TREATMENT OF ATRIAL FIBRILLATION: A REVIEW

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population and the most important cause of embolic stroke. The therapy for AF, particularly persistent AF, remains suboptimal. Current antiarrhythmic drugs are associated with a significant rate of adverse events, particularly proarrhythmia, which may explain why many highly symptomatic AF patients are not receiving any rhythm control therapy. This review focuses on antiarrhythmic drug therapy for AF today, reviewing molecular mechanisms, and the possible clinical use of some of the new atrial selective antifibrillatory agents, as well as drugs that target atrial remodeling, inflammation and fibrosis, which are being tested as upstream therapies to prevent AF perpetuation. Altogether, the objective is to highlight the magnitude and endemic dimension of AF, which requires a significant effort to develop new and effective antiarrhythmic drugs, but also improve AF prevention and treatment of risk factors that are associated with AF complications. This article also provides general principles for appropriate risk stratification, selection of anticoagulation therapy in AF and also explains stroke prevention, screening, rate and rhythm control, risk factor management, and integrated management of AF.

Keywords: Atrial fibrillation, Ischemic Stroke, Thromembolism, antiarrhythmic drugs, anticoagulation therapy.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia seen by the clinician in a general population [1-3]. It affects more than 33 million people worldwide and is also the number one cause of hospitalization for arrhythmia. Prevalence increases with advancing age and increases the risk of mortality and morbidity resulting from stroke, congestive heart failure and impaired the quality of life, explaining its enormous socioeconomic and healthcare implication [4]. AF is characterized by rapid and irregular activation of the atria without discrete P waves on the surface electrocardiogram (ECG). The pathophysiology of AF is complex, involving dynamic interactions among several factors, including substrate, triggers, and perpetuators, and the therapeutic approaches/strategies are informed by the disease progression from initiation of the abnormal electrical rhythm to its maintenance. Many drugs have been tried in persistent AF with limited success. Several class IA, IC, and III drugs, as well as class II drugs (beta-blockers), are moderately effective in maintaining sinus rhythm after conversion of atrial fibrillation. However, they increase adverse events, including proarrhythmia, and some like Disopyramide, Quinidine, and Sotalol, may increase mortality. In fact, antiarrhythmic drug therapy in general improves patients' symptom scores and exercise tolerance; however, large randomized trials have failed to show a mortality benefit with a rhythm-control compared with a rate-control strategy. Therefore, the availability of new oral anticoagulant drugs that overcome the intrinsic disadvantages of warfarin has shifted the focus of drug development toward enabling widespread application of effective thromboprophylaxis with oral anticoagulants, particularly in low-risk patients with AF. On the other hand, the development of new mapping and catheter-based ablation technologies, which have made the procedure safer, easier to perform and more effective after a single attempt, has greatly improved the outcomes in patients with paroxysmal AF. However, success rates for persistent AF ablation remain far lower than paroxysmal AF and there is large variation in the strategies used worldwide, which high lights the need and offers new opportunities for the development of a new generation of drugs for the prevention and termination of AF.

Paroxysmal AF is defined as recurrent AF episodes that terminate spontaneously or with intervention within 7 days of onset. Persistent AF is defined as continuous AF that is sustained beyond 7 days; long-standing Persistent AF is defined as continuous AF of greater than 12-month duration. The first diagnosed AF refers to AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and Severity of AF-related symptoms. From a clinical point of view, the latter is important as more than 50% of Patients with a first diagnosed AF episode will not experience recurrences over long-time follow up in the absence of antiarrhythmic drugs, cardiac structural abnormalities, and significant comorbidities. Early persistent AF is a new term defined as continuous AF of more than 7-day duration but less than 3-month duration. The latter subdivision is reasonable for patients who are candidates for an AF ablation procedure, because better results are obtained with shorter duration of the persistent AF. The term permanent AF is defined as AF in which the presence of the AF is accepted by the patient and physician, and no further attempts

will be made either to restore or maintain sinus rhythm. There are so many risk factors for development of Thromembolism in atrial fibrillation and some important risk factors are listed on table 1.

Following are the risk factors for Thromembolism in atrial fibrillation patient:

1. Previous ischemic stroke or transient ischemic attack.
2. Mitral valves disease.
3. Hypertension.
4. Diabetes mellitus.
5. Heart failure.
6. Age over 65 years.
7. Echocardiography feature of left ventricular dysfunction, left ventricular enlargement or mitral annular calcification.

Table 1: Risk factors for Thromboembolism in atrial fibrillation [5].

Epidemiology of atrial fibrillation:

AF represents a global health problem that predominantly affects developed nations, North America being the region with highest prevalence and incidence rates [6]. Overall both incidence and prevalence rates have been progressively increase in the world population [7]. This may result in more than 50 million AF patients worldwide by 2030. Current AF prevalence in general adult population of Europe ranges from 1.9% to 2.9% depending on the country. AF prevalence varies with age and sex. In individual younger than 50 years and older than 80 years, AF prevalence ranges from 0.1% to 10-18% respectively [8]. The prevalence was significantly greater in men than in women for all years [6]. Many of the risk factors for developing AF also lead to complications related to AF such as stroke and death. The AF is frequently associated with coronary artery disease, chronic obstructive pulmonary disease (COPD), Hypertension, Systolic HF, diabetes mellitus, obesity, Thyroid disease (hyperthyroidism) [8-10].

AF progression from paroxysmal or persistent episode to permanent stages show a slow but continuous trend that may reach 30% after 5 years of follow up despite appropriate clinical management[11]. Progression is related to the development of underlying heart disease, which also increases the risk of adverse cardiovascular event and mortality [11, 12]. Most admission occurred in patients aged ≥ 70 years and most frequent coexisting conditions were hypertension, HF and COPD.

Screening for atrial fibrillation:

The early detection of asymptomatic AF could prevent associated ischemic stroke associated by instituting appropriate anticoagulation [13, 14]. AF first diagnosed at the event of stroke comprises nearly 10% of total ischemic stroke cases. The incidence of screen-detected AF strongly depends on the population screened and screening duration/intensity [15].
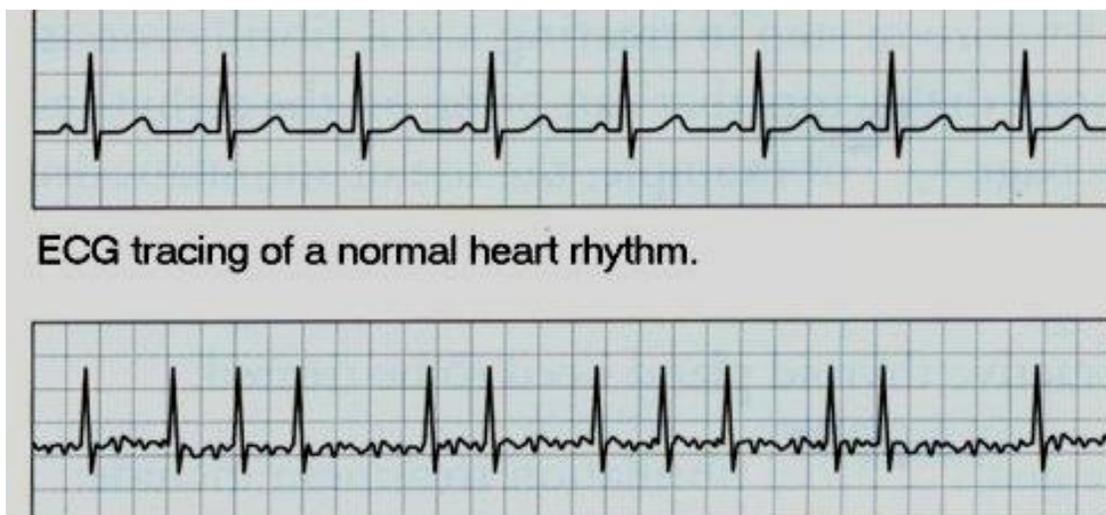
Diagnostic approach to atrial fibrillation:

