STROKE RISK PREDICTION IN ATRIAL FIBRILLATION

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Abstract

Atrial fibrillation (AF) is associated with an increased risk of thromboembolism, which can be significantly reduced with anticoagulant treatment. Key goals in the clinical management of AF are the identification of patients at high risk for developing AF and accurate stratification of the risk of stroke and systemic embolic events (S/SEE) as well as treatment-related major bleeding.

Key Words: Stroke Risk, Atrial fibrillation.

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Introduction.

Atrial fibrillation predicts ischemic stroke severity, recurrence, and mortality and increases stroke risk 3- to 5-fold in all age groups after adjusting other risk factors. In fact, the rate of stroke due to atrial fibrillation increases with each decade of life **(Benjamin et al., 2019)**.

Atrial fibrillation alone accounts for 15–20% of all strokes in the United States, and mortality in AF-related stroke patients (50%) is higher than that in non-AF-related stroke patients (27%) **(Azahar et al., 2022)**.

The pathophysiology of cardioembolic stroke in atrial fibrillation is primarily due to left atrium (LA) and left atrial appendage (LAA) stasis. In fact, the LAA is the most common site of thrombus formation, accounting for 90% of LA thrombi **(Armaretti et al.,2022)**.

Combined with hypercoagulability and endothelial dysfunction, all parts of the Virchow triad are affected, further promoting thrombus formation. Despite multiple mechanisms, stroke in atrial fibrillation is preventable with anticoagulant therapy and with left atrial appendage closure (LAAC) devices in patients who are not candidates for long-term anticoagulation **(Alkhouli et al., 2022)**. Therefore, risk stratification in patients with atrial fibrillation is important to reduce the incidence of cardioembolic stroke.

Risk Stratification with CHADS2 and CHA2DS2-VASc

CHADS2 Score

Developed in 2001, the CHADS2 score assigns 1 point each to congestive heart failure (CHF), hypertension, age 75 years or older, diabetes mellitus (DM), and 2 points to previous stroke or transient ischemic attack. However, CHADS2 had significant limitations, including underestimating the true risk of stroke in patients with low scores **(Rordorf et al. 2023)**. In a study of 541 patients with >48 hours of atrial fibrillation, 10% of those with a CHADS2 score of 0 had a left atrial appendage (LAA) thrombus on transesophageal echocardiogram (TEE) **(Yarmohammadi et al., 2012)**. Furthermore, not all risk factors contributing to a CHADS2 score of 1 were truly equivalent. For example, people aged 75 and older had a higher risk of stroke than those aged 65-74 . Therefore, when the CHA2DS2-VASc score became an evidence-based risk stratification model for predicting stroke in patients with atrial fibrillation, the CHADS2 score fell out of favor **(Gao et al., 2022)**.

CHA2DS2-VASc score

The CHA2DS2-VASc score, first proposed in 2010, gives 1 point for those aged 65-74 and 2 points for those aged 75 and over, in addition to the risk factors defined by CHADS2. In addition, 1 point each is added for vascular disease and female gender. This was first validated in a Swedish atrial fibrillation cohort study **(Friberg et al., 2012)** . This study compared the CHA2DS2-VASc score with his CHADS2 score in 90,490 patients with nonvalvular atrial fibrillation who had never received anticoagulation therapy. Over a median follow-up of 1.5 years, CHA2DS2-VASc finished marginally higher than CHADS2 at predicting the composite of thromboembolism (ischemic stroke and a composite of "ischemic stroke, unspecified stroke, TIA, and systemic embolism" . The c information for the CHADS2 and CHA2DS2-VASc schemes have been 0.66 (0.65–0.66) and 0.67 (0.67–0.68), respectively. More importantly, CHA2DS2-VASc changed into higher than CHADS2 rating at figuring out sincerely low-risk patients for stroke.Another study of 7384 patients with non-valvular AF from the Japanese J-RHYTHM Registry found a similar frequency of thromboembolic events in patients with a CHA2DS2-VASc score of 0 in the warfarin and non-warfarin groups **(Okumura et al., 2014)**; this suggests that these patients are truly low-risk and may not benefit from anticoagulation.

