin T, NT-proBNP), prior history of stroke	The ABC score yielded higher C-statistics than CHA_2DS_2-VASs in the derivation cohort (0.68 vs. 0.62; p < 0.001) and the external validation cohort (0.66 vs. 0.58; p < 0.001)
GARFIELD-AF Fox et al. (38)	GARFIELD-AF, ORBIT-AF registry N = 39,898	Computed machine learning model (web-based)	The GARFIELD-AF score yielded higher C-statistics than CHA_2DS_2-VASs 0.69 (0.67–0.71) vs. 0.64 (0.61–0.66) in the derivation cohort. In the validation cohort, GARFIELD-AF C-statistic was 0.68 (0.62–0.74)

*NRAF (National Registry of Atrial Fibrillation) data.

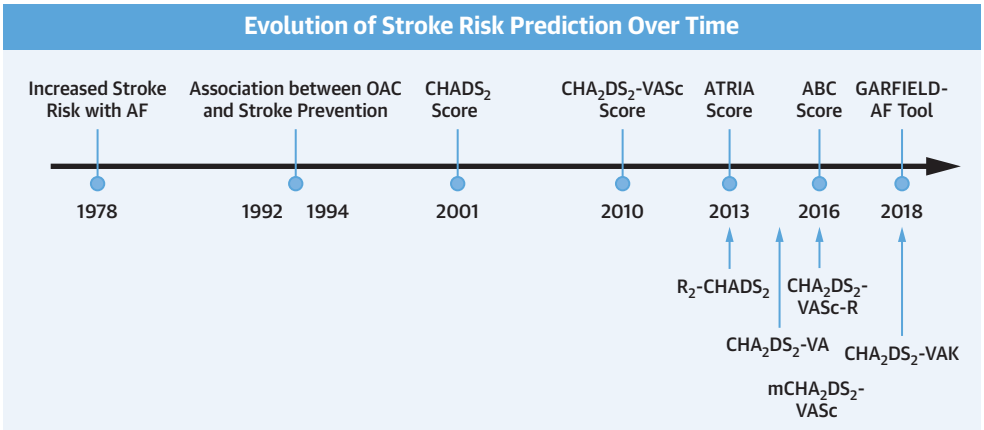
ABC = age, biomarker, clinical history; AFI = Atrial Fibrillation Investigators; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BNP = B-type natriuretic peptide; CHF = congestive heart failure; CVRN = Cardiovascular Research Network; GARFIELD = Global Anticoagulant Registry in the FIELD; GFR = glomerular filtration rate; hs = high-sensitivity; NRI = net reclassification index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NVAF = nonvalvular atrial fibrillation; ROCKET-AF = Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation trial; SPAF III = Stroke Prevention in Atrial Fibrillation III trial; STABILITY = The Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial; TIA = transient ischemic attack.

in selected populations (e.g., patients with renal insufficiency, Asian patients) stimulated a quest for a superior stroke prediction scheme. Between 2010 and 2018, novel clinical risk scores were derived and validated in large cohorts of patients including: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), ABC (Age, Biomarkers, Clinical History), and the GARFIELD-AF (Global Anticoagulant Registry in the Field) (**Table 1, Figure 1**) (35–42). However, none of these scores has gained the wide spread adoption that the CHA_2DS_2-VASc score has enjoyed.

Despite the proven utility of the CHA_2DS_2-VASc score, and the data supporting an incremental value of the newer risk scores in selected populations, these scores all share a common theme: they are solely based on clinical risk factors (e.g., age, hypertension, diabetes, vascular disease) that also increase the risk of stroke in patients without AF. Hence, concerns have been raised about the lack of specificity of the CHA_2DS_2-VASc score for predicting AF-related versus non-AF-related ischemic stroke. These concerns were substantiated by several studies that documented a similar predictive value for stroke with the application of the CHA_2DS_2-VASc score in patients with and without AF (13,31–34,43). Hence, investigators sought to identify AF-specific risk factors for ischemic stroke, and tested their additive value to the CHA_2DS_2-VASc and other clinical scores. Here, we summarize the published reports on anatomic, physiological, and electrocardiographic factors that have been shown to have an impact on the risk of stroke in patients with NVAF. It should be noted, nonetheless, that all of the established and emerging risk scores have been

JACC VOL. 74, NO. 24, 2019
DECEMBER 17, 2019:3050–65

FIGURE 1 Temporal Evolution of the Current Stroke Reduction Scores



AF = atrial fibrillation; OAC = oral anticoagulation.

evaluated in terms of their ability to predict clinical ischemic strokes in patients with NVAF. Future studies should consider silent ischemic strokes, which have been shown to be prevalent and to carry a negative prognostic impact in this population (44).

