Section A -Research paper

Prediction of Thromboembolic Stroke in Non-Valvular Atrial Fibrillation Patients with Low CHA2DS2-VASc Score

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Abstract

A supraventricular arrhythmia known as atrial fibrillation (AF) occurs when the atria are unable to contract effectively due to an abnormality in the electrical activity of the atrium. Worldwide, atrial fibrillation is becoming more common and more commonplace. Based on findings from the Framingham Heart Study (FHS), the probability of atrial fibrillation has tripled in the last fifty years. AF prevalence exhibits geographical variation. The areas with a high occurrence rate, specifically Western Europe as well as North America, contrast with the generally lower occurrence rate observed in Oceania, South Asia & the Middle East. AF is most significantly influenced by age. It is linked to a higher occurrence of atrial fibrillation, with a significant rise occurring beyond the age of 65. Chronic subclinical inflammation refers to the persistent, mild activation of the body's immunological response, which is a characteristic feature of biological aging in various organ systems. Elevated amounts of reactive oxygen species are linked to both AF and age. AF is linked to higher mortality rates. Individuals typically do not succumb to the arrhythmia itself, but rather to the presence of other concurrent diseases and consequences, for example myocardial infarction, heart failure, venous thromboembolism (VTE), chronic kidney disease, stroke, dementia, as well as cancer.

Key words: Thromboembolic Stroke, atrial fibrillation, Low CHA2DS2-VASc Score

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Introduction

Nonvalvular atrial fibrillation is the predominant as well as persistent abnormal heart rhythm, and it is the primary factor leading to stroke caused by blood clots in the heart. It is widely known that embolic strokes among individuals with nonvalvular atrial fibrillation are most commonly caused by left atrial appendage thrombi (LAAT)[1]. Transesophageal echocardiography (TEE) is widely acknowledged to be capable of detecting left atrial appendage thrombi as well as left atrial blood stasis. This is evident through the attendance of

spontaneous echo contrast (SEC), which is a recognized indicator of LAAT & systemic thromboembolism. The decreased relaxation of the heart's ventricles and the resulting increase in pressure during filling can cause the production of blood clots in the left atrium, which can then travel to other parts of the body as well as cause blockages in blood vessels [2]. The ChA2Ds2 – VASc score is a scoring system utilized to categorize the likelihood of stroke in people with atrial fibrillation. The abbreviation ChA2Ds2 – VASc represents the following medical conditions: hypertension, congestive heart failure, age at least seventy-five years (doubled), diabetes, vascular disease, stroke (doubled), & age sixty -five to seventy-four, & sex category (female). The individuals were categorized into three groups based on their ChA2Ds2 – VASc score, following the criteria of the European Society of Cardiology for atrial fibrillation. When the score is zero, the risk is minimal; when it's one, the risk is medium; as well as when it's two or more, the risk is severe [3]. The current emphasis in stroke prevention for nonvalvular AF has moved from forecasting high-risk individuals to firstly categorizing people with a genuinely decreased risk of ischemic stroke, for whom OAC provides no overall therapeutic advantage [4].

The objective of the research was to create more accurate and quantified risk models for predicting the risk of cardiogenic stroke among individuals with non-valvular atrial fibrillation (NVAF) who had a low CHA2DS2-VASc score.

Atrial fibrillation

AF is a type of arrhythmia that arises when there is an irregularity in the electrical activity of the atria, leading to a decrease in their capacity to contract effectively [5].

Classification of AF

Several classification schemes have been suggested, which differ in terms of time frame, underlying causes, as well as connections to valvular heart disease [6].

Based on temporality/pattern of episodes:

Both American & European societies share comparable descriptions for classifying atrial fibrillation depending on the pattern of occurrence: persistent AF, Paroxysmal atrial fibrillation, long-standing persistent AF, as well as permanent atrial fibrillation [7,3].