Integrated assessment of patients with atrial fibrillation:

A review of the history of systemic embolism including cardiac infarction and symptoms of AF and causes should be performed. The possible causes of correction should be accessed through interviews regarding lifestyle habits such as diabetes, hypertension, COPD, obesity, and sleep apnea; underlying diseases such as hyperthyroidism; and drinking or smoking [16-18]. The data showed that increased blood pressure and fasting blood sugar alone increased the incidence of AF in pre-hypertensive and pre-diabetic patients [16]. A 12-lead ECG should be used to evaluate the presence of cardiac conduction disturbances, ischemic heart disease, and structural heart disease. Transthoracic echocardiography should be performed on all patients to determine the treatment strategy for AF.

Screening for atrial fibrillation by 12-lead electrocardiography:

To diagnose AF, its documentation on electrocardiogram (ECG) is mandatory. As the misdiagnosis of AF could cause unnecessary risks and costs for patient management, confirming the diagnosis on ECG is essential. The ACC/AHA/HRS guideline of the management of AF recommends the ECG documentation of AF as a class I indication [2]. Moreover, AF is frequently asymptomatic, especially in older people [19]. As such, symptom-driven ECG has a substantial limitation for detecting AF. One study revealed that 161 of 476 individuals with new subclinical AF were at an increased risk of cardiovascular and all-cause mortality compared to patients with typical symptoms after the adjustment for age and stroke risk score[20]. The first-diagnosed AF patients, 10-year survival free of ischemic stroke or AF progression was worse in patients with an asymptomatic presentation [21]. A systemic review showed screening of elderly people revealed a prevalence of 2.3% for persistent AF using short-term ECG monitoring or ECG after pulse palpation [22]. These findings encourage the further evaluation of systematic AF screening programs in elderly or increased risk populations, such as stoke survivors or patients with intracardiac devices.

Figure 1: Electrocardiogram showing irregular R-R intervals that is irregular fibrillations wave with fast ventricular rate and absent of P-Wave.

Additional diagnostic methods for patients with atrial fibrillation:

Twenty-four-hour Holter monitoring is useful for evaluating heart rate and the relationship between symptoms and AF. In particular, information about heart rate during exercise or activity provided by 24-hour Holter monitoring can be used to determine if the goal of heart rate modulation through drug therapy has been achieved. Transesophageal echocardiography (TEE) is useful for evaluating left atrial function and screening for thrombus in the left atrium. Therefore, the evaluation of intracardiac thrombi through TEE is essential in patients who are undergoing invasive sinus rhythm conversion or radiofrequency ablation [23, 24].

Screening of patients with intracardiac device or previous stroke:

A cardiac-implanted electronic device (CIED) could continuously monitor atrial rhythm and detect atrial high-rate episodes (AHRE). However, AHRE has been not used to detect AF. Minimum 5-minute AHRE duration had clinical relevance in the MOST study [25]. The ASSERT study indicated that stroke risk was increased only in patients with AHRE ≥ 24 hours [26]. The stroke risk in AHRE patients seemed lower than that in patients with diagnosed AF [27] and strokes often occur without AHRE being detected within 30 days before the event [28]. Patients with CIED should be regularly screened for AHRE, while those with AHRE should undergo further assessments for stroke risk factors and overt AF, including ECG monitoring.

Stroke is the first manifestation of AF in >25% of AF-related stroke cases [29]. Cryptogenic stroke defined as the cause of ischemic stroke remains uncertain despite a complete diagnostic evaluation [30]. AF detection is not uncommon in unselected stroke patients but is more likely in patients with cryptogenic stroke with implantable loop recorders or who have undergone prolonged ECG monitoring [31]. Accordingly, prolonged ECG monitoring seems reasonable in all survivors of ischemic stroke without overt AF.

DETECTION AND MANAGEMENT OF RISK FACTORS AND CONCOMITANT CARDIOVASCULAR DISEASE:

Several concomitant conditions are closely related to AF development, recurrence, and complications. The prevention, detection, and treatment of these conditions are essential to preventing AF and reducing its burden. AF independently increases all-cause mortality, and only 1 in 10 deaths in AF patient are related to stroke, while >7 in 10 are cardiovascular[32]. Hence, cardiovascular and comorbidity risk management is essential as part of the holistic or integrated care of AF management to reduce deaths and hospitalizations [32]. HF and AF coexist in many patients and can exacerbate each other. HF is a risk factor of AF [33]. The principal of AF management in HF patients does not differ from that in patients without HF, and these efforts should be performed regardless of left ventricular ejection fraction (LVEF) [34]. Angiotensin-converting enzyme inhibitors (ACEIs)/Angiotensin receptor blockers (ARBs) with a beta-blocker or eplerenone reduced the risk of new-onset AF in patients with reduced LVEF HF patients [35, 36]. According to recently published data in the CASTLE-AF trial, catheter ablation of AF reduced the risk of all-cause death (47%) and cardiovascular death (51%) in patients with HF and reduced LVEF [37]. Catheter ablation of AF in HF patients could be a treatment option for improvement outcomes in selected patients.
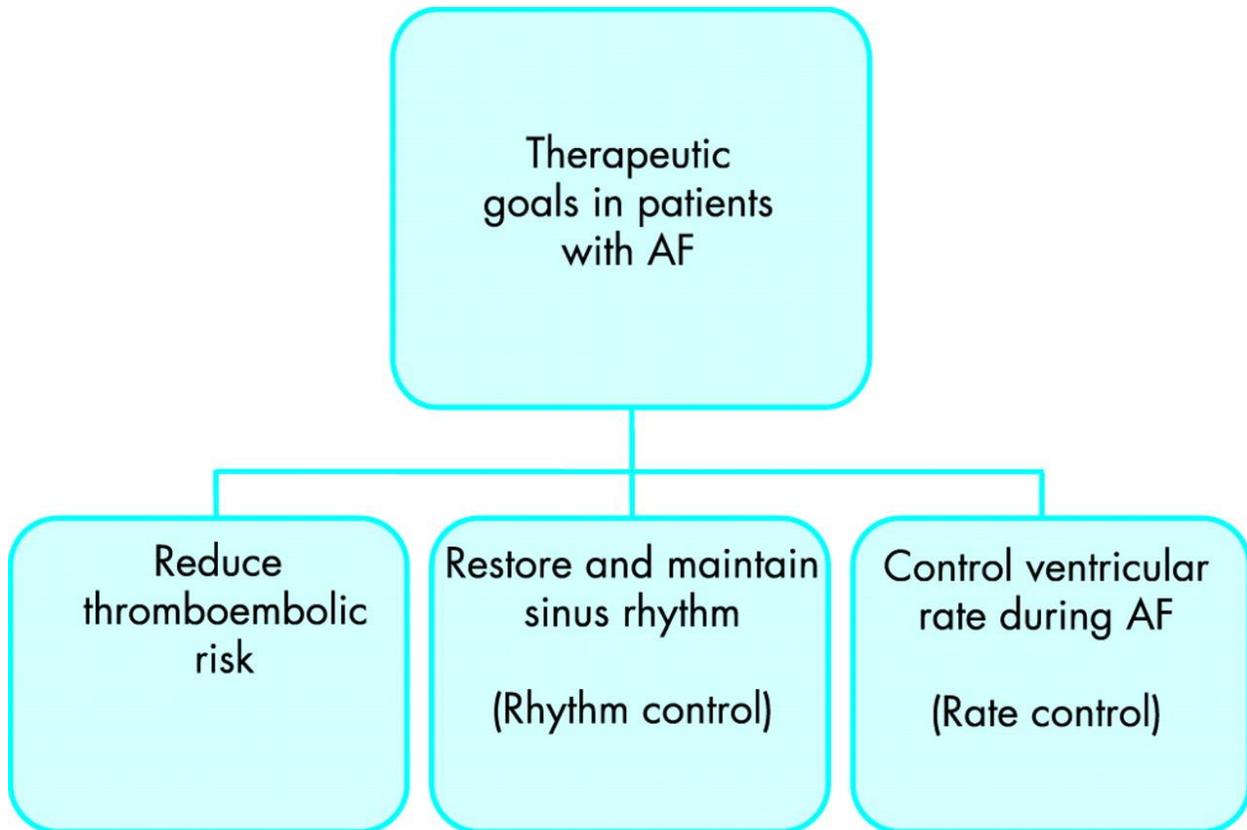
Figure 2: Flow chart showing therapeutic goals of treatment of patients with atrial fibrillations.