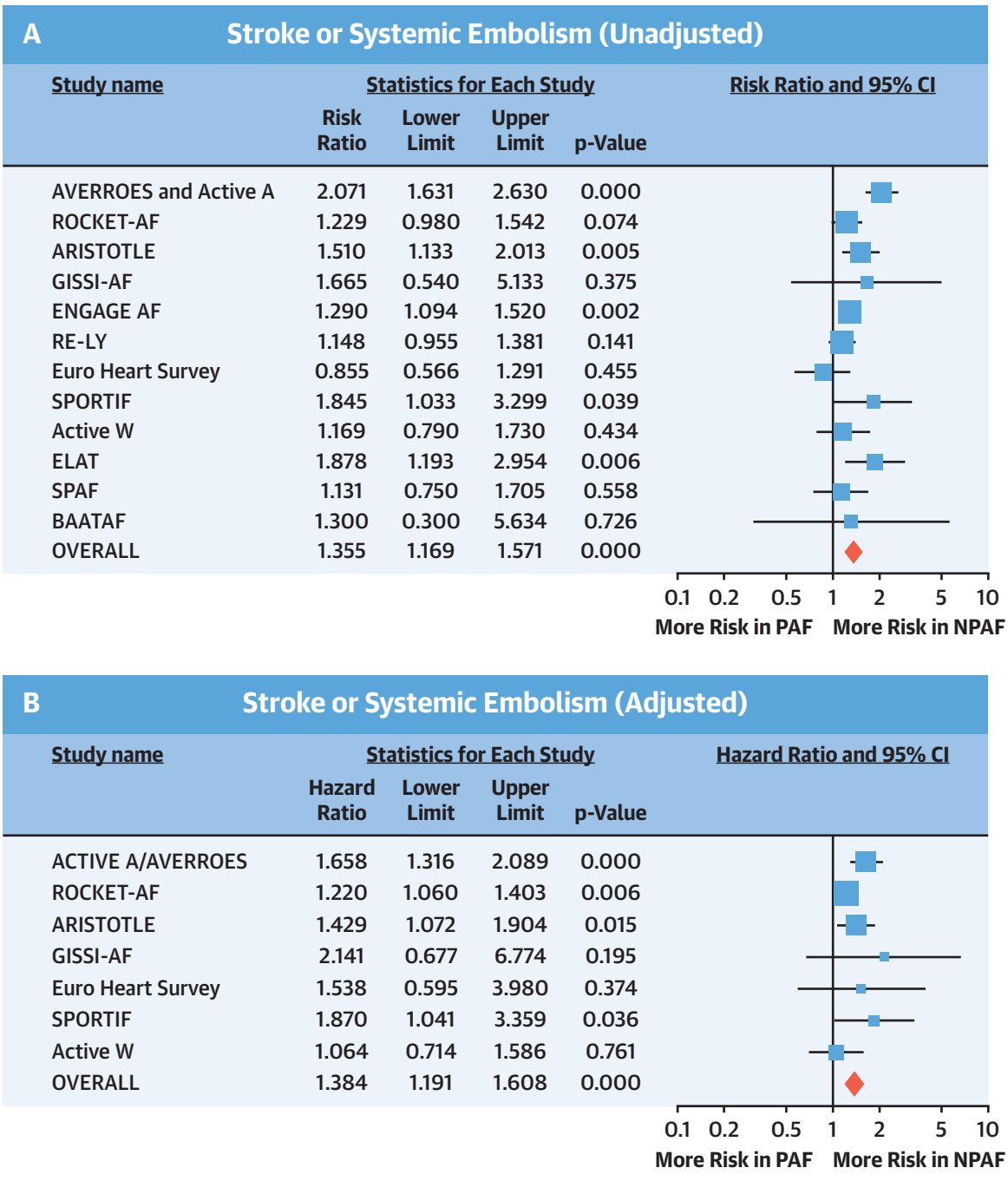
PREDICTORS OF STROKE RISK BEYOND CLINICAL RISK SCORES

1. BURDEN OF AF AND STROKE. Current guidelines recommend the use of clinical risk scores (e.g., CHA_2DS_2-VASc) to determine eligibility for anticoagulation in patients with NVAF and do not account for AF burden. These recommendations may be based on older studies showing no differential impact of AF burden on stroke risk. In the ACTIVE W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) (45), the risk of stroke/systemic embolization (SE) was 2.0% in patients with paroxysmal AF versus 2.2% in sustained AF (RR: 0.87; 95% CI: 0.59 to 1.30; p = 0.50) (45). Similarly, in the SPAF trial, the annualized rate of ischemic stroke of 3.2% in patients with intermittent AF was 3.3% in those with sustained AF (46). However, there is growing evidence suggesting a strong association between the burden of AF and the risk of subsequent ischemic events.

The ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial showed a linear association between AF burden and risk of stroke (47). In this trial, paroxysmal AF (<7 days) was associated with lower stroke/SE event rates compared with persistent AF (≥7 days, but <1 year) (1.83%/year; hazard ratio [HR]: 0.79; 95% CI: 0.66 to 0.90; p = 0.015), or permanent AF (≥1 year) (1.95%/year; HR: 0.78; 95% CI: 0.67 to 0.93; p = 0.004). These results were replicated in post hoc analyses of major RCTs assessing anticoagulation (ARISTOTLE [Apixaban for Reduction in Stroke and Other Thromboembolic Event], ROCKET-AF [Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation]), or antiplatelet therapy (ACTIVE A [Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events], AVERROES [A Phase III Study of Apixaban in Patients With Atrial Fibrillation]) for AF. Two study-level meta-analyses including RCTs, population-based studies, and reports from AF registries found a strong relationship between AF burden and stroke risk. In the first meta-analysis (12 studies; 99,996 patients), the unadjusted RR ratio of stroke/SE in patients with nonparoxysmal versus paroxysmal AF was 1.35 (95% CI: 1.17 to 1.57; p < 0.001), and this persisted after risk adjustment: 1.38 (95% CI: 1.19 to 1.61; p < 0.001) (**Figure 2**) (48). In the second meta-analysis (18 studies; 239,528 patient-years), the incidence rate of stroke or SE was 1.6% versus 2.3% in patients with in paroxysmal versus nonparoxysmal AF, respectively (RR: 0.72; 95% CI: 0.65 to 0.80; p < 0.001) (49).

It remained unclear, however, whether the risk of stroke in paroxysmal AF increases continuously or whether a threshold exists. Analyses of patients with pre-existing cardiac implantable electronic were confounded by several issues: AF burden cutoffs were arbitrarily pre-specified, stroke events were not

FIGURE 2 Meta-Analysis Comparing Stroke Rates Between Patients With PAF and NPAF



(A) Pooled hazard risk ratio for stroke or systemic embolization in paroxysmal versus nonparoxysmal atrial fibrillation (12 studies; n = 99,996). **(B)** Pooled adjusted hazard risk ratio for stroke or systemic embolization in paroxysmal versus non-paroxysmal atrial fibrillation (7 studies; n = 58,421). Multivariable risk adjustment was performed at the study level and was not uniform across the studies. Reprinted with permission from Ganesan and Chew (48).
CI = confidence interval; NPAF = nonparoxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation.