Guideline-Directed Anticoagulation

The CHA2DS2-VASc score first became part of guideline directed medical therapy as part of the 2012 European Society of Cardiology (ESC) guidelines**(Camm et al., 2012)** for the management of AF as well as the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guideline for the Management of Patients with AF. Current recommendations are based on ESC guidelines and focused updates of the AHA/ACC/HRS for AF management. Both **European 2020 and American guidelines 2019** explicitly recommend risk stratification using the CHA2DS2-VASc score, with a score of ≥2 in men and ≥3 in women in the absence of contraindications for oral anticoagulation. It further states that (AC) is justified a male with a score of 1 and a female with a score of 2 can be considered for AC.

Limitations of the CHA2DS2-VASc Score

Despite the favorable evidence, the CHA2DS2-VASc score has many limitations. First, it does not distinguish between types of AF. Studies have

shown that patients with persistent atrial fibrillation develop strokes or TIAs more frequently than those with paroxysmal atrial fibrillation **(Koga et al., 2016)**. Another study showed that anticoagulation therapy may not benefit populations with secondary causes of atrial fibrillation **(Quon et al., 2018)**, but the CHA2DS2-VASc score treats all types of atrial fibrillation equally. Second, CHA2DS2-VASc does not account for many physiological factors that contribute to atrial fibrillation and stroke risk. As well as taking into account the size of the LA and the shape of the LAA , it completely ignores the presence of thrombus in the LA, although this is the most important physiological mechanism of stroke in atrial fibrillation**(Vinereanu et al.,2017)**. Also, the score does not perform an accurate risk stratification of patients in some subpopulations. For example, stroke risk is age-dependent, but women receive 1 point regardless of age. Therefore, current guidelines do not recommend anticoagulant therapy for women with a CHA2DS2-VASc score of 1 **(January et al., 2019)**. Also, because the scores have not been validated in ethnically diverse populations, people of African American and Hispanic descent are treated the same as people of European descent, despite differing levels of risk . CHA2DS2-VASc may be better suited to identify truly low-risk patients, but its scoring capability fails to adequately identify older truly high-risk patients. Therefore, it should be viewed in the context of its limiting score **(Golwala et al.,2016)**.

Clinical Risk Factors

Obstructive Sleep Apnea

There are strong independent associations between stroke and OSA and between OSA and atrial fibrillation. Up to 70% of stroke patients have OSA, but only about 4% of the general population has OSA. There is also a dose-response relationship between OSA and stroke, with moderate-to-severe disease associated with an increased risk of stroke **(Jehan et al.,2018)**. A study of 53 patients found that cardioembolic stroke occurred more frequently in OSA patients than controls ($p = 0.01$) **(Lipford et al.,2015)**. Among patients with atrial fibrillation, OSA patients have a higher risk of hospitalization and a poorer prognosis after stroke but rates of serious adverse cardiovascular events were similar including death from cardiovascular causes, myocardial infarction (MI), and stroke/transient ischemic attack (TIA) **(Staerk et al., 2017)**. Adjusting for other risk factors such as atrial fibrillation, hypertension and diabetes, OSA patients have higher overall stroke and overall mortality **(Jehan et al., 2018)**. Whether obstructive sleep apnea confers an additional risk of stroke in patients with atrial fibrillation, independent of CHA2DS2-VASc score, needs further investigation in clinical trials.

Renal failure:

In a study of 90,490 patients with non-valvular atrial fibrillation not receiving anticoagulant therapy, renal failure was significantly associated with the combined thromboembolic endpoint of stroke, TIA, or systemic embolism but was not associated with ischemic stroke alone. Renal dysfunction - detected or not associated with increased in-hospital mortality and severe disability at discharge in stroke patients **(Pereg et al.,2016)**. In a study of 3080 patients with atrial fibrillation subdivided by creatinine clearance (CrCl) category, patients with CrCl < 30, 39–49, and ≥50 were statistically significantly different in the incidence of stroke/systemic embolism rates with more events occurring in patients with reduced renal function ($p=0.0002$) **(Abe et al., 2017)**. Comparison of patients with CrCl<30 and those ≥ 50, after adjusting other risk factors, the risk of stroke/systemic embolism was statistically higher in the group with increased impairment (HR 1.68; 95% CI 1.04 to 2.65; $p=0.04$) [41].A new R2-CHADS2 index that adds 2 points to the CHADS2 score for CrCl <60 mL/min was assessed with ROCKET-AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism forprevention of stroke and Embolism Trial in Atrial Fibrillation) patient cohort. This score improved stroke risk reclassification by 8.2% compared to his CHADS2 score and 6.2% compared to his CHA2DS2VASc score. This new measure was validated in 13,559 patients in the ATRIA (AnTicoagulation and Risk Factors In Attrial Fibrillation) cohort and resulted in a 17.4% improvement in net stroke risk reclassification compared to CHADS2 scores **(Jagadish et al., 2019)**. . In a study of 219 patients with atrial fibrillation, Fu et al., the addition of creatinine clearance (CrCl) or glomerular filtrate rate (GFR) to CHADS2 and CHA2DS2VASc regimens was observed to improve mortality prediction in elderly Chinese patients with atrial fibrillation and renal impairment . Models with GFR showed better improvement than the current model with CrCl., however, this study did not evaluate the impact of the new model on stroke risk stratification **(Fu et al.,2017).** Therefore, further studies are needed to verify whether the addition of renal insufficiency improves stroke prediction in patients with atrial fibrillation.