Hypertension is a risk factor of AF development and a risk factor of stroke and bleeding in AF patients. Good blood pressure control should be considered part of the optimal care of AF patients [38, 39]. Several previous reports suggested that ACEIs or ARBs had a beneficial effect on new-onset AF and the prevention of AF recurrence [40, 41].

Diabetes is a commonly prevalent comorbidity with AF sharing common risk [42, 43]. Diabetes is a risk factor of AF and a risk factor of stroke in AF patients, with no profound differences between type I and type II diabetes [44, 45]. Although there is no evidence that intensive glycemic control does not reduce AF development, diabetes severity is associated with an increased risk of AF development (e.g. diabetic retinopathy) [44, 46].

INTEGRATED TREATMENTS FOR ATRIAL FIBRILLATION PATIENTS:

One important issue for implementing integrated care management of AF is how to get people to remember the components of such an approach. The latter should streamline the holistic management pathway whether in primary care, hospitals and even understanding by patient.

Use of the ABC pathway of integrated care management is suggested as follows: 1) A Avoid stroke with Anticoagulation; 2) 'B' Better symptom management (i.e. patient-centered, symptom directed decisions on rate vs. rhythm control); 3) 'C' Cardiovascular and comorbidity management, including lifestyle factors [47].

Application of the simple ABC pathway allows the streamlining of integrated care for AF patients in a holistic manner and has been reported to be associated with a lower risk of adverse outcomes [32].

To accurately assess the effect of AF on cardiovascular disease, it is necessary to refer to a cardiologist after an initial diagnosis, especially if acute treatment is required, as follows: 1) unstable vital signs including uncontrollably fast heart rate; 2) symptomatic bradycardia despite reduction or stopping of nodal blocker; 3) ongoing or severe angina with reduced left ventricular function; and 4) transient ischemic attack, stroke, or thromboembolic events.

Components of integrated care:

Integrated AF care includes patient's active participation, multidisciplinary approach technology use, and all treatment approach.

Active patient participation:

Chronic diseases such as AF can be expected to have a better long-term therapeutic effect if the patient is well aware of the disease and his or her responsibility in the treatment process [48]. Patient-oriented treatment, including the involvement of patients in the decision-making stage, can increase compliance and respect individual preferences, requirements, and autonomy [49]. However, the awareness rate of AF was <10% in 2017. The increase awareness of the general public through information campaigns, including risk factor information, recognition, treatment, and self-management of the disease.

Self-management includes adapting to the treatment process, changing lifestyles, such as smoking cessation and weight control, and requires patients to be aware of the treatment method and goal [50, 51].

Multidisciplinary approach:

A multidisciplinary approach involving primary care physicians, cardiologists, cardiovascular surgeons, arrhythmia specialists, and stroke specialists who first encounter the patient can help the patient actively participate in treatment. By engaging the patient in the stage, the patient can adhere to the treatment, which enhances its effect [52, 53]. Thus, a multidisciplinary approach to AF involves not only specialized medical knowledge but also good communication and education between the patient and physician.

Technological use for smooth communication among medical staff:

For the integrated treatment of AF, it is essential to communicate and exchange smoothly among members. This requires technical support for free communication between patients and physicians, primary care physicians, and arrhythmia specialists. Digital programs and Smartphone apps can help with this process [54]. One pilot study using a Smartphone App shows how this can be operationalized [55].

All treatments for atrial fibrillation:

The ABC pathway described above includes proactive assessment and management of cardiovascular disease and risk factors (cardiovascular and comorbidity risk reduction). To this end, the active management of related diseases such as obesity, hypertension, sleep apnea and diabetes should be performed, and lifestyle corrections such as smoking, drinking, and exercise should be corrected [16, 17].

STROKE PREVENTION THERAPY IN ATRIAL FIBRILLATION PATIENTS:

Prediction of stroke risk:

Stroke prevention is the principal management priority in patients with AF. Compared to control or placebo, OAC therapy reduces the risk of stroke by 64% and the risk of death by 26% [56] but also increases bleeding risk, which can be fatal. As non-vitamin K oral anticoagulants (NOAC) showed improved efficacy and safety compared with warfarin, the threshold for initiating OAC therapy decreased from an annual stroke rate of 1.7% with vitamin K antagonists to 0.9% with NOAC [57].

The CHA2DS2-VASc score is now used in most guidelines for stroke prevention in patients with AF [2, 58]. The adjusted incidence rates of ischemic stroke were 3.79, being 0.26 in low-risk patients (CHA2DS2-VASc score 0 [male] or 1 [female]), 1.18 in intermediate-risk patients (CHA2DS2-VASc score 1 [male]), and 5.30 in high-risk patients (CHA2DS2-VASc ≥2). The incidence rates of patients with a CHA2DS2-VASc score of 1 (male), 2, 3, 4, 5, 6, and 7 or more were 1.04, 1.91, 2.54, 4.72, 5.79, 8.36, and 8.82, respectively [59].