JACC VOL. 74, NO. 24, 2019
DECEMBER 17, 2019:3050–65

TABLE 2 Knowledge Gaps in the Association Between the Burden of NVAF and Stroke Risk

Unified definitions AF burden
Monitoring technologies that accurately measure the burden of AF
Threshold of AF that increases stroke risk in AF patients
Differential impact of AF burden on patients with various CHA_2DS_2-VASc scores
Association between AF burden and stroke severity and outcomes
Association between AF burden and cognitive function
Relationship between AF burden and quality of life
Reasons for the weak temporal relationship between AF episodes and stroke events
Impact of AF burden reduction therapies on stroke risk

AF = atrial fibrillation; NVAF = nonvalvular atrial fibrillation.

found to be temporally related to AF episodes, and data from patients with implantable devices were not deemed generalizable given the high prevalence of advanced comorbidities in the implantable electronic devices' population. Nonetheless, post hoc analysis of prospective randomized trial data suggests a dose effect for AF burden and stroke, with various studies proposing increased risk above 6 min, 6 h, and 24 h (50). A recent study by Go et al. (51) attempted to mitigate these issues by assessing the impact of various durations of paroxysmal AF on stroke/SE rates in patients not on anticoagulation, using 14-day continuous ambulatory electrocardiographic monitoring. In this study, the median burden of AF was 4.4% (interquartile range: 1.1% to 17.2%). After adjusting for the CHA_2DS_2-VASc score, the highest tertile of AF burden (≥11.4%) was associated with a >3-fold higher adjusted rate of stroke/SE (adjusted HR: 3.16, 95% CI: 1.5 to 6.6) compared with the combined lower 2 tertiles of AF burden. A recent statement from the American Heart Association acknowledged the limitations of the current guidelines that classify AF in a binary fashion (AF vs. no AF), and called for further research to bridge the knowledge gaps in our understanding of the association between AF burden and stroke (**Table 2**) (52). Furthermore, the lack of temporal association between AF and stroke has raised the question as to whether AF is pathogenic for stroke or simply a marker of the extent of atrial fibrosis and dysfunction necessary for stroke. This has important implications for some stroke prevention strategies such as a "pill in the pocket approach" for paroxysmal AF (53).

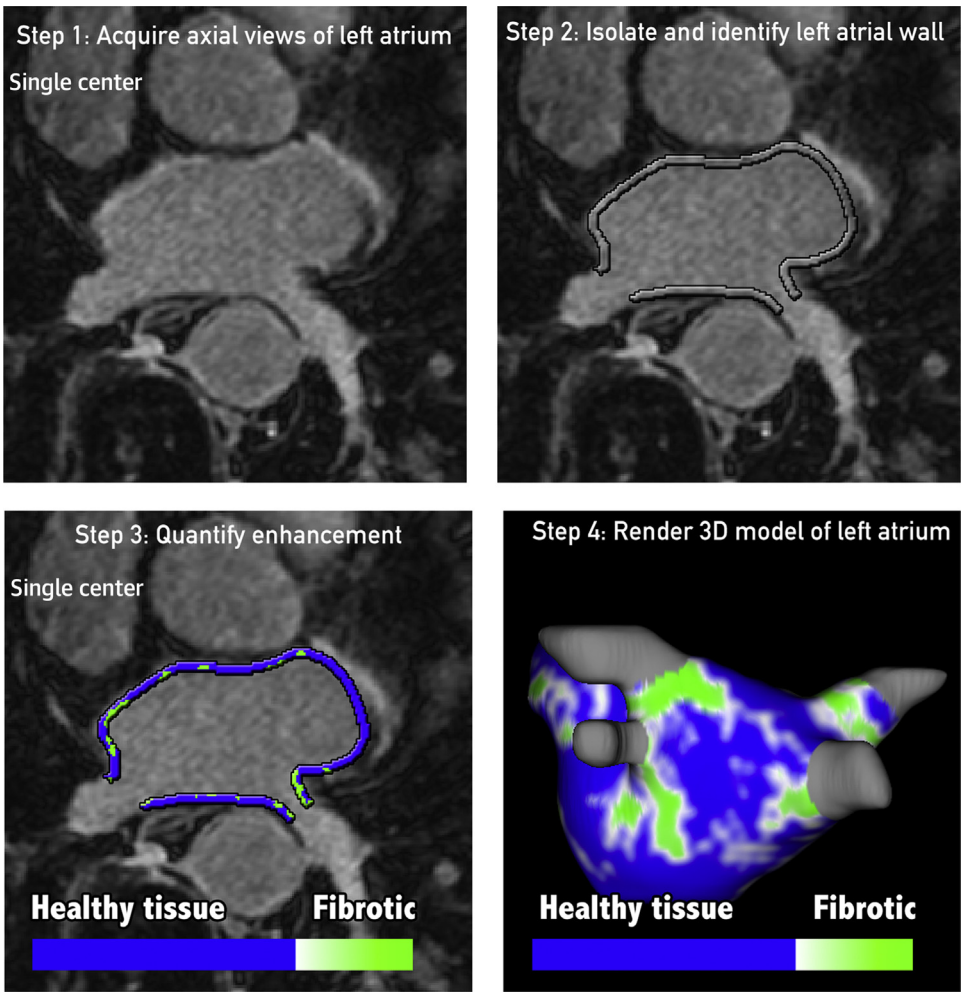
2. LA ANATOMY AND FUNCTION. The size, function, and structure of the LA have been shown to modify the risk of stroke in patients with NVAF (**Figure 3**).