In regards to the existence of concomitant valvular disease:

While not widely acknowledged as a predictable method of AF categorization, this distinction holds practical significance as it aids in determining the appropriate anticoagulant treatment. Valvular AF refers to atrial fibrillation occurring in individuals with moderate to severe mitral stenosis & mechanical heart valves. In contrast, nonvalvular AF comprises mechanical heart valves as well as all other types of valvular heart disease without moderate to severe mitral stenosis.

In light of Etiology of atrial fibrillation (ESC 2016 guidelines)

The ESC has officially supported this classification as an expert consensus to aid

in determining therapeutic strategies based on the underlying cause, as the pattern of atrial fibrillation may be similar in all of these situations [3].

Epidemiology

AF is the most predominant cardiac arrhythmia in clinical practice. Its occurrence is directly linked with age, with a prevalence of 0.5 percent in persons up to 60 years old, & a higher prevalence of ten percent in elderly individuals over 80 years old. Men have a 50 percent greater probability of having AF compared to females [5].

Risk factors or AF

Risk factors for atrial fibrillation [6]

Nonmodifiable: Mutations involving Na & Ca channels, as well as mutations that influence a variety of myocyte proteins, age, Caucasian race, and male gender are all factors that can be considered.

Modifiable: The individual has a medical history that includes hypertension, coronary artery disease, diabetes mellitus, obesity, dyslipidemia, alcohol & drug abuse, obstructive sleep apnea, poor physical conditioning, hyperthyroidism, HF, cardiomyopathy, pericarditis & myocarditis, postcardiac operation, pulmonary embolism, valvular heart disease, chronic renal disease, as well atrial septal defect.