The more recent focus of stroke prevention in patients with non-valvular AF has shifted away from predicting "high-risk" patients toward initially identifying patients at a "truly low risk" of ischemic stroke in whom NOAC has no net clinical benefit [60, 61].

Individual stroke risk factors: sex, age, and hypertension:

Coronary and peripheral artery disease has been reported to be important independent risks for stroke in AF [62, 63]. Several cohort studies have shown that female sex is a risk factor for stroke, although this is dependent on age and the presence of other non-sex risk factors [64]. Other risk factors are older age, previous stroke or TIA history, HF, and hypertension remained independent stroke risk factors. Older age is the most important predictor of ischemic stroke.

Recommended anticoagulation:

For patients with AF without valvular heart disease, including those with paroxysmal AF, who are at low risk of stroke (e.g., CHA2DS2-VASc score of 0 in males or 1 in females), we suggest no antithrombotic therapy (class III). The next step is to consider stroke prevention (i.e., OAC therapy) for patients with 1 or more non-sex CHA2DS2-VASc stroke risk factors. For patients with a single non-sex CHA2DS2-VASc stroke risk factor, we suggest OAC rather than no therapy, aspirin, or combination therapy with aspirin and Clopidogrel (class IIa); and for those at high risk of stroke (e.g., CHA2DS2 ≥2 in males or ≥3 in females), we recommend OAC rather than no therapy, aspirin, or combination therapy with aspirin and Clopidogrel (class I).
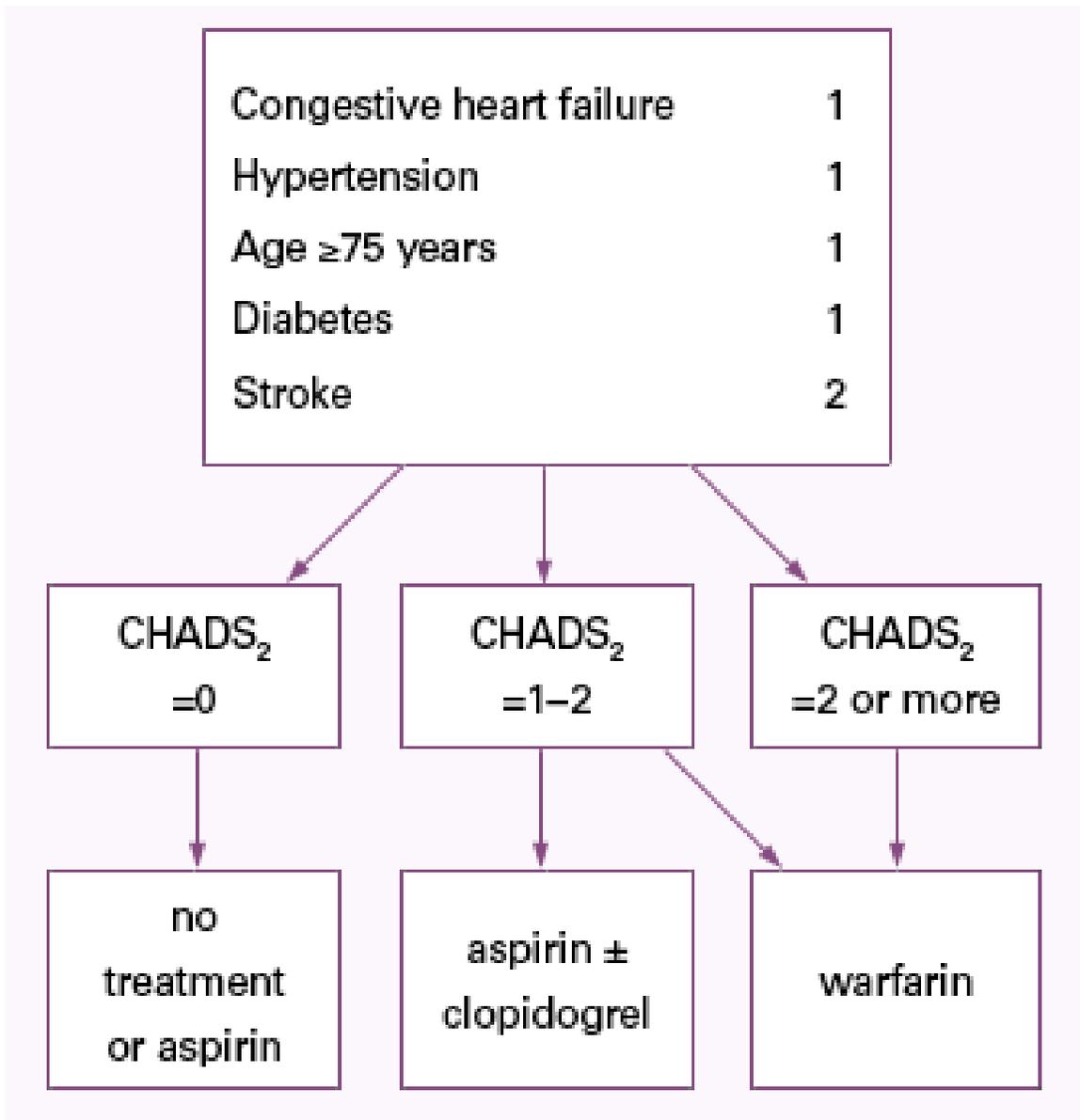
Figure 3: Flow Chart showing choice of Anticoagulation therapy.

Where we recommend or suggest in favor of OAC, we suggest using a NOAC rather than adjusted-dose vitamin K antagonist therapy. With the latter, it is important to aim for good quality anticoagulation control with a time in therapeutic range (TTR) >70%. Attention to modifiable bleeding risk factors (e.g., uncontrolled blood pressure , labile INRs, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in an anticoagulated patient, alcohol excess) should be made at each patient contact, and the HAS-BLED score used to assess the risk of bleeding whereby 'high risk' patients (score ≥3) should be reviewed and followed up more frequently. While NOACs are increasingly the preferred option, warfarin is still widely used and the SAMe-TT2R2 score (which has been validated even in Asian cohorts)[65], can help identify patients less likely to do

well on warfarin, so as to arrange more frequent INR checks, education and counseling – or to consider a NOAC instead of warfarin.

Dynamic adjustment of stroke and bleeding risk:

Many clinical variables of stroke and bleeding risk score have "dynamic" variation through follow-up [66, 67]. Age increases annually in all patients, and incident hypertension, diabetes mellitus, vascular disease, congestive HF, and prior stroke or transient ischemic attack may become evident in some patients. These dynamic changes in risk factors may increase the CHA2DS2-VASc score, stroke risk category, and absolute ischemic stroke rate. Despite using only baseline CHA2DS2-VASc score to predict the risk of ischemic stroke in AF patients, a time-dependent CHA2DS2-VASc score and "delta CHA2DS2-VASc score" (follow-up minus baseline) improved the prediction of ischemic stroke [67].

Recommended non-vitamin K oral anticoagulants:

The benefits of NOAC were more profound in Asian population than non-Asian population [68]. Based on the standard dose group, NOAC was more effective and safer in Asians than non-Asians. Among high-risk Asian AF population, Dabigatran, rivaroxaban, and apixaban demonstrated similar risk of ischemic stroke and lower risk of intracerebral hemorrhage compared with warfarin. All-cause death was significantly lower only with Dabigatran and apixaban, whereas not with rivaroxaban [3].