Left atrial size and stroke risk. Benjamin et al. (54) documented an ~40% and >100% increase in adjusted stroke rates for each 10-mm increase in LA size in women and men enrolled in the Framingham Heart Study, respectively. Several other studies have corroborated a similar relationship between LA size and stroke risk specifically in patients with NVAF (55–57). Moreover, the LA size has also been found predictive of ischemic stroke recurrence in patients with NVAF (58,59).

LA function and stroke risk. The pathogenesis of AF is complex. However, certain LA functional and structural abnormalities are common in patients with AF including: loss of LA reservoir function, LA fibrosis, reduced LA flow, and LA electrical remodeling. The prognostic implications of these abnormalities have been an area of interest. The association between LA abnormalities and AF recurrence after transcatheter AF ablation has been documented in several studies (60). However, data on the association between LA structural abnormalities and stroke risk remain limited. In a study by Leong et al. (61), each 1% reduction in LA reservoir function (as measured by speckle tracking longitudinal strain imaging) was associated with 7% increase in stroke ($p < 0.001$). In another study by Daccarett et al. (62), patients with AF with a history of stroke had significantly more LA fibrosis on cardiac magnetic resonance imaging (CMR) compared with those without a history of stroke (24.4 ± 12.4% vs. 16.2 ± 9.9%, respectively; $p < 0.001$). Incorporating the extent of LA fibrosis into the $CHADS_2$ score improved the predictive value of the score (C-statistics = 0.58 to 0.72) (62). In the MESA (Multi-Ethnic Study of Atherosclerosis) study, LA phasic function (LA ejection fraction) as measured by CMR was associated with incident ischemic stroke (HR: 0.85/SD; 95% CI: 0.74 to 0.98; $p = 0.027$) (63). However, technical issues related to LA imaging in patients with NVAF have tempered the enthusiasm for these approaches, given the relatively simple and readily available clinical risk scores.

3. LA APPENDAGE ANATOMY AND FUNCTION. The role of the LA appendage (LAA) in the causation of stroke in patients with NVAF has been an area of increasing interest since Blackshear first showed that the LAA is the nidus for thrombus in 91% of patients with NVAF (64). This unique observation led to the development of the concept of mechanical exclusion of the LAA as an alternative strategy to OAC for stroke prevention. The proliferation of innovative technologies in this field has shed more light on the enormous variation in the size, shape, and function of the LAA (**Figure 4**). The impact of these variations on stroke risk is now supported by a large body of evidence (65).

FIGURE 3 Assessment of LA Fibrosis by CMR in Patients With AF

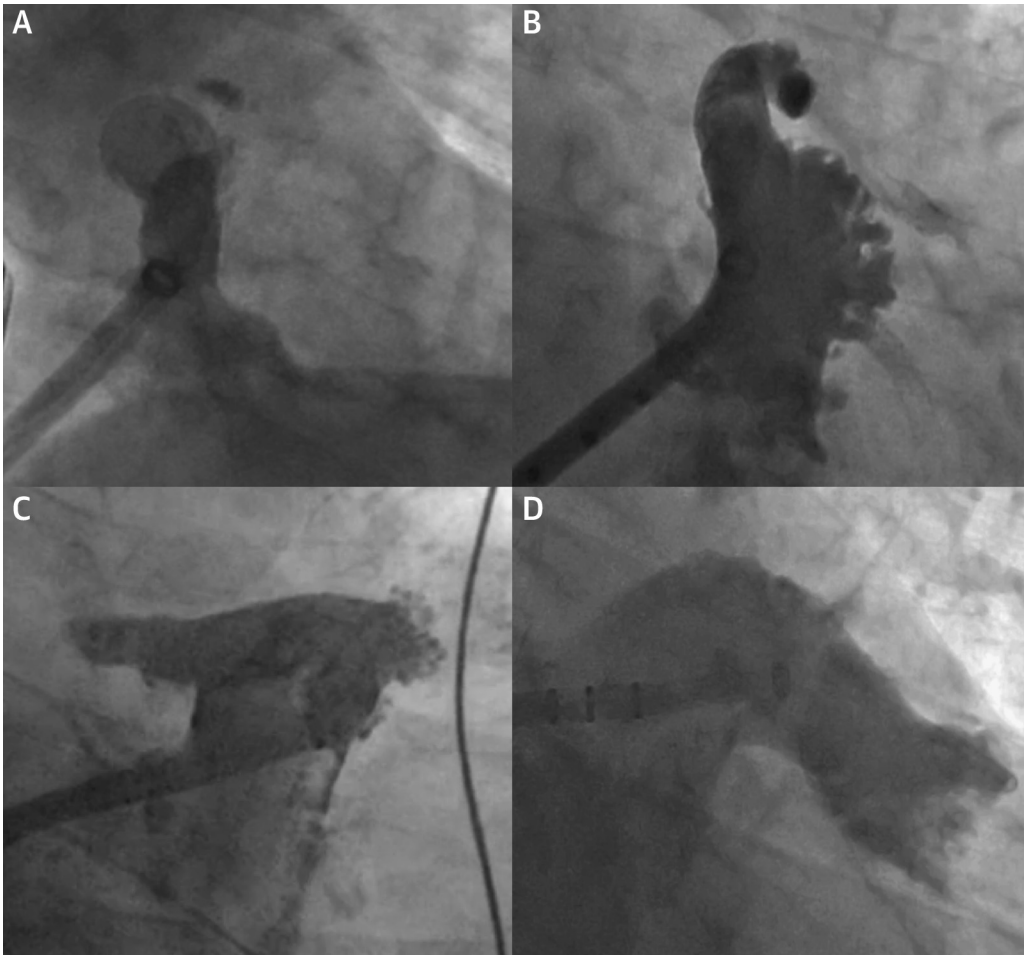


(Reprinted with permission from Siebermair J, Kholmovski EG, Marrouche N. Assessment of left atrial fibrosis by late gadolinium enhancement magnetic resonance imaging: methodology and clinical implications. J Am Coll Cardiol EP 2017;3:791–802). 3D = 3-dimensional; AF = atrial fibrillation; CMR = cardiac magnetic resonance; LA = left atrial.