Laboratory Predictors of Stroke in AF

Brain Natriuretic Peptide

Brain natriuretic peptide (BNP) is a known correlate of stroke and heart failure. It is a chemical synthesized by myocardial cells in response to stress and is significantly increased during circulatory overload due to hypertension and salt and water retention . It is also secreted by the hypothalamus in response to cerebral ischemia **(Hayashi et al., 2018)** .In a study of 40 stroke patients, **Sayan et al.** BNP was found to rise sharply in the first 24-72 hours after stroke. Elevated BNP is an indicator of poor prognosis and mortality, but it cannot accurately predict infarct volume **(Sayan et al., 2106)**. Even at low values, BNP is a good predictor of stroke, and with prognostic differences for individuals with a BNP < 13 pg/mL versus those with levels below 34 pg/mL **(Sughrue et al.,2106).** Based on study data from the "Reasons for Geographical and Racial Differences in Stroke" (REGARDS) cohort of 30,239 individuals aged 45 years and older, **Cushman et al.** N-terminal pro-BNP (NT-proBNP) was found to be higher in the elderly, people with heart disease, kidney disease, atrial fibrillation, and elevated low-density lipoprotein cholesterol . Specifically, among 576 participants with a first ischemic stroke, NT-proBNP was a marker of cardioembolic stroke. The hazard ratio for stroke increased with each increasing quartile of baseline NT-proBNP **(Cushman et al., 2014)**. The Japanese Hokuriku-Plus AF registry was used to study the effects of BNP . Among 1013 patients with atrial fibrillation aged 30 to 94 years, thromboembolic events occurred significantly more in patients with BNP levels ≥170 pg/mL, whereas those with levels ≥147 pg/mL , thromboembolic events occurred and cardiovascular death occurred**(Hayashi et al.,2018)**. Based on these results, BNP/NT-proBNP has a potential role in predicting stroke and thromboembolism in AF patients and determining prognosis.

Imaging Predictors of Stroke in Atrial Fibrillation

Left Atrial/Left Atrial Appendage (LAA) Thrombi and LAA Morphology:

Thrombus formation in the left atrium, especially in the left atrial appendage (LAA), is associated with thromboembolic events, including embolic stroke in patients with atrial fibrillation. Studies have shown that patients with atrial fibrillation and LA/LAA thrombi have a 10-33% increased risk of stroke, systemic embolism, and death over 1-3 years of follow-up **(Vinereanu et al.,2017)**. Risk factors for LAA thrombi include larger LA and higher LAA location, decreased left ventricular ejection fraction (LVEF), increased left ventricular end-diastolic volume, grade of spontaneous echocardiography (SEC), and increased LAA volume. increase, and morphology of LAA **(Marsico et al., 2017)**. Forms of LAA have been classified into four types: cactus, chicken wings, windsock, and cauliflower . After adjusting for the presence of comorbidities and stroke risk based on the CHADS2 score, patients with the chicken wings LAA morphology were found to have fewer embolic events than others . Searching for LAA morphology as well as the presence of LA/LAA thrombi may improve echocardiographic stroke prediction in patients with atrial fibrillation. Spontaneous Echo Contrast (SEC), commonly known as smoke, is defined as the echogenicity of blood without injected contrast agent **(Anan et al., 2019).** This occurs when RBC aggregates scatter the ultrasound signal **(Vinereanu et al., 2017)**, creating dynamic smoke-like echoes within the LA cavity or appendage, unlike artifacts due to noise or injected air bubbles **(Anan et al., 2019)**. It can be detected by transthoracic echocardiography (TTE), but is more commonly identified by transesophageal echocardiography (TEE). It is considered a predictor of future embolic events and mortality in patients with non-valvular atrial fibrillation. In a prospective cohort study of 206 patients with nonvalvular AF, TEE was performed at baseline to assess for left atrial appendage thrombus. In addition, left atrial thrombus (LAT), the five-grades of left atrial spontaneous echo contrast (LASEC) and video intensity (VI) value of LASEC were measured. Over 2 years of follow-up, 20 patients (9.7%) had stroke. The authors noted that the VI value of LASEC in patients with stroke was higher than the patients without stroke (25.30 ± 3.61 vs. 8.65 ± 0.81, $p < 0.001$). They also observed that LAT, qualitative LASEC, graded LASEC, VI value of LASEC, and CHADS2 and CHA2DS2-Vasc score were independent predictors of stroke on logistic regression analysis, of which VI value of LASEC had the highest area under the curve of receiver operating characteristic (ROC) in predicting stroke ($p < 0.05$). Based on these results, quantification of LASEC by VI value is a strong predictor of stroke in patients with NVAF **(Zhao et al., 2016)**.