Elderly patients with AF (such as those aged ≥80 years) and patients with impaired renal function were included in the landmark NOAC trials, but these important subgroups comprised only a small proportion of the patient populations. For Dabigatran, reduction of the daily recommended dose to 110 mg twice daily (b.i.d.) is indicated for patients aged ≥80 years. This dose can be reduced to 110 mg b.i.d. if the patient is aged 75–79 years and has other comorbidities that could affect bleeding risk such as previous gastritis, peptic ulcer disease, and moderate renal impairment. Indeed, label (or guideline) – adherent use of Dabigatran is clearly associated with better outcomes for stroke, major bleeding, and mortality [69, 70]. Insufficient published data for apixaban, edoxaban, and rivaroxaban indicate that further work is needed to clarify the bleeding risks of NOAC in the elderly.

BLEEDING RISK:

Risk factors for bleeding with non-vitamin K antagonist oral anticoagulant, vitamin K antagonist, and antiplatelet therapy:

Bleeding risk varies from person to person depending on their pre-existing comorbidities, current antithrombotic regimen and adherence, concomitant medication, and lifestyle choices. Many of these factors cannot be altered but some are modifiable or potentially modifiable [71, 72].

❖ **BP control:** Good control of BP is vital to reduce the risk of stroke and is essential to decrease the risk of bleeding (particularly intracranial haemorrhage) on antithrombotic therapy.

❖ **Anticoagulation control:** Among patients receiving vitamin K antagonist, maintenance of an INR in the therapeutic range (2.0–3.0) is essential. The proportion of TTR should be at least 65% but the ultimate aim/target should be 100%.

❖ **Concomitant medication predisposing to bleeding:** Nonessential use of concomitant antiplatelet drugs and NSAIDs should be avoided since these medications increase the risk of bleeding in patients receiving OACs.

❖ **Alcohol intake:** Excessive alcohol intake increases the risk of bleeding predominantly due to the risk of trauma, but in chronic alcohol abuse through poor medication adherence, hepatic and variceal disease.

❖ **Lifestyle factors:** Avoidance of work and/or leisure activities that have the potential to cause serious trauma should be advised.

❖ **Bridging periods off anticoagulation:** Interruption of OAC should be avoided to reduce stroke risk since the majority of cardiovascular procedures (e.g., pacemaker implantation or percutaneous coronary intervention [PCI]) can be safely performed on OAC. Bridging (i.e., stopping OAC and providing anticoagulation cover with heparin) should be used in patients with mechanical heart valves but does not appear to be otherwise advantageous [73, 74].

❖ **Appropriate choice of OAC:** Choice of OAC should be made on an individual basis after stroke and bleeding risk assessment, discussion with the patient and adherence to the prescribe label.

❖ **Falls risk and cognitive impairment:** The benefits of ischemic stroke reduction generally outweigh the risk of harm from serious bleeding with OAC use. One estimate was that the patient would need to fall 295 times per year for the risk from falls to outweigh the benefits of stroke reduction [75].

❖ **Reversal of biochemical anomalies:** Patients with anemia or reduced platelet count or impaired hepatic/renal function should be investigated and proactively managed.

Bleeding risk assessment:

Attentions to modifiable bleeding risks are important. There are multiple bleeding risk scores that have been proposed for bleeding risk stratification, with the HEMORR2HAGES (hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, hypertension, anemia, genetic factors, excessive fall risk, and stroke), HAS-BLED (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile INR, elderly [0.65], drugs/alcohol concomitantly [1 point each]), ATRIA, ORBIT, and ABC-bleeding scores that have been derived and validated in AF populations[76].

The simple HAS-BLED score has been shown to be similar or outperform older bleeding scores, as well as more simple bleeding scores that include fewer clinical parameters. A high bleeding risk score is not a reason to withhold OAC, as the net clinical benefit is even greater in those patients with high bleeding risk.

LEFT ATRIAL APPENDAGE OCCLUSION AND EXCLUSION:

Left atrial appendage occlusion devices:

Transcatheter left atrial appendage (LAA) occlusion or percutaneous LAA ligation has been performed since LAA was proven to be the major source of thrombus formation in patients with non-valvular AF. A high

implantation success rate (98%) with an acceptable procedure-related complication rate of 4% at 30 days was reported [77]. AF patients with contraindications for long-term OAC therapy, a recurrent thromboembolic event, or a high risk of stroke despite OAC therapy may be considered to have LAA occlusion for stroke prevention purposes.

Left atrial appendage occlusion or exclusion:

Surgical LAA occlusion or exclusion in conjunction with cardiac surgery has been performed with multiple techniques for many decades. The showing a clear benefit of LAA exclusion for stroke prevention in the subgroup undergoing AF surgery. The guideline recommends that patients with AF undergoing cardiac surgery may benefit from surgical occlusion or the exclusion of LAA for stroke prevention. Patients undergoing thoracoscopic AF surgery may benefit from surgical occlusion or the exclusion of LAA for stroke prevention.

RATE CONTROL:

Heart rate control is important part of the treatment of patients with AF. An adequately and appropriately controlled ventricular rate can reduce or eliminate symptoms, improve hemodynamic, and prevent tachycardia-induced cardiomyopathy. Rate control can be achieved with beta-blockers, non-dihydropyridine calcium channel blockers, digoxin, or combination therapy shown in table 2. Certain antiarrhythmic agents including Amiodarone and Sotalol also have rate-controlling effects, but they should be reserved for patients requiring rhythm control therapy. When considering which drug to use, clinicians should consider the patient's symptoms, hemodynamic status, presence of HF, and precipitating factors for AF.
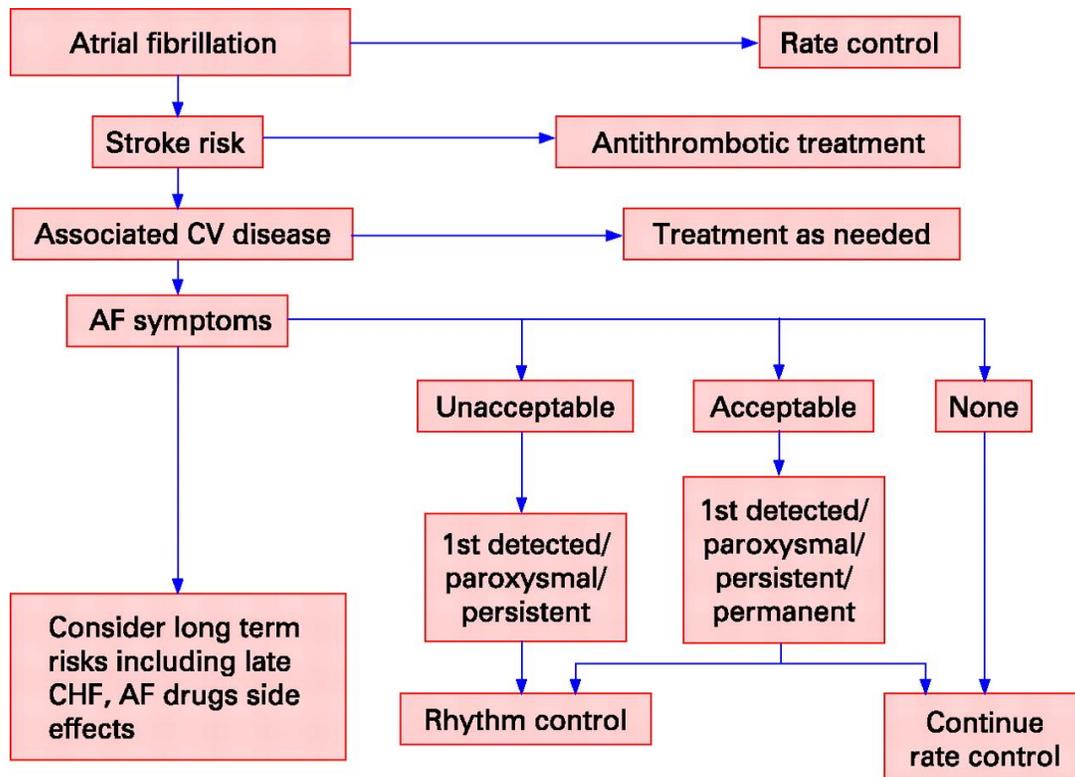