LAA size/function and stroke risk. The plausible hypothesis that large and/or less mobile LAAs may be associated with higher odds of clot formation and subsequent embolic events compared with small contractile LAAs has been confirmed in several studies. In a cross-sectional study of 218 patients, Lee et al. (66) found that large LAA orifice area confers a 6-fold increase in the adjusted risk of stroke (OR: 6.2; 95% CI: 2.67 to 14.18; $p < 0.001$). In another study using CMR, LAA volume >34 cm^3 was associated with a 7-fold increase in adjusted stroke rate (OR: 7.1; $p = 0.003$). Fatkin et al. (67) documented a substantial correlation between low LAA emptying velocity (<35 cm/s) and LAA thrombus/spontaneous echo contrast (OR: 28; 95% CI: 9.1 to 84.4). In the SPAF-III (Stroke Prevention in Atrial Fibrillation) study, peak antegrade flow velocity <20 cm/s was independently associated with LAA thrombus (RR: 2.6; $p = 0.02$) (68). Similarly, Kamp et al. (69) found that LAA peak velocity <20 cm/s was an independent predictor of subsequent thromboembolic events (OR: 4.1; 95% CI: 1.4 to 11.6; $p < 0.01$). Extent of LAA fibrosis may also play a role in the assessment of stroke risk in patients with NVAF (70).

LAA morphology and stroke risk. The role of the LAA anatomy in stroke prediction has also been assessed in a number of studies. In a multicenter

FIGURE 4 LAA Angiography Illustrating the Variation in the LAA Size and Shape in 4 High-Risk Patients With Paroxysmal AF



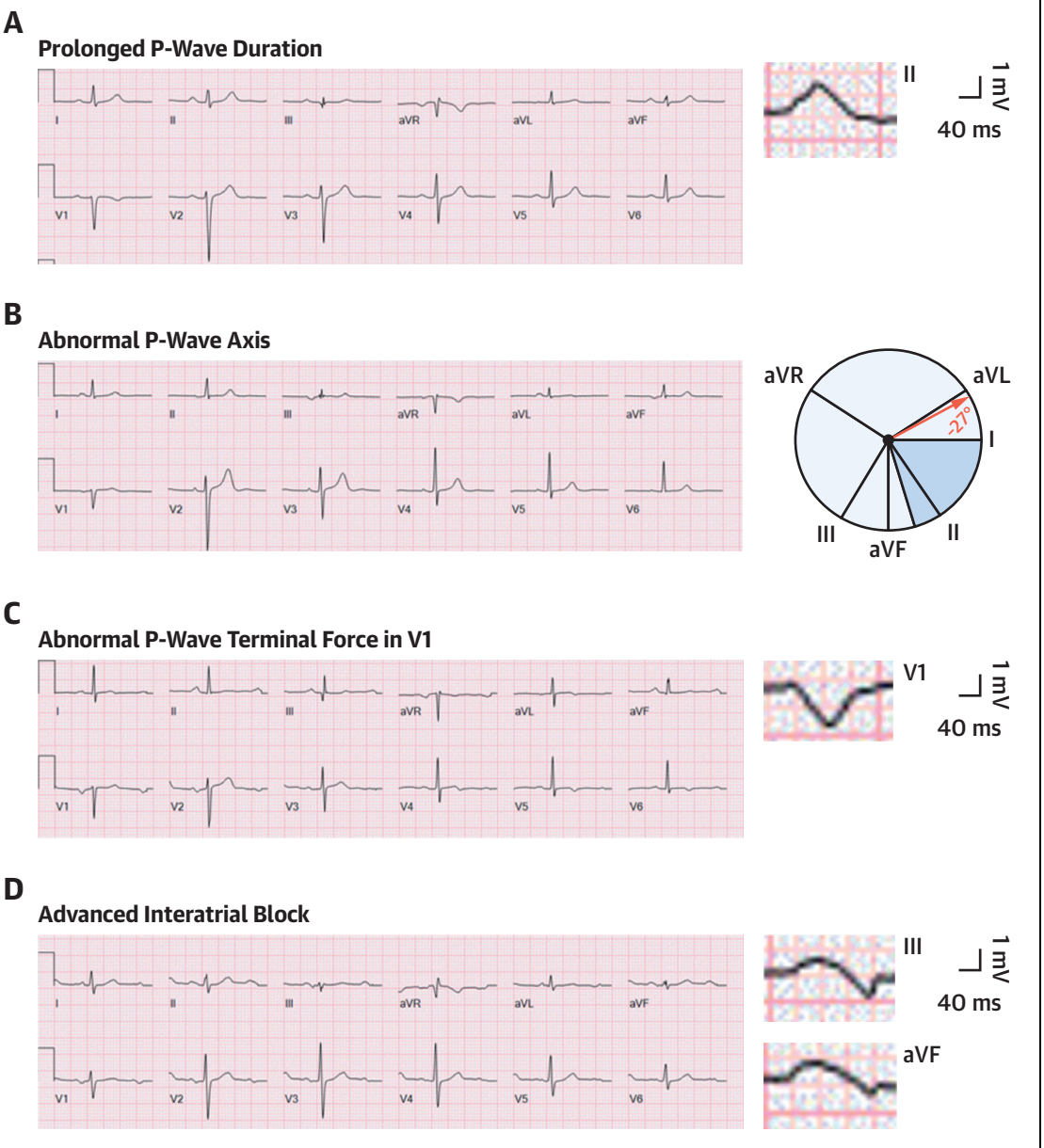
(A) Small nontrabeculated appendage, **(B)** medium-size heavily trabeculated appendage, **(C)** large anterior chicken wing–shaped appendage, **(D)** very large windsock shape appendage. All 4 patients had a CHA_2DS_2-VASc score of 4. AF = atrial fibrillation; LAA = left atrial appendage.