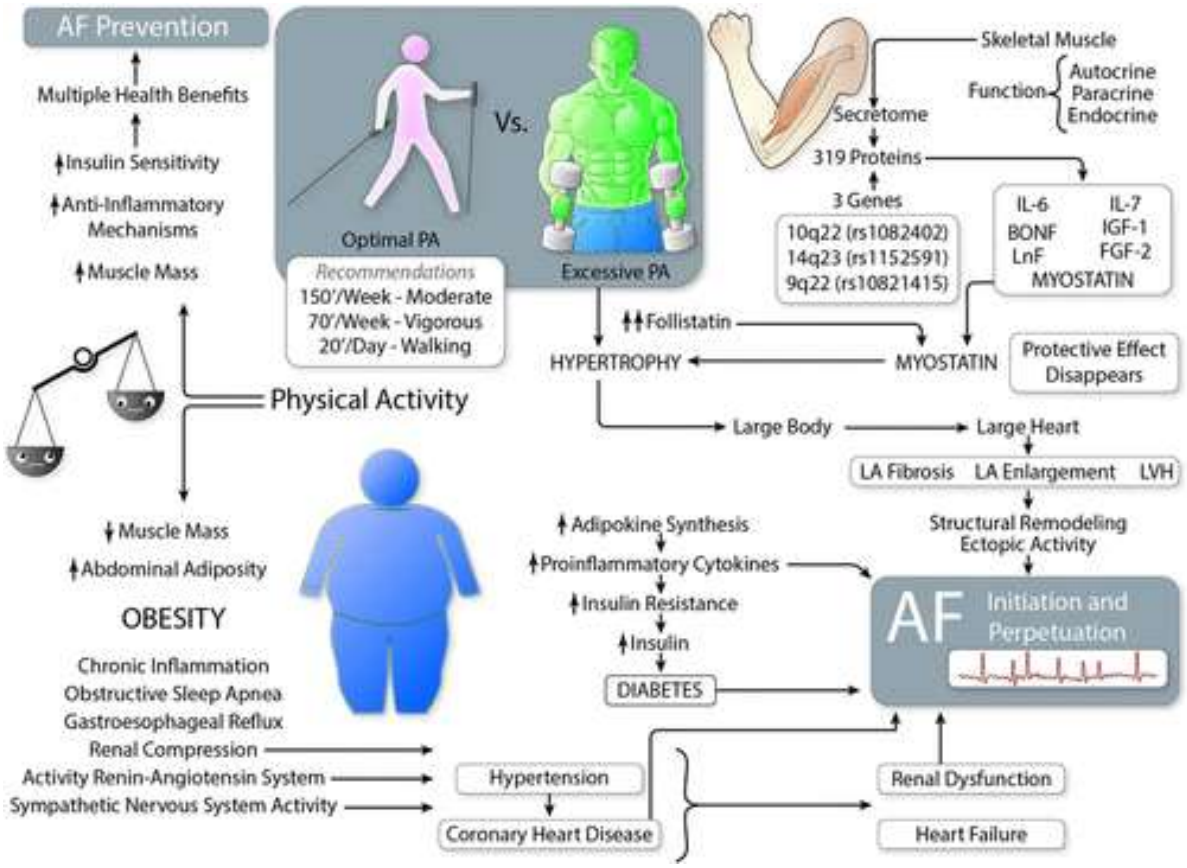

Figure (1): Connection amongst obesity, physical activity, & lean body mass in atrial fibrillation [8]

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Pathophysiology

The etiology of AF is intricate as well as lacks comprehensive understanding. Nonetheless, the fundamental electrophysiological anomaly comprises three primary elements: the presence of "triggers" that initiate abnormal activity in the atria or pulmonary veins, functional & structural abnormalities ("drivers") that facilitate as well as sustain reentry, as well as ultimately the existence of an abnormal substrate that contributes to the continuation of atrial fibrillation [9-10].

Focal atrial ectopic activity is triggered by three main mechanisms: (1) increased automaticity due to alterations in inward rectifier potassium (I KI) & pacemaker currents (I f); (2) early after depolarization caused by abnormal I caL channels & prolonged action potential duration; & (3) delayed after depolarization resulting from excessive atrial calcium (Ca 2+) levels as well as abnormal release of excessive atrial calcium from the sarcoplasmic reticulum during diastole [11].

The fast ectopic activity can be found specifically in the "muscular sleeves" of the pulmonary veins in approximately 90% of individuals with atrial fibrillation, particularly in those with paroxysmal atrial fibrillation. The remaining 10% of cases of atrial fibrillation are caused by triggers other than PV contractions. These triggers commonly occur in various locations, including the interatrial septum (especially at the fossa ovalis), crista terminalis, inferior mitral annulus, left atrial posterior wall & appendage, Eustachian ridge, ligament of Marshall, & other veins for example the superior in addition to inferior vena cava[11].