Coronary Artery Calcium Score

Previous research has shown that the calcium score in the coronary arteries is an independent risk factor for stroke in the general population. A coronary CT angiogram was performed on 401

patients with non-valvular AF who were admitted for ischemic stroke to assess for coronary artery disease and coronary artery calcium score (CACS) **(Yang et al., 2018)**. In addition to the CHA2DS2-VASc score, CACS was found to have an additive value in predicting non-cardioembolic risk factors of stroke, such as complex aortic plaque, significant carotid, or intracranial arterial stenosis. Based on these findings, CACS extends the current determinants of CHA2DS2-VASc scores to provide additional information for stroke risk in AF patients **(Jagadish et al.,2019).**

Ethnicity and Stroke Prediction in AF

Despite having lower rates of AF, African-American patients have a disproportionately higher risk of fatal stroke than whites. They have a higher overall stroke incidence, and their age-adjusted stroke mortality is 2-4 times higher than whites **(Shin et al.,2023)**. This has been linked to a number of risk factors, including hypertension, diabetes, and a lower socioeconomic status. Only half of the excess stroke incidence in African-Americans was attributable to traditional risk factors and socioeconomic status in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort, while the other half was attributed to other unknown factors and pathways**(Jagadish et al., 2019)**. Stroke is also more common in African-American patients with AF compared to white patients. A study of 517,941 Medicare patients over the age of 65 with newly diagnosed AF looked at racial differences in stroke and mortality outcomes **(Jagadish et al., 2019)**. 452,986 (87%) of these patients were nonHispanic white, 36,425 (7%) were black, and 28,530 (6%) were Hispanic. Over a median of 20.3 months of follow-up, blacks had a significantly higher risk of stroke than whites (HR = 1.66; 95% CI 1.57 to 1.75; p 0.001), which persisted even after controlling for pre-existing comorbidities (HR = 1.46; 95% CI 1.38 to 1.55; p 0.001). A subsequent study hypothesised that adding one point to the CHA2DS2-VASc score for African-American ethnicity would improve stroke prediction **(Kabra et al., 2016)**. This novel CHA2DS2-VASc-R score was compared to the CHA2DS2-VASc score in 460,417 patients with newly diagnosed AF aged 65 and up. There were 390,590 (85%) non-Hispanic whites and 31,702 (7%) non-Hispanic African Americans in the population. When compared to the CHA2DS2-VASc score, CHA2DS2-VASc-R significantly improved model fit, as measured by the log likelihood ratio statistic (p 0.001) **(Jagadish et al., 2019)**.

The c-statistic for CHA2DS2-VASc was 0.60 (95% CI, 0.59-0.61), while the c-statistic for CHA2DS2-VASc-R was 0.61 (95% CI, 0.60-0.62). Only prior history of stroke, age 75 years, and female sex were more important in predicting stroke in this population than African-American ethnicity in the CHA2DS2-VASc-R score **(Kabra et al., 2016)**. Other race-related coefficients (Hispanics, Native Americans, Asians/Pacific Islander descent) were either small or non-significant, so additional points for these races in the CHA2DS2-VASc-R score were not justified. Based on these findings, there is strong evidence that ethnicity, in addition to the CHA2DS2-VASc score, should be considered for stroke prediction in AF patients.