study including 433 patients with drug-refractory AF who underwent computed tomographic imaging before AF ablation, the rates of ischemic stroke were 4.08-fold, 4.5-fold, and 8.0-fold higher in patients with cactus, windsock, or cauliflower LAA anatomy compared with those with chicken wing anatomy ($p = 0.046$, 0.038, and 0.056, respectively) (71). In a meta-analysis of 8 studies including 2,596 patients with NVAF, thromboembolism risk was lower in patients with chicken wing morphology versus those with non-chicken wing morphology (OR: 0.46; 95% CI: 0.36 to 0.58) (72). A recent proof-of-concept study showed that a simplified classification of LAA anatomy into low and high risk on the basis of an acute angle bend or fold in the proximal/middle portion of the appendage is useful, not only in identifying high-risk patients, but also in predicting subtypes of ischemic strokes (73).

4. BIOMARKERS. AF is a chronic condition with a variable disease burden. Cardiac and inflammatory biomarkers in patients with AF might be surrogates for the chronicity and/or severity of the disease (74,75). Hence, the incorporation of such biomarkers into the current clinically based stroke risk prediction models may improve their performance (74).

Cardiac biomarkers. The incremental value of troponin-I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in predicting stroke risk in patients with NVAF was tested in a substudy of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (76). In this trial, rates of

FIGURE 5 LA Abnormalities Associated With Stroke on 12-Lead Electrocardiograms in Patients With Paroxysmal AF

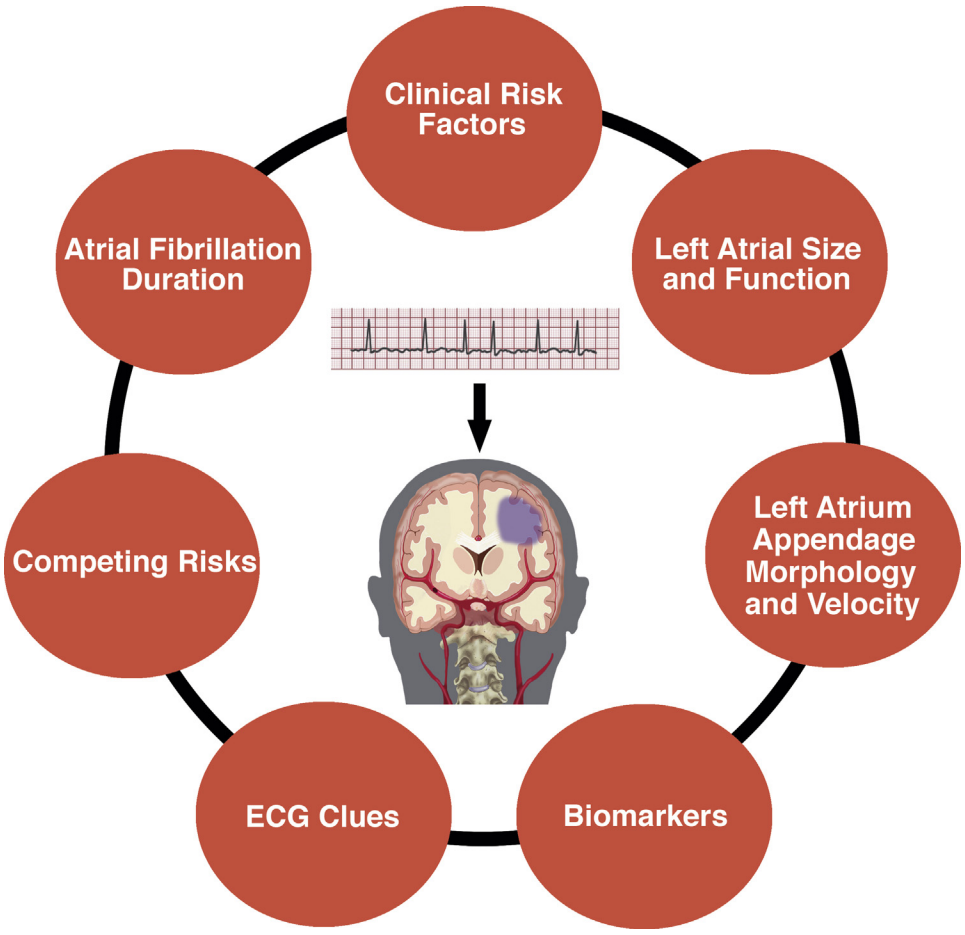


Reprinted with permission from Maheshwari et al. (84). AF = atrial fibrillation; LA = left atrial.

stroke were 2.1% versus 0.8% per year in the highest versus the lowest troponin-I quartile groups (HR: 1.99; 95% CI: 1.17 to 3.39; p = 0.004), and to NT-proBNP with 2.3% versus 0.9% per year in the highest versus the lowest NT-proBNP quartile groups (HR: 2.40; 95% CI: 1.41 to 4.07; p = 0.001). Similarly, in the ARISTOTLE trial, stroke rates were 2.1% versus 0.9% per year in the highest versus the lowest high-sensitivity troponin-T quartile groups (HR: 1.94; 95% CI: 1.35 to 2.78; p = 0.001), 2.2% versus 0.7% per year in the highest versus the lowest NT-proBNP quartile groups (HR: 2.35; 95% CI: 1.62 to 3.40; p < 0.0001) (77,78). Other observational studies have shown similar findings (79,80). These observations formed the foundation for the first hybrid score (ABC score), which included risk factors (age, prior stroke) and cardiac biomarker levels (39).

