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GUIDELINES

2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation☆

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Atrial fibrillation (AF) is the most common sustained arrhythmia. Both the incidence and prevalence of AF are increasing, and the burden of AF is becoming huge. Many innovative advances have emerged in the past decade for the diagnosis and management of AF, including a new scoring system for the prediction of stroke and bleeding events, the introduction of non-vitamin K antagonist oral anticoagulants and their special benefits in Asians, new rhythm- and rate-control concepts, optimal endpoints of rate control, upstream therapy, life-style modification to prevent AF recurrence, and new ablation techniques. The Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology aimed to update the information and have appointed a jointed writing committee for new AF guidelines. The writing committee members comprehensively reviewed and summarized the literature, and completed the 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the Management of Atrial Fibrillation. This guideline presents the details of the updated recommendations, along with their background and rationale, focusing on data unique for Asians. The guidelines are not mandatory, and members of the writing committee fully realize that treatment of AF should be individualized. The physician's decision remains most important in AF management.

Contents

Preamble

Many innovative advances have emerged in the past decade for the diagnosis and management of atrial fibrillation (AF), including epidemiological information, a new scoring system for the prediction of stroke and bleeding events, the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) and the their special benefits in Asians, new rhythm- and rate-control concepts, optimal endpoints of rate control, upstream therapy, lifestyle modification to prevent AF recurrence, and new ablation techniques. The Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology aimed to update the information and have appointed a jointed writing committee for new AF guidelines. Although writing committee members comprehensively reviewed and summarized the literature, the search of publications was not systemic and new data are emerging rapidly. Nevertheless, recommendations or suggestions in the guidelines were developed by experienced experts in Taiwan and were agreed on by consensus or majority decision. We have not graded the quality of evidence objectively or systemically.

The 2016 Guidelines of the Taiwan Heart Rhythm Society (THRS) and the Taiwan Society of Cardiology (TSOC) for the management of AF provide the most updated information about AF, focusing on data unique for Asians. The guidelines are not mandatory, and members of the writing committee fully realize that treatment of AF should be individualized. The physician's decision remains most important in AF management.

1. Epidemiology

1.1. Atrial fibrillation in the world

AF is the most common cardiac arrhythmia. The lifetime risk of developing AF for adults is about 20—25%, similar in white people and in Chinese.[1–3] According to recently published data from the Global Burden of Diseases 2010 study,[4] the estimated global prevalence of AF in 2010 was 33.5 million, including 20.9 million men, and 12.6 million women. It is possible that these numbers were underestimated, since many asymptomatic AF patients could be undetected.[5] Between 1990 and 2010, there were significant increases in the estimated age-adjusted prevalence and incidence of AF.[4] The annual new cases of AF globally in 2010 were estimated at close to 5 million.[4] Burden associated with AF, measured as disability-adjusted life-years, increased by 18.8% in men and 18.9% in women from 1990 to 2010.[4] Mortality associated with AF was higher in women and increased by 2-fold and 1.9-fold in men and women, respectively.[4]

The exact reasons for these trends are unknown, but they may be explained by ageing trends and an increase in the prevalence of obesity.[4,6] Other contributing factors include increase in the prevalence of diabetes,[7] heart failure,[8] obstructive sleep apnea syndrome,[9] and improved survival following myocardial infarction (MI).

1.2. Atrial fibrillation in Asia

According to several Asian cohort studies and registries, the prevalence rate of AF in most of the Asian countries is around 1% in the adult population (Figure 1), lower than that in white people (about 2%).[10,11] Two recent reports from the USA also confirmed a lower incidence rate of AF in Asians compared with the white population.[12,13] About half of the total population in the world are living in Asia, and elderly population is growing fast in Asia. The burden of AF in Asia will become huge.[14] In 2050, there will be 72 million AF patients in Asia,[14] more than double the combined numbers of patients from Europe and the USA.[15,16]

1.3. Atrial fibrillation in Taiwan

According to a community-based cohort study in Taiwan, the incidence rates of AF were 1.68 per 1000 person—years for men and 0.76 per 100 person—years for women; the overall prevalence of AF in Taiwanese is 1.4% in men and 0.7% in women.[17] The prevalence and incidence of AF increased substantially with age[17] and are consistent with