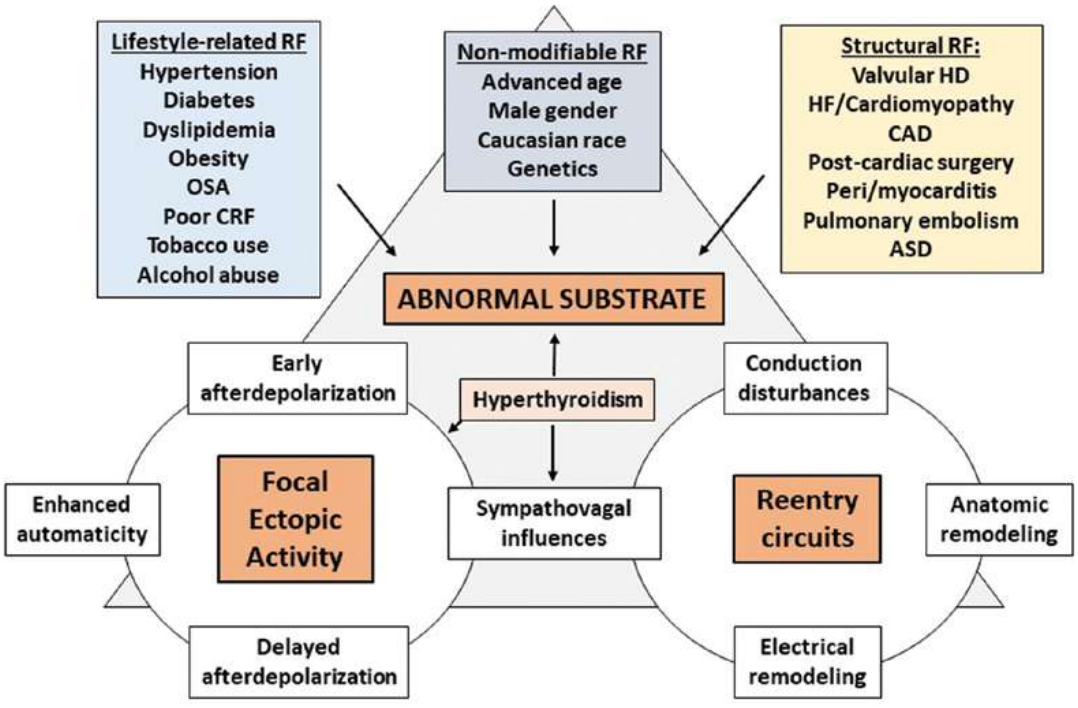

Figure (2): Interplay among several factors of risk & electrophysiological devices resulting in also perpetuating atrial fibrillation [6]. HF, heart failure.

Screening & Diagnosis

Basic evaluation of the patient with AF

Confirmation of AF diagnosis necessitates an ECG recording, which may be obtained using bedside telemetry or ambulatory Holter recordings. Analysis of ambulatory ECG records as well as device-based monitoring indicates that individuals can have episodes of both symptomatic & asymptomatic atrial fibrillation [12].

Nevertheless, as many as ninety percent of AF episodes may not exhibit any symptoms. Additional severe indications & symptoms, for example intense difficulty in breathing, angina, as well as unstable blood circulation, could be attributed to concomitant cardiac conditions such ischemic heart disease or heart failure. A 12-lead ECG is indicated as the initial diagnostic step when suspicion arises [13].

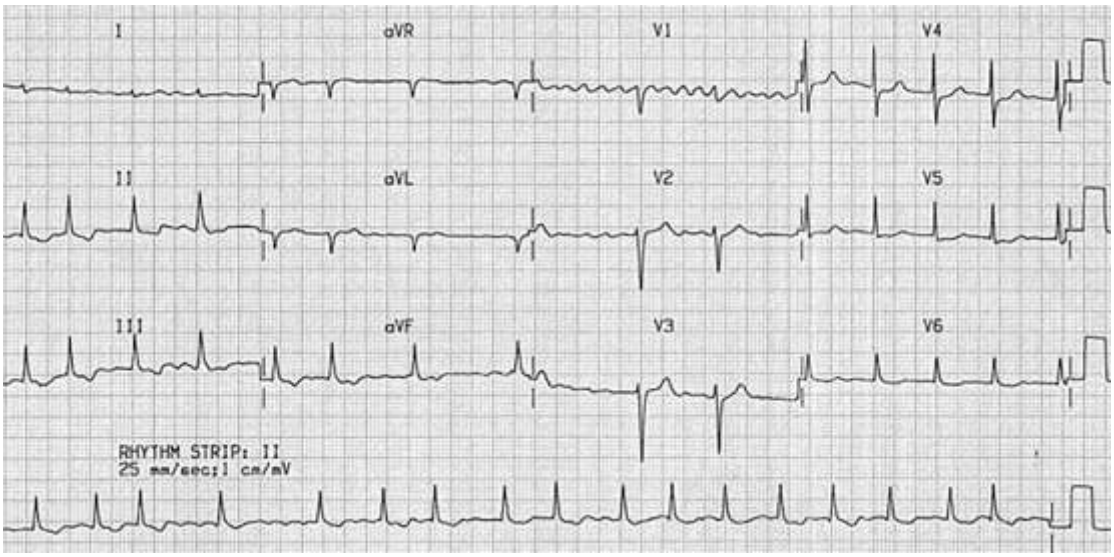

Figure (3): 12 lead ECG showing AF [14]