Inflammatory biomarkers. Inflammatory biomarkers are elevated in patients with AF compared with those without AF (75). However, studies assessing their

CENTRAL ILLUSTRATION Factors Predictive of Ischemic Stroke in Patients with NVAF



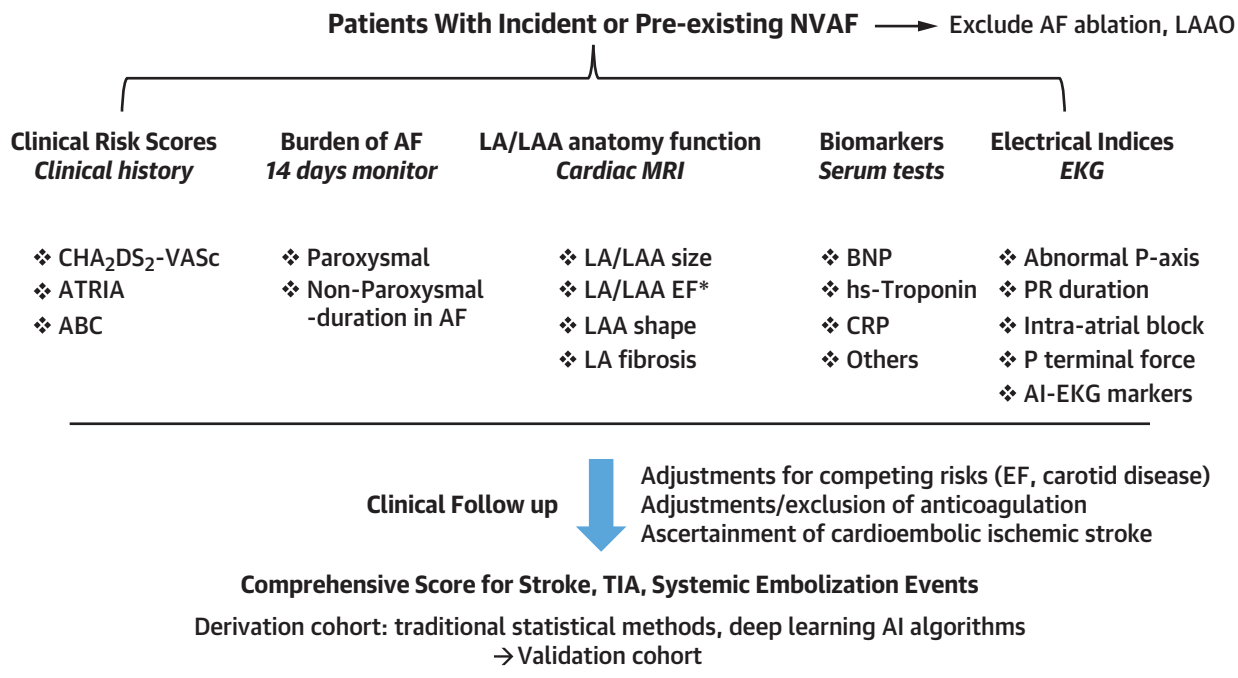
Alkhouli, M. et al. J Am Coll Cardiol. 2019;74(24):3050–65.

AF = atrial fibrillation; ECG = electrocardiogram; NVAF = nonvalvular atrial fibrillation.

values in predicting stroke in patients with AF yielded mixed results. In the SPAF-III study, C-reactive protein levels were associated with all-cause mortality, but not with stroke events (81). In the RE-LY study, C-reactive protein and fibrinogen were not associated with stroke, whereas interleukin-6 showed a modest association with stroke/SE (C-statistics for CHA_2DS_2-VASc increased from 0.615 to 0.642 [p = 0.002]) (82). In the ARISTOTLE trial, interleukin-6 was not associated with stroke after adjusting for clinical risk factors and other cardiac biomarkers (83). Although some biomarkers do correlate with stroke risk, none have reached a discriminatory power and ease of use sufficient for widespread adoption.

5. ELECTROCARDIOGRAPHIC MARKERS. The presence of a P wave during a period of sinus rhythm in patients with paroxysmal AF allows measurements of several P-wave indices that have been shown to be surrogates for atrial cardiopathy (84). This has led to several investigations seeking to assess the potential prognostic value of these indices in predicting subsequent ischemic events (34,84–86). The largest relevant study assessed the association between 4 P-wave indices (abnormal P-wave axis, PR duration, advanced intra-atrial block, abnormal P-wave terminal force in lead V_1) and stroke events in 2,229 patients enrolled in the ARIC (Atherosclerosis Risk In Communities) study and 700 patients enrolled in the MESA study (**Figure 5**) (84). The study found that an abnormal P-wave axis was the only P-wave parameter that was associated with higher odds of stroke independent of the CHA_2DS_2-VASc score (HR: 1.84; 95% CI: 1.33 to 2.55). Incorporating the P-wave axis in the CHA_2DS_2-VASc score improved its C-statistics from 0.68 (95% CI: 0.52

FIGURE 6 A Proposed Outline for a Prospective Study to Comprehensively Assess Stroke Risk in Patients With NVAF



AI = artificial intelligence; BNP = B-type natriuretic peptide; CRP = C-reactive protein; EF = ejection fraction; EKG = electrocardiogram; hs = high-sensitivity; LAAO = left atrial appendage occlusion; MRI = magnetic resonance imaging; TIA = transient ischemic attack; other abbreviations as in Figures 3 and 4.

to 0.84) to 0.75 (95% CI: 0.60 to 0.91). These observations, albeit intriguing, remain to be confirmed in additional studies, especially in light of the emergence of other data suggesting that surrogates of abnormal atrial substrates (e.g., P-wave terminal force in V*1*, intra-atrial block) are indeed predictive of incident stroke independent of the presence of AF (87,88).