Figure 4: Flow chart showing treatment of atrial fibrillations.

Acute rate control:

In patients with new-onset AF, heart rate control is often needed to control symptoms. Clinicians should identify causes of increased heart rate, such as infection, anemia, and thyrotoxicosis. Beta-blockers and non-dihydropyridine calcium channel blockers (diltiazem /verapamil) are preferred for acute rate control because of their rapid action and effectiveness at high sympathetic tone [78-81]. Lenient rate control (heart rate <110/min) is sufficient in most cases.

In patients with congestive HF or left ventricular dysfunction, beta-blockers, digoxin, or their combination should be used because diltiazem and verapamil have negative inotropic effects in those with an LVEF <40% [176, 177]. In patients with hemodynamic instability or severely reduced ejection fraction (EF), intravenous Amiodarone would be an option [82, 83]. Urgent electrical cardioversion should be considered in hemodynamically unstable patients despite thromboembolic risk unless they are first anticoagulated.

Long-term rate control:

Beta-blockers are most commonly used to achieve long-term rate control, followed by non-dihydropyridine calcium channel blockers (diltiazem/verapamil), digoxin, and Amiodarone. Physicians should evaluate the patient's comorbidities, such as HF, asthma, or COPD, to ensure appropriate drug selection [84].

In patients with left ventricular dysfunction (EF <40%), beta-blockers, digoxin. or their combination are preferred [116]. However, beta-blockers should be avoided in patients with asthma or COPD. Beta-blockers help rate control but may not have prognostic benefit in HF [85]. Lenient rate control (heart rate <110/min) is usually acceptable regardless of HF status, but stricter rate control is required if symptoms remain uncontrolled [86].

Atrioventricular (AV) nodal ablation consisting of permanent pacemaker implantation could be an option in selected patients with a rapid ventricular rate refractory to medical therapy. However, AV nodal ablation is usually reserved for the elderly because of their life-long pacemaker dependency.

Drugs	Acute rate control(IV)	Long term control(po)
1. Beta blockers:		
Bisoprolol:	Not available	1.25-10 mg q.d
Carvedilol	Not available	3.125-25 mg b.i.d.
Metoprolol	Not available	12.5-100 mg b.i.d.
Nebivolol	Not available	1.25-10 mg b.i.d.
Esmolol	500 mcg/kg/Iv bolus then 50-250 mg/kg/min	
2. Calcium channel blockers:		
Diltiazem	0.25 mg/kg IV bolus then 5-15 mg/h.	60-120 mg t.i.d
Verapamil	0.075-0.15 mg/kg IV bolus then 5 mcg/kg/min	40-120 mg t.i.d
3. Cardiac glycosides:		
Digoxin	0.25 mg IV repeated dose with max 0.75-1 mg in 24 h	0.0625-0.25 mg b.i.d

4. Specific indication:

Amiodarone   300 mg IV over 1 h then 10-50 mg/h over 24 h   100-200 mg q.d.

Table 2: Rate control therapy in patients with atrial fibrillation [87]

IV= Intravenous. PO= per oral. B. i. d= twice a day.   q.d= once a daily. T.i.d=three time a day.

RHYTHM CONTROL:

The purpose of rhythm control management is to improve hemodynamic instability and AF-related symptoms for restoring and maintaining sinus rhythm [88]. The restoration and maintenance of sinus rhythm after AAD treatment are more effective than those after placebo treatment [89-91]. However, it remains inconclusive whether superior rhythm control management improves prognosis in anticoagulated patients with AF [88, 89, 92, 93]. Additional invasive ablation therapy has been developed for and applied in medically refractory AF patients [94, 95]. The quality of life and prognosis improvements to the beneficial effect of rhythm control strategies in patients with AF [96, 97].

Acute rhythm control strategy:

Electrical direct current cardioversion is the only rapid and effective procedure to restore sinus rhythm in hemodynamically unstable AF patients [98, 99]. Electrical cardioversion was safely conducted in sedated or anesthetized AF patients with intravenous midazolam or propofol; when used, vital signs, especially O2 saturation, should be monitored [100]. During the post-cardioversion period, the skin to which the patch is attached and serial ECG should be monitored for burns or severe bradycardia [98, 99].

Pretreatment with flecainide [90], propafenone [101], Amiodarone [102, 103] and Sotalol [103] (not beta-blocker, verapamil or digoxin) could improve the efficacy of restoration and maintenance of sinus rhythm during the post-cardioversion period. AADs for pharmacological cardioversion are presented in **Table 3**. Proper anticoagulation is needed in AF patients prior to electrical cardioversion [104] because anticoagulation dramatically reduced the risk of embolic stroke [105]. AF patients planned to undergo electrical cardioversion should be anticoagulated from 3 weeks before to 4 weeks after unless permanent anticoagulation is indicated.

Drugs	Dosage	Side effects
1. Amiodarone:	• 600-800 mg daily in divide dose, give upto 10 mg	AV block, hypotension.
	Then 200 mg once a daily.	Gastrointestinal upset.
	• 150 mg over 10 minute then 1 mg/min for 6 h	QT interval prolongations.
	Then 0.5 mg/min for 18 hours then change to oral.	Hypotension.
2. Flecainide:	200-300 mg orally	atrial flutter, AV block.
3. Propafenone:	450-600 mg	atrial flutter, AV block.

Table 3: Antiarrhythmic drugs for pharmacological Cardioversion [87]

A meta-analysis demonstrated that AADs could also efficiently restore and maintain sinus rhythm as rhythm control management [106, 107]. In AF patients with stable hemodynamic status, prescription AADs could be the main option in general practice without sedation or starvation during pretreatment compared with electrical cardioversion. Flecainide and propafenone are the most common AADs for acute rhythm

management [108, 109] but they are relatively contraindicated in AF patients without structural heart disease. Amiodarone could be prescribed to AF patients with structural heart disease and reduce the heart by >10–12 beats per minute within intravenous infusion after 8–12 hours [106]. Both Amiodarone and flecainide are more efficient at restoring sinus rhythm than Sotalol [110, 111]]. A single oral dose of flecainide 200–300 mg or propafenone 450–600 mg could be taken to control paroxysmal AF-related symptoms and restore sinus rhythm out of the hospital in experienced AF patients as confirmed in previous hospitalization [112].