Novel Screening Tools

Timely detection as well as initiation of suitable therapy for AF can help avoid adverse outcomes like stroke, heart failure, and the advancement of the underlying condition. The 2020 guidelines suggest that individuals aged over seventy-five years or those who are at a extraordinary risk of stroke should undergo systematic screening (IIaB). Additionally, opportunistic screening is recommended for adults over 65 years of age (IB) [15]. Furthermore, in order to confirm the diagnosis of AF, it is still necessary for a physician who specializes in ECG to review and analyze the ECG tracing recording for a minimum duration of thirty seconds. The latter is crucial in order to prevent misinterpretation, which can result in over diagnosis, unneeded further tests, along with overtreatment [16].

Administration of Atrial High-Rate Episodes (AHRE) & Subclinical Atrial

Fibrillation in CIED

Atrial high-rate episodes are typically characterized as sudden bouts of atrial rates over 175-180 beats per minute, lasting for a duration of over five to six minutes, and identified by CIEDs. If the intracardiac electrogram is visually examined and approves the existence of AF, it can be designated as "subclinical atrial fibrillation." [17]. It is advisable to assess these people for risk factors & co-morbidities linked to AF. However, there is ongoing debate regarding the specific level of AHRE as well as subclinical AF that requires medical intervention. The efficiency of rate or rhythm control interventions in preventing development to clinical AF at this time is uncertain, in addition to no recommendations are provided on their beginning [18].

The ABC Pathway

In order to address the increasing intricacy of AF management resulting from a multitude of therapy choices, the 2020 recommendations have implemented a straightforward and simple treatment algorithm to guarantee efficient and suitable AF care for every individual. The ABC pathway [16].

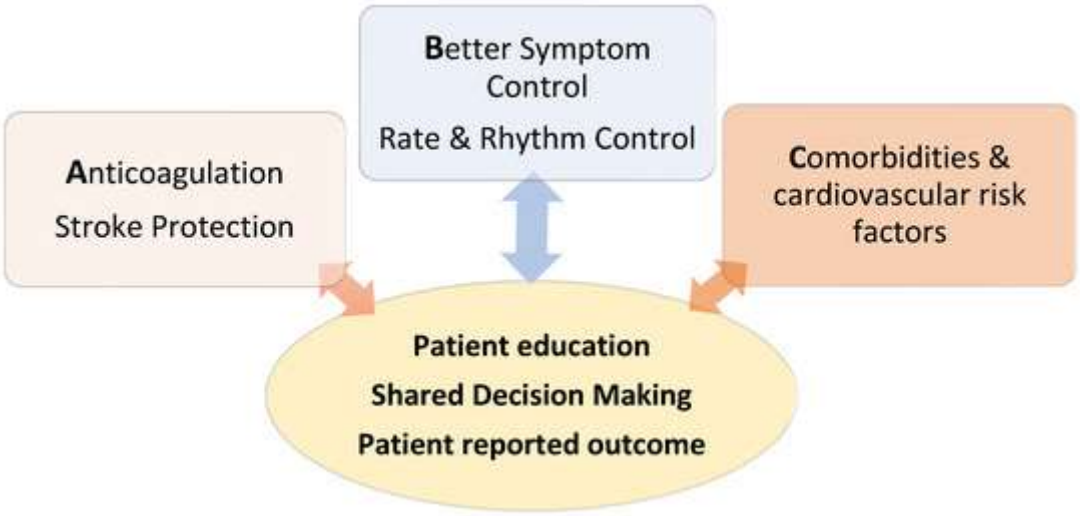

Figure (4): The diagram depicts the many elements of the ABC of AF Management in 2020, aimed at guaranteeing efficient management of atrial fibrillation for every individual person [16]. An integrated care approach should include the incorporation of three treatment pillars: shared decision making, patient education & patient reported outcome. These pillars serve as the foundation for effective care.