The advances in artificial intelligence (AI) algorithms might also provide an additional opportunity to optimize stroke prevention in patients with AF. Recent studies have shown that AI permits identification of occult or recent AF on a simple 12-lead electrocardiogram in patients with sinus rhythm (89). This may prove useful for determining therapy in patients with embolic stroke of undetermined source. In patients with embolic stroke of undetermined source, or with an elevated CHA_2DS_2-VASc score, it is possible that a positive AI electrocardiogram indicating recent or impending AF may obviate the need for prolonged monitoring, and identify individuals who may benefit from stroke prevention therapies. This strategy has not been clinically tested and will require validation.

6. COMPETING RISKS. Patients with AF have a large burden of cardiovascular diseases that can cause stroke regardless of AF. Those include: complex aortic plaque, carotid or intracranial arterial stenosis, uncontrolled hypertension, advanced left ventricular dysfunction, or structural heart defects (e.g., patent foramen ovale, atrial septal aneurysm) (90–93). Unfortunately, data on the relative contribution of these concomitant pathologies to stroke risk in patients with NVAF are scarce (87). In a prospective stroke registry, a concomitant potential source of cardiovascular atheroembolic events was present in 38.8% of patients (94). In another study, the presence of carotid stenosis in patients with NVAF was not uncommon and was associated with doubling in the risk of stroke after adjusting for risk factors and antithrombotic therapy (8.1 vs. 3.6 events/100 follow-up years; $p = 0.005$) (95).

CURRENT CHALLENGES AND FUTURE DIRECTIONS

It is evident that the currently used clinical risk scores for ischemic stroke prediction in NVAF (e.g., CHA_2DS_2-VASc) suffer from marked limitations. Yet, these scores continue to be the main determinant of eligibility for various stroke prevention strategies in current practice, highlighting the need for better stroke prediction tools. The weak performance of

JACC VOL. 74, NO. 24, 2019
DECEMBER 17, 2019:3050–65

the available risk scores might partially stem from their exclusion of key anatomic, physiological, and electrical factors that are now proven to have an independent value in identifying patients at risk for AF-related strokes. However, studies attempting to address this issue have mostly focused on assessing the association of a single variable and the odds of stroke (e.g., duration of AF, non-chicken wing LAA anatomy, abnormal P-wave axis, etc.). Hence, these studies are unlikely to have an impact on the current practice.

A study that provides a holistic assessment of clinical, anatomic, and other measurable factors that are associated with excess stroke risk in patients with NVAF is direly needed (**Central Illustration**). Nonetheless, conducting such a study faces significant logistical challenges. First, the absolute annual event rate in patients with NVAF who are not on anticoagulation is small (e.g., a CHA_2DS_2-VASc of 4 corresponds with an annual stroke risk of 4.8%, and an annual risk of SE of 6.7%). This suggests that a large number of patients and/or long-term follow-up are needed to avoid the proposed study being underpowered. Second, the majority of patients with NVAF are on various anticoagulation regimens with marked variations in compliance, which further complicates the risk assessment. Third, a comprehensive risk assessment will require multiple tests (transesophageal echo, computed tomography, CMR, loop recorders, etc.). This might not be feasible (e.g., cost) nor practical (e.g., presence of a pacemaker, intolerance of transesophageal echo) in many patients. Indeed, the strongest argument for the adoption of CHA_2DS_2-VASc is that it is simple and costless, which would not be the case with any risk models that incorporate imaging, electrocardiographic, or laboratory data. In addition, given the wide adoption of the simple CHA_2DS_2-VASc in current practice, concerns arise about the potential for more complicated scores to sway some clinicians (e.g., general practitioners) from prescribing appropriate anticoagulation (96). Fourth, some of the proven and suggested clinical (age, hypertension, diabetes, congestive heart failure) and nonclinical (LAA velocity, AF burden, biomarkers, etc.) risk factors for AF-associated stroke are dynamic (97). A single recording/measurement of those factors might underestimate or overestimate the actual risk of an individual patient. For example, well controlled and poorly controlled hypertension or diabetes are viewed equally in the current risk prediction models, although their association with a heightened risk of stroke might be remarkably different.

Despite these challenges, the unmet needs for a proper stroke risk assessment scheme in the growing population with NVAF mandates practical solutions. Machine learning techniques might provide an opportunity to better understand the interplay between various risk factors in large populations of patients with NVAF. Potential sources of data for such analyses may be the completed randomized trials of catheter ablation or LAAO, as those trials would have recorded multiple clinical, imaging, electrocardiographic, and laboratory variables and have adequate follow-up and credible adjudications of events. Nonetheless, the modifications of stroke risk introduced by those interventions (catheter ablation, LAAO) will be difficult to control for. Another source would be large single or multicenter databases of patients who were referred for cardioversion and underwent LAA imaging, although data completion, variability of follow-up, and ascertainment of clinical events may lead to major limitations. A prospective long-term observational study will ultimately be needed to arrive at meaningful conclusions. A proposed outline for such study is shown in **Figure 6**. The availability of novel tools such as smartphone-based echocardiography and the application of AI to interpretation of the images acquired may significantly lower the cost and improve the availability of additional important parameters useful for risk stratification at the bedside. Integrated electronic medical records may provide additional assistance, although to date, these have been wanting.

CONCLUSIONS

The prevalence of AF and the burden of its associated morbidities continue to rise worldwide. Despite the advances in ischemic stroke prevention strategies in these patients, our current stroke risk prediction tools remain basic and imprecise. There is an unmet need to incorporate various elements to the current risk factor-based stroke prediction schemes to optimize our stroke prevention practices. The time has come for a comprehensive study that provides a holistic approach to risk assessment in this high-risk population.

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