Alternative Stroke Prediction Models for Atrial Fibrillation

TIMI-AF

The Thrombolysis in Myocardial Infarction-Atrial Fibrillation (TIMI-AF) score was developed to predict net clinical outcome in patients receiving warfarin therapy, including disabling stroke, life-threatening bleeding, or all-cause mortality, while also advising on the use of a NOAC versus warfarin in anticoagulant-naive patients. It is based on the randomised clinical trial ENGAGE AF-TIMI 48, which compared edoxaban to warfarin in patients with AF **(Fanola et al.,2017)** . This score awards three points for age > 75 years and LVEF 30%, and two points for age 66 to 74 years, LVEF 30-49%, haemoglobin less than 13 g/dL, and nonwhite race. Unknown LVEF, baseline AF or atrial flutter, prior ischemic stroke, creatinine 110 mmol/L, male sex, diabetes mellitus, carotid disease history, and prior myocardial infarction are all worth one point **(Pérez et al.,2018)**. A person can receive up to 17 points**.** In warfarin-naive patients with AF who were started on warfarin or edoxaban for stroke prevention, the TIMI-AF score predicted a net clinical outcome. Edoxaban and warfarin were comparable in low-score patients, but edoxaban outperformed warfarin in intermediate and high-score patients **(Fanola et al.,2017)**.The TIMI-AF score outperformed the CHA2DS2-VASc, SAMeTT2R2, and HAS-BLED scores in identifying patients at higher risk of cardiovascular events as well as those with a "poor net clinical outcome" of life-threatening bleeding, disabling stroke, or all-cause mortality in a single centre retrospective study of 426 patients with nonvalvular AF **(Pérez et al.,2018)**. Larger prospective studies are needed to confirm these findings.

The ATRIA Score

Based on the self-titled cohort, the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) score was developed to better identify patients at highest risk for stroke while also taking bleeding risk into account . The risk score incorporates renal dysfunction into CHADS2 and takes age groups into account heavily. It also considers the interaction of age and prior stroke, indicating that patients with a prior history of stroke have a higher risk of stroke regardless of age **(Jagadish et al., 2019)**.This model awards a maximum of fifteen points to patients based on previous stroke and age with one point awarded for female sex, diabetes, CHF, hypertension, urine dipstick proteinuria, and either eGFR 45 or end-stage renal disease. ATRIA– Cardiovascular Research Network (ATRIA-CVRN) cohort of 33,247 patients with AF was used to validate the score, and it outperformed CHADS2 and CHA2DS2VASc in terms of c-index and net reclassification improvement (NRI) for stroke and thromboembolism prediction. These scores were also compared in 60,594 untreated AF patients in the UK Clinical Practice Research Datalink cohort **(van et al., 2015)**. The ATRIA score outperformed the CHA2DS2VASc score in identifying low-risk AF patients who had previously been classified as high risk.Based on these findings, the ATRIA score may aid in the risk stratification of patients with very low to low stroke risk AF (CHA2DS2-VASc score of 0 or 1 [men] and 1 or 2 [women]) **(Deering et al.,2017)**.

The GARFIELD-AF Risk Tool

In AF patients, the GARFIELD-AF risk tool is a novel computer-generated machine learning risk model that predicts all-cause mortality **(figure 1)**, ischemic stroke/systemic embolism (SE), and hemorrhagic stroke/major bleeding. It is based on data from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF Registry), which includes data from 35 countries on adults with newly diagnosed AF and at least one additional risk factor for stroke, and it has been externally validated using data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) database. The GARFIELD-AF risk tool outperformed CHA2DS2-VASc in predicting ischemic stroke risk and all-cause mortality, and it outperformed HAS-BLED in predicting major bleeding in both the total population and low-risk patients. This risk model could be integrated into electronic health records to risk stratify patients for ischemic stroke, all-cause mortality, and major bleeding all at the same time **(Fox et al., 2017).**

Table 1: Stroke risk stratification models for atrial fibrillation:

$CHADS_2$ score		
Letter	**Risk factors**	**Points**
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75	1
D	Diabetes mellitus	1
S_2	Stroke/transient ischemic attack	2
	Maximum points	6
CHA_2DS_2VASc score		
Letter	**Risk factors**	**Points**
C	Congestive heart failure	1
H	Hypertension	1
A_2	Age 65–74	1
	Age ≥ 75	2
D	Diabetes mellitus	1
S_2	Stroke/transient ischemic attack	2
VA	VAscular disease	1
Sc	Sex category—female sex	1
	Maximum points	9
TIMI-AF score		
Risk factors		**Points**
Left ventricular ejection fraction < 30%		3
Unknown LVEF		1
Baseline AF or atrial flutter		1
Prior ischemic stroke		1
Creatinine ≥ 110 μmmol/L		1
Male sex		1
Diabetes mellitus		1
Carotid disease history		1
History of myocardial infarction		1
Age 66–74		2
Age > 74		3
Hemoglobin < 13 g/dL		2
Non-white race		2
	Maximum points	17
ATRIA score		
Risk factors	**Points without stroke history**	**Points with stroke history**
Congestive heart failure	1	1
Hypertension	1	1
Diabetes mellitus	1	1
Female sex	1	1
Urine dipstick proteinuria	1	1
Estimated glomerular filtration rate < 45 or end-stage renal disease	1	1
Age < 65	0	8
Age 65–75	3	7
Age 75–84	5	7
Age ≥ 85	6	9
Maximum points	12	15

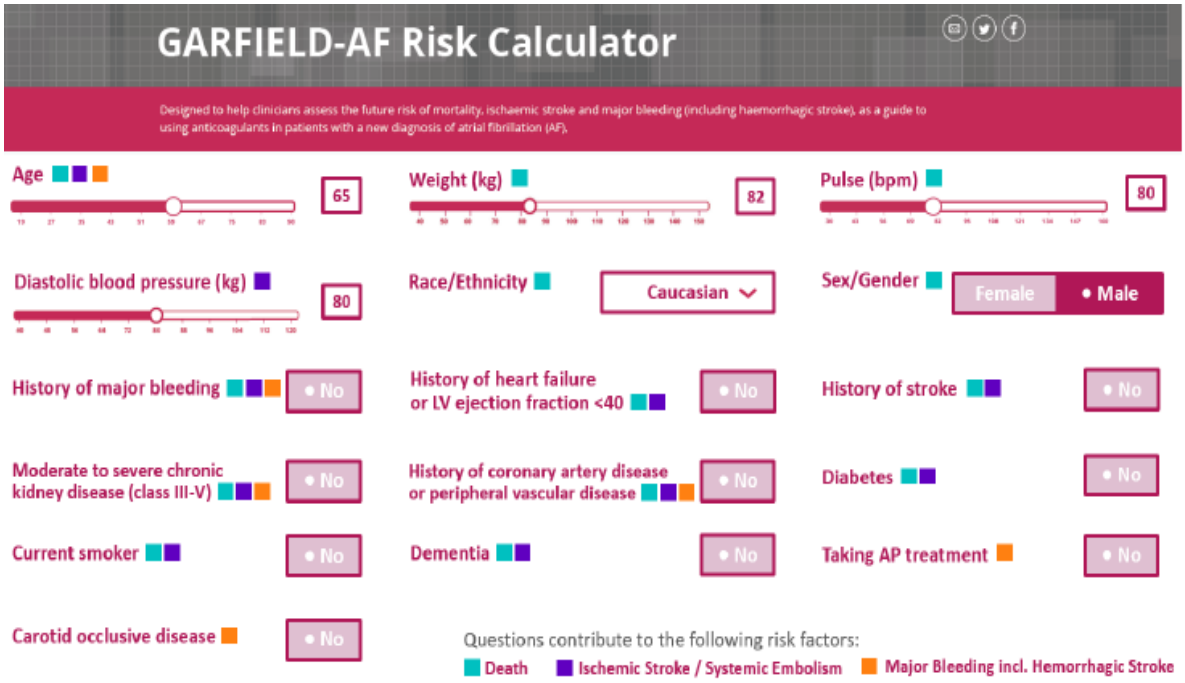

Figure 1: The GARFIELD-AF Risk Tool **Fox et al.,2017.**

References:

1. **Abe M, Ogawa H, Ishii M, Masunaga N, Esato M, Chun Y-H, et al.** Relation of stroke and major bleeding to creatinine clearance in patients with atrial fibrillation (from the Fushimi AF registry). Am J Cardiol. 2017;119:1229–37.
2. **Alkhouli, M., Moussa, I., Deshmukh, A., Ammash, N. M., Klaas, J. P., & Holmes, D. R. (2022**). The heart brain team and patient-centered management of ischemic stroke. JACC: Advances, 1(1), 1-16.
3. **Anan, A. R., Fareed, J., Suhaib, J., Rafat, R., Murad, D., Isam, B., ... & Abhishek, D. (2019).** Left atrial appendage morphology as a determinant for stroke risk assessment in atrial fibrillation patients: systematic review and meta-analysis. Journal of atrial fibrillation, 12(2).
4. **Armaretti, M. L., Balian, N. R., & Zurrú, M. C. (2022).** Atrial Cardiopathy and Cryptogenic Stroke. Cerebrovascular Diseases: Elucidating Key Principles, 67.
5. **Azahar, S. N., Sulong, S., Wan Zaidi, W. A., Muhammad, N., Kamisah, Y., & Masbah, N. (2022).** Direct medical cost of stroke and the cost-effectiveness of direct oral anticoagulants in atrial fibrillation-related stroke: a cross-sectional study. International Journal of Environmental Research and Public Health, 19(3), 1078.
6. **Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al.** Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139:e56–528 Available from: http://www.ncbi.nlm.nih.gov/
7. **Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al.** Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation–developed with the special contribution of the European Heart Rhythm Association. Europace. 2012;14:1385–413
8. **Cushman M, Judd SE, Howard VJ, Kissela B, Gutiérrez OM, Jenny NS, et al.** N-terminal pro-B-type natriuretic peptide and stroke risk: the reasons for geographic and racial differences in stroke cohort. Stroke. 2014;45:1646–50.
9. **Deering TF.** Incorporating stroke and bleeding risk stratification tools into atrial fibrillation management making sense of the alphabet soup. J Atr Fibrillation. 2017;9:1497
10. **Fanola CL, Giugliano RP, Ruff CT, Trevisan M, Nordio F, Mercuri MF, et al.** A novel risk prediction score in atrial fibrillation for a net clinical outcome from the ENGAGE AF-TIMI 48 randomized clinical trial. Eur Heart J. 2017;38:888–96
11. **Fox KAA, Lucas JE, Pieper KS, Bassand J-P, Camm AJ, Fitzmaurice DA, et al.** Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open. 2017;7:e017157