Anticoagulation

The central focus of AF management continues to be achieving the most effective stroke prevention. Oral anticoagulation can decrease the likelihood of ischemic stroke by 65 percent, however it comes with a trade-off of a 0.3 percent annual increase in hemorrhagic stroke [19].

Better Symptom Control

The 2nd component of the ABC route pertains to the management of symptoms through the use of medicine, cardioversion, or invasive interventions to regulate heart rate or rhythm. The alleviation or improvement of symptoms has consistently been one of the primary motivating factors for therapy. Restoring & maintaining sinus rhythm not only helps control symptoms, but also has additional benefits for instance improving exercise capacity & quality of life, reducing left atrial size, increasing ventricular ejection fraction, lowering cardiac hospitalizations, decreasing atrial arrhythmia burden, as well as decreasing mortality [20-21].

Rate Control

Rate control can be accomplished with the use of either a mono- or combination therapy using non-dihydropyridine calcium channel blockers, betablockers, and/or digoxin. The previous observations of increased mortality in atrial fibrillation cases using digoxin were ascribed to a preference that existed within the choosing as well as prescribing procedure [16].

Choice of Rhythm Control Modalities

Cardioversion: Cardioversion utilizing synchronized electrical shocks is the preferred initial treatment for those who are experiencing unstable hemodynamic conditions. On the other hand, persons who are hemodynamically stable can be managed with either electrical or pharmaceutical (Vernakalant, Propafenone, Flecainide, Amiodarone, or Ibutilide) cardioversion.

Antiarrhythmic drugs: As of 2020, there have been no new antiarrhythmic medications introduced for long-term pharmacological rhythm regulation. The available options are confined to class I pharmaceuticals (Propafenone, Flecainide) or class III drugs (Dronedarone, Sotalol, Amiodarone).

Catheter ablation: Catheter ablation has emerged as a widely accepted, secure, as well as a better option than antiarrhythmic medications for the treatment of sinus rhythm disorders & their associated symptoms. There is evidence in favor of this technique from multiple randomized studies in both chronic AF & paroxysmal atrial fibrillation.

Hybrid approaches: Hybrid techniques that combine endo- and minimally invasive epicardial ablation are now being used more frequently as an alternative for patients with drug-resistant atrial fibrillation as well as unsuccessful percutaneous ablation. These approaches should be taken into consideration. The CONVERGE study in 2020 indicated that a combination of epi- & endocardial ablation can effectively manage the rhythm of prolonged persistent AF, with sixty-seven percent of patients maintaining a normal sinus rhythm after 1 year [22].

Complications of AF

Comorbidities of atrial fibrillation & Their Influence on Prognosis

Atrial fibrillation is linked to higher mortality rates. Persons typically do not succumb to the arrhythmia itself, but rather to the presence of other existing medical

conditions & associated problems, for example heart failure, myocardial infarction, chronic kidney disease, venous thromboembolism, dementia, stroke & cancer.

Heart Failure

HF is strongly linked to atrial fibrillation, as well as both conditions occur together, it is connected with significantly higher rates of illness & death. Both AF as well as HF are linked to a higher occurrence of the other condition, indicating a reciprocal relationship [23]. Among a subgroup of FHS persons who developing new AF, 37 percent had a prior diagnosis of HF. Conversely, 57 percent of cases who developed heart failure had preexisting atrial fibrillation. The prevalence of these diseases rises significantly after the age of 60 [24].

Myocardial Infarction

There is an approximately two-fold higher risk of myocardial infarction in persons with atrial fibrillation. Acute AF is more prevalent among individuals with MI. The actual frequency might be substantially greater if asymptomatic AF is considered. Among people monitored in a post-MI trial who had implantable cardiac devices, the incidence rate of atrial fibrillation at one year was 32 percent [24]. There are multiple pathways through which MI encourages the progression of AF. Atrial fibrillation can develop in the acute phase following MI if there is left ventricular dysfunction, hypertrophy, or an increased heart rate. Soon after a MI, atrial ischemia can produce atrial fibrillation. In addition, atrial stretching due to severe HF following MI might enhance atrial excitability, as well as pericarditis caused by infarction has been identified as a primary cause of atrial fibrillation [25].