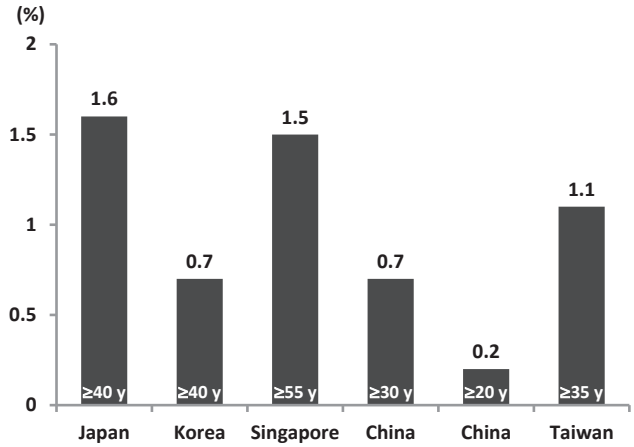

Figure 1 Prevalence rate of atrial fibrillation in Asian countries.

cross-sectional survey data in the USA, where the AF prevalence ranged from 0.1% among adults younger than 55 years to 9% among octogenarians.[10] In hospitalized patients, a nationwide hospital-based data analysis showed that the mean annual frequency of diagnosed AF was 127 per 100,000 persons for Taiwanese and was higher in men than in women (137 per 100,000 vs. 116 per 100,000).[18] The analysis also demonstrated that although there was an upward linear trend in the annual frequency of patients with AF, the trends of in-hospital mortality rate decreased,[18] which was in accord with a recent nationwide inpatient survey in the USA.[19]

2. Mechanism and pathophysiology

2.1. Atrial structural remodeling

Any kind of structural heart disease may trigger a slow but progressive process of structural change or remodeling in both the ventricles and the atria. In the atria, enhanced connective tissue deposition and fibrosis are the hallmarks of this process. The cellular mechanisms may involve activation of the renin—angiotensin system,[20] triggering of inflammatory response, and an increase in oxidative stress.[21] Structural remodeling consists of electrical dissociation between muscle bundles, local conduction heterogeneities, and conduction slowing. These changes may facilitate the initiation of multiple small re-entrant circuits, and perpetuate AF. Several clinical situations are commonly associated with atrial structural abnormalities, such as congestive heart failure, ventricular hypertrophy and dilation, myocardial ischemia and infiltrative diseases.

2.2. Electrophysiological mechanisms

The initiation and perpetuation of AF requires both triggers for its onset and a substrate for its maintenance. These mechanisms are not mutually exclusive and are likely to coexist at various stages of AF. Focal rapid firing in a locus of the atrium (focal mechanism) may potentially contribute to the initiation and perpetuation of AF.[22] Cellular mechanisms of focal activity may involve increased automaticity (autonomic nervous system activation), triggered activity (abnormal calcium handling and autonomic nervous system activation), and microreentry. Due to shorter action potential duration and abrupt changes in the orientation of myocyte fiber, the pulmonary veins (PVs) and their adjacent areas have a stronger potential to initiate and perpetuate atrial tachyarrhythmias, particularly in paroxysmal AF. In persistent AF, potential sources of focal mechanism may reside in sites throughout the entire atria.

Another mechanism for the perpetuation and maintenance of AF is the multiple wavelet theory. According to the multiple wavelet theory, AF is perpetuated by continuous conduction of several independent wavelets propagating through the entire atria. Fibrillation wavelets continuously undergo wavefront—waveback interactions, resulting in wave-break and the generation of new wavelets, while block, collision, and fusion of wavelets tend to reduce their number. As long as the number of wavelets does not decline below a critical level, the multiple wavelets will sustain the arrhythmia. The number of wavelets is in reverse relationship to action potential duration. Action potential duration of atrial myocytes tends to shorten when the duration of AF prolongs, an adaptive process called electrical remodeling. Therefore, when the duration of AF prolongs, THAT fibrillation wavelet becomes more and more stable, because the number of wavelet increases (AF *begets* AF). It is widely accepted that this multiple wavelet theory plays a more important role in the pathophysiology of persistent or permanent AF than in paroxysmal AF. By contrast, focal firing may be more important in sustaining paroxysmal AF.