12. **Friberg L, Rosenqvist M, Lip GYH.** Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33:1500–10.
13. **Fu S, Zhou S, Luo L, Ye P.** R2 (GFR) CHADS2 and R2(GFR)CHA2DS2VASc schemes improved the performance of CHADS2 and CHA2DS2VASc scores in death risk stratification of Chinese older patients with atrial fibrillation. Clin Interv Aging. 2017;12:1233–8
14. **Gao, X., & Passman, R. (2022).** Stroke Prevention in Atrial Fibrillation. Current Cardiology Reports, 24(11), 1765-1774.
15. **Golwala H, Jackson LR, Simon DN, Piccini JP, Gersh B, Go AS, et al.** Racial/ethnic differences in atrial fibrillation symptoms, treatment patterns, and outcomes: insights from Outcomes Registry for Better Informed Treatment for Atrial Fibrillation registry. Am Heart J. 2016;174:29–36
16. **Hayashi K, Tsuda T, Nomura A, Fujino N, Nohara A, Sakata K, et al.** Impact of B-type natriuretic peptide level on risk stratification of thromboembolism and death in patients with nonvalvular atrial fibrillation - the Hokuriku-Plus AF Registry. Circ J. 2018;82:1271– 8
17. **Jagadish, P. S., & Kabra, R. (2019).** Stroke risk in atrial fibrillation: Beyond the CHA 2 DS 2-VASc score. Current cardiology reports, 21, 1-9.
18. **January CT, Wann LS, Calkins H, Field ME, Chen LY, Furie KL, et al.** AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart R. Hear Rhythm. 2019.
19. **Jehan S, Farag M, Zizi F, Pandi-Perumal SR, Chung A, Truong A, et al.** Obstructive sleep apnea and stroke. Sleep Med Disord Int J. 2018;2:120–5
20. **Kabra R, Girotra S, Vaughan SM.** Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. J Am Coll Cardiol. 2016;68:461–70
21. **Koga M, Yoshimura S, Hasegawa Y, Shibuya S, Ito Y, Matsuoka H, et al.** Higher risk of ischemic events in secondary prevention for patients with persistent than those with paroxysmal atrial fibrillation. Stroke. 2016;47:2582–8
22. **Lipford MC, Flemming KD, Calvin AD, Mandrekar J, Brown RD, Somers VK, et al.** Associations between cardioembolic stroke and obstructive sleep apnea. Sleep. 2015;38:1699–705
23. **Marsico F, Cecere M, Parente A, Paolillo S, de Martino F, Dellegrottaglie S, et al**. Effects of novel oral anticoagulants on left atrial and left atrial appendage thrombi: an appraisal. J Thromb Thrombolysis. 2017;43:139-48
24. **Okumura K, Inoue H, Atarashi H, Yamashita T, Tomita H, Origasa H, et al.** Validation of CHA2DS2-VASc and HAS-BLED scores in Japanese patients with nonvalvular atrial fibrillation: an analysis of the J-RHYTHM Registry. Circ J. 2014;78:1593–9
25. **Pereg D, Rozenbaum Z, Vorobeichik D, Shlomo N, Gilad R, Bloch S, et al.** Prevalence and significance of unrecognized renal dysfunction in patients with stroke. Am J Med. 2016;129:1074–81
26. **Pérez Cabeza AI, Bravo Marques R, Chinchurreta Capote PA, Ruiz Mateas F, Fanola CL, Rosas Cervantes G, et al.** TIMI-AF score and cardiovascular events in vitamin K antagonists-naïve outpatients with atrial fibrillation. Clin Cardiol. 2018;41:1252–8 pubmed/30700139
27. **Quon MJ, Behlouli H, Pilote L.** Anticoagulant use and risk of ischemic stroke and bleeding in patients with secondary atrial fibrillation associated with acute coronary syndromes, acute pulmonary disease, or sepsis. JACC Clin Electrophysiol. 2018;4:386–93
28. **Rordorf, R., Iacopino, S., Verlato, R., Arena, G., Tondo, C., Molon, G., ... & Pieragnoli, P. (2022).** Role of CHA2DS2-VASc score in predicting atrial fibrillation recurrence in patients undergoing pulmonary vein isolation with cryoballoon ablation. Journal of Interventional Cardiac Electrophysiology, 1-8.
29. **Sayan S, Kotan D.** Levels of brain natriuretic peptide as a marker for the diagnosis and prognosis of acute ischemic stroke. Arch Med Sci Atheroscler Dis. 2016;1:e16–22
30. **Shin, J., Andrews, M., DeJean, L., Debski, N., Exarchakis, A., Fleming, J., ... & Roy, S. (2023).** Risk Factors Associated With Atrial Fibrillation in Elderly Patients. Journal of Clinical Medicine Research, 15(3), 148-160.
31. **Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH.** Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. Circ Res. 2017;120:1501–17

32. **Sughrue T, Swiernik MA, Huang Y, Brody JP.** Laboratory tests as short-term correlates of stroke. BMC Neurol. 2016; 16:–112
33. **van den Ham HA, Klungel OH, Singer DE, Leufkens HGM, van Staa TP.** Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke in patients with atrial fibrillation: results from a National Primary Care Database. J Am Coll Cardiol. 2015;66:1851–9
34. **Vinereanu D, Lopes RD, Mulder H, Gersh BJ, Hanna M, de Barros E Silva PGM, et al.** Echocardiographic risk factors for stroke and outcomes in patients with atrial fibrillation anticoagulated with apixaban or warfarin. Stroke. 2017;48:3266–73
35. **Yang P-S, Pak H-N, Park D-H, Yoo J, Kim T-H, Uhm J-S, et al.** Non-cardioembolic risk factors in atrial fibrillation-associated ischemic stroke. PLoS One. 2018;13:e0201062 Available from:
36. **Yarmohammadi H, Varr BC, Puwanant S, Lieber E, Williams SJ, Klostermann T, et al.** Role of CHADS2 score in evaluation of thromboembolic risk and mortality in patients with atrial fibrillation undergoing direct current cardioversion (from the ACUTE trial substudy). Am J Cardiol. 2012;110:222–6 Available from: http:// www.ncbi.nlm.nih.gov/pubmed/22503581.
37. **Zhao, Y., Ji, L., Liu, J., Wu, J., Wang, Y., Shen, S., ... & Bin, J. (2016).** Intensity of left atrial spontaneous echo contrast as a correlate for stroke risk stratification in patients with nonvalvular atrial fibrillation. Scientific reports, 6(1), 1-9.