Chronic Kidney Disease

Additional risk factors for AF include albuminuria, mild renal impairment, as well as decreasing renal function. Results showed that the risk of atrial fibrillation was thirty-two percent greater for those with glomerular filtration rates among thirty and fifty-nine mL/min in contrast to those with normal renal function. The risk was fifty-seven percent greater for cases with a glomerular filtration rate below thirty mL/min [26].

Venous Thromboembolism

Despite their outward differences, VTE and AF are really rather similar disorders that share many pathophysiology characteristics and frequently co-occur. Incidences of atrial fibrillation following a diagnostic of VTE & VTE following an AF diagnosis are at least seventy percent greater than the general population. A person's risk of contracting another disease increases over the first six months following a diagnosis of AF or VTE [27].

Stroke

Even in its subclinical form, atrial fibrillation is linked with a four- to fivefold difficult risk of stroke. Stroke risk is greater in persistent AF types equated to paroxysmal AF types [28]. Stroke & thrombus formation in AF are caused by changes in blood flow, atrial enlargement, and atrial fibrosis. Even though it is not a

direct reason for AF, hemorrhagic stroke is related with an increase in new-onset atrial fibrillation. Pathophysiological pathways may involve inflammation & deregulation of the autonomous nervous system [29].

Dementia

Dementia increases the possibility of stroke in heart failure persons. Roughly one-third of the people with stroke experienced new-onset dementia within five years. Dementia is 2.7 times people who have a higher susceptibility to AF following a first or subsequent stroke, indicated to a meta-analysis [30].

Cancer

Cancer as well as AF often occur together, although the relationship amongst the two has received little research. Within the first three months following the commencement of new-onset atrial fibrillation, the risk of newly diagnosed malignancy is about three times higher. There is a marked rise in the likelihood of incident AF in cases with newly diagnosed malignancy [31].

of stroke & thromboembolic events in AF

Scores

CHA2DS2-VASc Score: The CHADS2 score is the gold standard for AF stroke risk stratification. one point for hypertension, One point is awarded for congestive heart failure, one point for diabetes mellitus, one point for age 75 years or older, as well as two points for a previous stroke or transient ischemic attack in the CHADS2 scoring system, which is utilized to evaluate the risk of stroke [32].

Table (3): Components of the $CHADS_2$ & CHA_2DS_2-VASc scores that are utilized to evaluate the risk of stroke in AF in addition to guide the decision of anticoagulation therapy [33].

Condition	$CHADS_2$	Points	CHA_2DS_2-VASc	Points
Congestive heart failure (or left ventricular systolic disorders)	C	1	C	1
Hypertension (BP over 140/90 or treated hypertension on medication)	H	1	H	1
Age above 75	A	1	A2	2
Diabetes mellitus	D	1	D	1
Stroke or TIA or thromboembolism in history	S2	2	S2	2
Vascular disease (myocardial infarction, peripheral vascular disease, & aortic plaque)			V	1
Age over 65			A	1
Gender (Female)			SC	1

ATRIA score: Stroke risk stratification based on the ATRIA score is suggested. An ATRIA cohort was used to derive this score. In this study, only individuals who were not taking anticoagulants were considered (n = 10, 927). The median duration of anticoagulant treatment was 2.4 years. Table 4 shows that the ATRIA score is based on a point-based stratification scheme, as well as that it is computed independently for individuals with and without a history of stroke. A low risk ATRIA score (event rates of less than 1% per year), a moderate risk score (one to two percent event rate), & a high risk score (at least 2% per year) are all represented by scores from seven and fifteen points [34].