Another evolving electrophysiological mechanism of AF is the combination of focal mechanism and multiple wavelet theory, in which the conducting multiwavelets are driven by single or several mother rotors or major reentry circuits.[23] The evidence came from onsite mathematical signal analyses of multisite local electrograms throughout the atria during AF ablation, which revealed driving rotors perpetuating the rhythm of AF.[24] Furthermore, ablation of driving rotor(s) could successfully terminate AF.[25] This mechanism may contribute to the maintenance and perpetuation of any type of AF. However, the effectiveness of this ablation strategy has to be confirmed in more clinical trials.

2.3. Genetic predisposition

AF has a familial component, especially in patients with early-onset AF. Many inherited cardiac syndromes or channelopathies associated with AF have been identified recently. Both short and long QT syndromes and Brugada syndrome are associated with supraventricular arrhythmias, including AF. AF also frequently occurs in a variety of inherited conditions, including hypertrophic cardiomyopathy and dilated cardiomyopathy. Some familial forms of AF are associated with mutations in the genes coding for atrial natriuretic peptide, loss-of-function mutations in the cardiac sodium channel gene SCN5A, or gain of function in cardiac potassium channels. Furthermore, several genetic loci close to the *KCNN3*, *PRRX1*, *PITX2*, *WNT8A*, *CAV1*, *C9orf3*, *SYNE2*, *HCN4*, and *ZFHX3* genes, identified by

Table 1 Comorbidities of atrial fibrillation in Asians versus non-Asians in survey and cohorts.

	Asians							Non-Asians						
	J-Rhythm[33]	RECORDAF AP[34]	China[35]	REALISEAF Taiwan[30]	RELY AF South-East Asia[36]	HK[37]	Euro Heart Survey[38]	RECORDAF[39]	ORBIT AF[40]	REALISEAF Europe[41]	RELY AF West Europe[36]	EORP AF[42]	PREFER[43]
CHF (%)	34.4	25	21.2	40.7	26.3	22.8	33	26	32	33.2	21.2	47.5	21.3
Hypertension (%)	71.1	58	72.5	72.9	64.1	54.7	63	68	83	78.1	59.9	70.9	72.0
Age (mean)	69.7	64	75	70.2	69.5	76.9	66	66	75	68.1	69.4	68.8	71.5
Diabetes (%)	22.1	18	36.8	27.0	29.2	22.0	18	16	29	20.2	17.1	20.6	22.4
Stroke/TIA (%)	17.3	13	20.2	21.9	22.1	23.1	9	10	16	13.5	12.0	10.5	8.4
CHD (%)	11.6	19	59.4	34.5	10.9[a]	18.2	32	18	32	36.4	18.2[a]	36.4	23.4
Female (%)	31.1	40	27.1	40.2	44.6	52.1	43	43	42	40.4	38.8	40.4	39.9

CHD = coronary heart disease; CHF = congestive heart failure; TIA = transient ischemic attack.
[a] Prior myocardial infarction.

genome-wide association studies, have been shown to be closely associated with the risk of nonfamilial or common AF.[26,27] The pathophysiological role of these genetic defects in the initiation and perpetuation of AF is currently unknown. The associations of *PITX2* and *KCNN3* genes with AF have been replicated in our Taiwanese population.[28,29]

3. Comorbidities of atrial fibrillation

Patients with AF generally have multiple cardiovascular (CV) comorbidities.[30] It has become difficult to identify patients with *lone* AF, which is a diagnosis of exclusion whereby no comorbid CV diseases could be found.[31] In the RealiseAF survey, just 5% in the total population and 3% in the Taiwanese population had lone AF.[30,32] Table 1 shows several important stroke-related CV comorbidities or risk factors in recent cohort studies or registries,[30,33–43] In general, the prevalence rate of these risk factors were comparable among Asians and non-Asians. About 20–30% of patients had congestive heart failure, and 60-70% had hypertension. The mean age was around 70 years. Type 2 diabetes was identified in about 20–30% of patients. A higher prevalence rate of a history of previous stroke or transient ischemic attack (TIA) was found in Asians. Coronary heart disease (CHD) seemed more common in non-Asian cohorts. About 40% of Asians and non-Asians were female.

As AF progressed from paroxysmal to persistent and permanent forms, the prevalence of comorbidities, such as heart failure, CHD, cerebrovascular disease, and valvular disease, increased, and the prevalence of lone AF decreased.[38,44] Permanent AF is a high-risk subset of AF,[44] and > 80% of these patients had at least one comorbidity.[44,45]

Recommendation

- In patients with AF, detailed history of comorbidities, including hypertension, heart failure, CHD, diabetes mellitus, and previous stroke, should be obtained.