Long-term rhythm control strategy:

Physician preference and the improvement of AF-related symptoms, drug compliance, pro-arrhythmic side effects, and extra-cardiac toxicities should be considered in long-term rhythm control management. AADs for the maintenance of sinus rhythm are presented in **Table 4**. In addition, lifestyle modifications and well-controlled cardiovascular disease could be additionally beneficial for preventing AF recurrence and maintaining sinus rhythm in patients treated with AADs during long-term rhythm control management [113].

Drugs	Dosages	Contraindications
1. Amiodarone:	400-600 mg daily in divide doses for 2-4 weeks. Then 100-200 mg once daily	SA/AV node dysfunction Prolong QT interval.
2. Dronedarone:	400 mg twice a day.	HF, permanent AF.
3. Flecainide:	50-200 mg twice a day.	CHD, HF, SA node dysfunction
4. Pilsicainide:	50 mg three time a day.	IHD reduced LVEF.
5. Propafenone:	150-300 mg three times a day.	IHD reduced LVEF.
6. Sotalol:	40-160 mg twice a day.	HF, LVH, prolonged QT interval

Table 4: Oral antiarrhythmic drugs used to maintain sinus rhythm in patients with AF [87]

SA node= Sinoatrial node. AV nod= Atrioventricular Node, HF= Heart failure. AF= Atrial fibrillation. CHD= Coronary heart disease. IHD= Ischemic Heart disease. LVEF= Left ventricular ejection fraction. LVH= Left ventricular hypertrophy.

AAD safety must be considered in terms of pro-arrhythmic side effects and extra-cardiac toxicities. Flecainide, propafenone, and Pilsicainide are indicated to control rhythm in AF patients without structural heart disease but are contraindicated in AF patients with ischemic heart disease or with left ventricular dysfunction due to poor prognosis [114]. Extra-cardiac toxicity is rarely reported [115]. Flecainide, propafenone, and Pilsicainide should be prescribed with an AV nodal blocker for the prevention of use dependency (increased ventricular rate in atrial flutter) [116].

Amiodarone can be prescribed in patients with left ventricular dysfunction [117]. QT interval and U wave should be monitored to prevent torsade de pointes [118]. In particular, long-term Amiodarone therapy may have extra-cardiac toxicity in the liver, thyroid, lung, skin, and cornea. Therefore, Amiodarone should be replaced by an alternative AAD if any side effects or toxicities appear during long-term therapy [119]. Dronedarone reduces the heart rate, maintains sinus rhythm, and reduces cardiovascular mortality and hospitalization in paroxysmal or persistent AF patients [120]. However, Dronedarone increased the mortality

rate in decompensate HF [121]. Sotalol showed inferior efficacy to Amiodarone and similar efficacy to propafenone for maintaining sinus rhythm [122]. Sotalol could effectively suppress the re-entry mechanism. Sotalol may be the first choice for long-term rhythm control management in AF patients with ischemic heart disease. However, Sotalol is prone to inducing QT prolongation, and caution is needed in females, renal impairment and if left ventricular hypertrophy is present [123].

Anticoagulation in patients who undergo cardioversion:

The periprocedure risk of thromboembolic events during cardioversion can be substantially reduced by adequate anticoagulation. In patients with AF or an atrial flutter ≥ 48 hours or with an unknown duration, OAC with vitamin K antagonist (INR, 2.0–3.0) is recommended for at least 3 weeks before electrical or pharmacological cardioversion and 4 weeks afterward regardless of CHA2DS2-VASc score. If early cardioversion is attempted, TEE should be performed to exclude the presence of left atrial thrombus [124]. After 4 weeks, long-term anticoagulation is decided based on each patient's risk of stroke using CHA2DS2-VASc score. Patients with a CHA2DS2-VASc score ≥2 require long-term use of OAC irrespective of the cardioversion results. Therefore, anticoagulation using NOAC can be an alternative to vitamin K antagonist in patients who undergo cardioversion. It is common practice to perform cardioversion after a single dose of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) without TEE. Although data are limited, it is reasonable to administer a single dose of NOAC ≥ 4 hours before cardioversion instead of UFH or LMWH. Importantly, TEE or anticoagulation ≥3 weeks before cardioversion can be considered in patients with a high stroke risk or an AF duration ≤48 hours.

ANTICOAGULATION IN SPECIFIC CONDITIONS:

Atrial fibrillation patients undergoing percutaneous coronary intervention:

Antithrombotic regimen:

An estimated 5–15% of AF patients may undergo PCI in the future. However, it is very challenging to choose optimal antithrombotic regimens for AF patients treated with PCI [256]. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (Clopidogrel) is essential for patients treated with PCI to prevent stent thrombosis [125]. On the other hand, OAC is imperative to preventing stroke in AF patients [126]. Thus, theoretically, triple therapy, combining all drugs including DAPT and OAC, may be a reasonable choice as an initial antithrombotic regimen. However, prolonged triple therapy has been associated with an increased risk of bleeding and even mortality [69].

The dual therapy with a single antiplatelet agent and an OAC might be safer and show similar efficacy to triple therapy for preventing ischemic/thromboembolic events [127]. Dual therapy with Clopidogrel and NOAC was suggested to be a safe initial alternative regimen to triple therapy [128]. First, as initial antithrombotic treatment, triple therapy should be used for as short a duration as possible unless patients are at high risk of ischemic events. Second, dual therapy should be continued after the cessation of the triple therapy until 12 months after PCI. Third, dual therapy with Clopidogrel and NOAC could be considered as an

alternative initial antithrombotic regimen in patients with a high risk of bleeding (e.g. HAS-BLED ≥3). Fourth, monotherapy with OAC should be considered 12 months after PCI.

Dual therapy with Clopidogrel and warfarin:

In an RCT dual therapy with Clopidogrel and warfarin reduced the bleeding risk by 64% and adverse cardiac events by 40% compared with triple therapy with aspirin, Clopidogrel, and warfarin [129]. Although this study was underpowered to compare ischemic/ thromboembolic events, it has great implications for demonstrating the safety of dual therapy with Clopidogrel and warfarin compared to that of triple therapy.

Dual therapy with Clopidogrel and non-vitamin K oral anticoagulants:

The efficacy and safety of dual therapy with Clopidogrel and NOAC have been demonstrated in RCTs. In the PIONEER AF-PCI trial, dual therapy with a fixed dose of rivaroxaban 15 mg and a P2Y12 inhibitor (mostly Clopidogrel) was compared with triple therapies with very-low-dose rivaroxaban (2.5 mg b.i.d.) or warfarin[128]. In that study, the two rivaroxaban arms reduced the risk of clinically significant bleeding compared with triple therapy with warfarin, while the ischemic/thrombotic events were comparable.