Clinical Biomarkers

To improve the score's specificity as well as sensitivity, several clinical biomarkers have been suggested for inclusion in the literature. Current evidence suggests that certain clinical markers along with circulating biomarkers display promise for the prediction of IS in cases with NVAF. These markers include non-paroxysmal type of atrial fibrillation in addition to carotid plaque, as well as N-terminal pro-B-type natriuretic protein, cardiac troponin, as well as D-dimer. Determination of these markers is both practical & simple. In accordance with a recent extensive assessment, a large number of possible biomarkers can be categorized as either "clinical" or "circulating." [35].

Cardiac Imaging and ECG Biomarkers

Vascular injury, blood stasis, & hypercoagulability are the three main components of venous thrombosis, as stated by Virchow's triad. The development of intra-atrial thrombus and aberrant blood flow patterns through the atrium are consequences of atrial fibrillation, which worsens with time owing to endocardial denudation, atrial dilatation, as well as oedematous or fibroelastic infiltration of the extracellular matrix [35].

Left Atrial Appendage Structure & Function

The statistical shape analysis of LAA as well as the angle bend from the proximal/middle region of the Left Atrial Appendage are two quantitative assessments that have been studied for their potential involvement in predicting stroke risk [36].

LA Structure & Function

In individuals with non-valvular atrial fibrillation, the structure as well as function of LA could potentially aid in the prediction of IS (72, 73). Whether oral anticoagulant were administered or not, a larger LA diameter (LAD) was a robust predictor of stroke or TE in the Fushimi AF Registry, a large community-based cohort investigating Japanese NVAF subjects (HR = 1.74, 95% CI: 1.25-2.42, P < 0.01) [37].

Left Ventricular (LV) Structure & Function

After adjusting for many possible confounders, Tezuka et al. demonstrated that non-valvular atrial fibrillation subjects with high Left Ventricular relative wall thickness (RWT) were independently linked to IS (HR = 1.81, 95 percent CI: 1.34-2.47, P under

0.01), suggesting that LV morphology significantly contributes to TE. It was also believed that LV systolic function, as measured by LV ejection fraction (LVEF), was a critical predictor of TE events in NVAF. The CHA2DS2-VASc score already includes LVEF, the most essential diagnostic indication of HF [38].

Circulating Biomarkers

Cardiac Troponins: Troponin has long been utilized as a diagnostic tool for cardiac necrosis. Its application as a biomarker for cardiovascular disease is unparalleled. Its usefulness in identifying myocardial damage is beyond question & it can be employed to evaluate numerous significant pathophysiological aspects related to the progression and prognosis of the disease[39].

B-type natriuretic peptide & NT-proBNP: Indications of heart failure include the secretion of B-type natriuretic peptide (BNP) as well as NT-proBNP in reaction to elevated end-diastolic pressure and/or volume expansion. Enzymatic cleavage of BNP generated by cardiac myocytes yields NT-pro B-type natriuretic peptide. A higher possibility of IS may be indicated by their increase if atrial dysfunction is present [40].

D-Dimer: As a biomarker of active coagulation as well as fibrinolysis, D-dimer is a byproduct of cross-linked fibrin breakdown. There is evidence that IS is more likely in patients with higher levels of D-dimer [41].

Mean Platelet Volume: The risk of thrombotic problems is correlated with mean platelet volume (MPV), which represents the intensity of an inflammatory process. One study identified that MPV is a strong indicator of IS among individuals with non-valvular atrial fibrillation. The sensitivity for IS prediction was 72.1 percent as well as the specificity was 81.5 percent when the CHA2DS2-VASc score as well as MPV were combined [42].

Plasma Fibrinogen: Those with AF had elevated plasma fibrinogen levels, which were positively linked to leukoaraiosis as well as periventricular hyperintensity in stroke in addition to AF individuals, respectively [43].

Biomarkers of Inflammation: Uricemia, C - reactive protein, TMAO, Soluble CD40L & GDF-15, IL-1ra, IL-6

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