Monotherapy with oral anticoagulation:

In a nationwide observational study of 8,700 AF patients with a history of PCI ≥1 year prior, the addition of the antiplatelet agent to warfarin was not associated with a reduced risk of ischemic/thromboembolic events but significantly increased bleeding risk [130]. The efficacy and safety of NOAC monotherapy in patients with stable coronary artery disease has not been well evaluated. However, global guidelines recommend the use of OAC monotherapy in AF patients with stable coronary artery disease [131].

Anticoagulation in patients who undergo catheter ablation of atrial fibrillation:

Since catheter ablation of AF carries a risk of periprocedure thromboembolic complications, anticoagulation is indicated before, during, and after the procedure irrespective of the patient's CHA2DS2-VASc score. AF ablation under uninterrupted vitamin K antagonist use is recommended based on previous studies showing that this strategy was associated with better safety and efficacy outcomes [132]. The periprocedure anticoagulation using Dabigatran [[133], apixaban, rivaroxaban, and edoxaban, demonstrated similar thromboembolic and bleeding events compared with uninterrupted vitamin K antagonist. Therefore, anticoagulation with NOAC can be an alternative to vitamin K antagonists in patients who undergo catheter ablation of AF. During the ablation, the intravenous administration of heparin is recommended to maintain a target activated clotting time ≥300 seconds. NOACs can be re-administered 3–5 hours after the procedure once adequate hemostasis is achieved. Anticoagulation should be continued for at least 2 months after ablation regardless of the patient's stroke risk or procedure results due to a thrombogenic state following ablation After 2 months, long-term anticoagulation should be decided based on each individual patient's risk of stroke independent of the procedure's success.

Anticoagulation therapy and renal function:

Patients with AF and moderate to severe renal dysfunction are at an increased risk of simultaneous ischemic stroke and major bleeding [134]. Therefore, the use of OACs in AF patients with renal dysfunction is troublesome. In AF patients with moderate to severe renal dysfunction and a CHA2DS2-VASc score ≥2, the use of OACs was approved as beneficial for lowering the event rate of ischemic stroke despite the mildly increased risk of bleeding [282]. NOACs were better than warfarin for reducing the risk of stroke/systemic embolism as well as major bleeding in AF patients with mild to moderate renal dysfunction [135]. During NOAC use, renal function should be monitored carefully [136].

In patients with moderate renal dysfunction, NOAC dose should be reduced. Dabigatran should be reduced to 110 mg b.i.d. in patients with creatinine clearance of 30–50 mL/min. Rivaroxaban should be reduced to 15 mg q.d. in patients with creatinine clearance of 15–50 mL/min. Apixaban should be reduced to 2.5 mg b.i.d. in patients with serum creatinine ≥1.5 mg/dL and age ≥80 years or body weight ≤60 kg. Edoxaban should be reduced to 30 mg q.d. in patients with creatinine clearance of 15–50 mL/min.

In patients with severe renal dysfunction (creatinine clearance <15 mL/min), NOAC use is not recommended. OAC use may be inappropriate in patients with renal dysfunction who are on dialysis, although the data are weak and often do not consider TTR [137]. However, if TTR is >70%, warfarin may have some benefits even in dialysis patients [138].

Anticoagulation therapy in elderly patients:

Increasing age is a risk factor for simultaneous stroke and major bleeding in patients with AF [139]. The elderly population is fragile and prone to falls. Nonetheless, OAC use is recommended in elderly AF patients because of the high benefit/risk ratio [140]. Recent Asian data showed that among patients with AF ≥90 years of age, warfarin was associated with a lower risk of ischemic stroke and positive net clinical benefit. Compared with warfarin, NOACs were associated with a lower risk of intracranial haemorrhage. Thus, OACs may still be considered as thromboprophylaxis for elderly patients, with NOACs being the more favorable choice [141].

Dabigatran 150 mg b.i.d. reduced major bleeding in patients <75 years of age but an increased risk of major bleeding in patients >75 years of age compared with warfarin.

Prognosis of atrial fibrillation:

Among prevalent AF patients, annual event rates for all-cause mortality, ischemic stroke, intracranial bleeding, HF admission, and myocardial infarction significantly declined for a decade. Over the last 5 decades, AF-associated mortality decreased by 25% in the Framingham Heart Study [142].

Overall in-hospital mortality decreased from 7.5% in 2006 to 4.3% in 2015[143]. The in-hospital mortality was highest in patients ≥80 years of age (7.7%) and in those with chronic kidney disease (7.4%). Improved survival after AF onset may arise from: 1) earlier detection (lead time) owing to heightened awareness; 2) changed diagnostic criteria (as described above); 3) enhanced surveillance of AF patients; 4) advances in guideline-recommended treatments for AF32) including oral anticoagulation (OAC) therapy to

reduce the risk of embolization3); and 5) more aggressive treatment of complications and comorbidities such as hypertension, ischemic heart disease, HF, and hypercholesterolemia.

Given the high mortality associated with HF [144], and stroke [145], the 52% reduction in HF subsequent to AF observed over the study period and the 9% reduction in risk of ischemic stroke is likely to have contributed substantially to the improved survival.

Follow-up of patients with atrial fibrillation:

Most AF patients require periodic follow-up for continuous optimal treatment. Follow-up can be performed by primary care physicians, cardiologists, or arrhythmia specialists. Follow-up of the treatment plan, continued patient participation, and any needed treatment modifications are necessary. The treatment of AF involves prognosis-related treatment (anticoagulant therapy and treatment of cardiovascular disease) and symptom-related treatment (heart rate or cardiac rhythm control) [146]. In addition, if AF is partially recurrent, if the overall frequency, duration of AF decrease, and clinical symptoms are controlled, it is considered successful. The management of diseases (obesity, hypertension, HF, diabetes mellitus, sleep apnea) related to AF should be provided continuously [16, 38, 71, 147]. While lifestyle factors such as smoking and drinking should be monitored in an integrated manner [148].

CONCLUSIONS

For AF detection, ECG screening is necessary, especially in stroke survivors and the elderly. Integrated AF management, including active patient participation, a multidisciplinary approach, and technology use, is recommended from diagnosis to treatment and systematic follow-up. Such a holistic approach (the ABC pathway) can improve treatment outcomes, by considering lifestyle modifications, OAC, rate control, rhythm control by AADs, catheter ablation, and surgical intervention. Patient awareness of the disease, education and engagement with management decisions are important.

Abbreviations:

AF: Atrial fibrillation.

ECG: Electrocardiogram.

COPD: Chronic obstructive pulmonary disease.

ACC: American college of cardiology.

AHA: American Heart association.

HRS: Heart rhythm Society.

TEE: Transesophageal echocardiogram.

AHRE: Atrial high rate episodes.

TIA: Transient Ischemic strokes.

HF: Heart failure.

IHD: Ischemic Heart disease.

LAA: Left atrial appendage.

NOAC: Non Vitamine k oral antagonists.

ACEI: Angiotensin converting enzyme inhibitors.

ARB: Angiotensin receptors blockers.

CCBs: Calcium channel blockers.

CAD: Coronary artery disease.

MI: Myocardial infarction.

Conflicts of Interest:

There authors have no Conflicts of interest to declare.

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