4. Outcomes in patients with atrial fibrillation

Patients with lone AF have a benign prognosis. In a 30-year follow-up study from the USA, patients with lone AF and a mean age of 44 years had a similar survival, risk of heart failure, and risk of stroke or TIA, compared to matched control up to 25 years of follow-up.[46] The largest lone AF study demonstrated that these patients do have a favorable prognosis as long as they have truly lone arrhythmia.[47] However, with ageing and/or the occurrence of CV comorbidities in such patients, the risk of development of AF-related complications (e.g., thromboembolic events or heart failure) increases.[47]

Most AF patients have increased risk of future CV events. In general, white AF patients had two-fold risk of death, three-fold risk of hospitalization, and five-fold risk of stroke, compared with patients without AF.[48–51] Similarly, Asian AF patients had two-fold risk of death,[17,52] and three-

Table 2 Symptoms and European Heart Rhythm Association (EHRA) score of atrial fibrillation in Taiwanese versus non-Taiwanese.

	Taiwanese	Non-Taiwanese	*p*
Symptoms (%)			
Palpitation	28.2	34.2	< 0.001
Dyspnea	25.1	40.5	< 0.001
Fatigue	16.3	36.9	< 0.001
Lightheadedness/ dizziness	19.5	15.0	0.001
Cheat pain	14.2	15.4	0.361
Syncope	1.9	1.9	0.992
$\geq$ 1 symptom	55.3	61.1	0.002
EHRA score (%)			
I	18.5	23.9	< 0.001
II	69.5	50.5	
III	11.2	20.8	
IV	0.8	2.0	
II–IV	81.5	73.3	< 0.001

to four-fold risk of stroke,[17,53–55] compared with those without. In a recent cohort study of nonpermanent AF, the annual risk of CV events was 17.7%, including CV death, MI, stroke and TIA, CV admissions, and CV procedures.[56]

5. Symptoms

AF patients may present with varying symptoms. Besides palpitation, dyspnea and fatigue were not uncommon.[32] In a recent global AF survey, the symptomatology of Taiwanese was compared with that in non-Taiwanese (Table 2).[30] It seems that, during the week prior to outpatient visit, palpitation, dyspnea, and fatigue were more common in non-Taiwanese, and lightheadedness/dizziness was more common in Taiwanese. Overall, 61.1% of non-Taiwanese complained of at least one symptom, more than that in Taiwanese (55.3%, $p = 0.002$). When the European Heart Rhythm Association (EHRA) AF cardiac symptom classification score was compared in both groups,[57] Taiwanese had 81.5% of patients with an EHRA score II-IV, more than that in non-Taiwanese (73.3%, $p < 0.001$).[30] These data suggest that majority of AF patients were very symptomatic, both in Taiwan and in the world.

In a report of quality of life in patients with intermittent AF,[58] AF patients were either significantly worse or as impaired as either PTCA or post-MI patients on all domains of the SF-36.[59] Similarly, AF was associated with modestly impaired quality of life in Taiwanese patients,[30] measured by EQ-5D visual analogue scale.[60]

Recommendation

- In patients with AF, a record of symptoms, including palpitation, dyspnea, fatigue, chest pain, lightheadedness/dizziness, and an EHRA symptom score should be obtained.

Table 3 Classification of atrial fibrillation (AF).

Paroxysmal AF	1. Recurrent AF that terminate spontaneously within 7 d 2. AF of $\leq$ 48 h duration that are terminated by electrical or pharmacologic cardioversion
Persistent AF	1. A continuous AF that is sustained more than 7 d 2. AF in which a decision is made to electrically or pharmacologically cardiovert the patient after $\geq$ 48 h of AF, but prior to 7 days, should be classified as persistent AF
Longstanding persistent AF	A continuous AF that is sustained $>$ 12 mo
Permanent AF	A condition of continuous AF rhythm was accepted by patient and physician, and a decision of ceasing further attempts to restore and/or maintain sinus rhythm was made by physician and patients

6. Classifications

A variety of classification schemes for AF have been proposed.[61,62] A pattern-based classification scheme for AF,[63] as shown in Table 3, is simple, and correlated well with degree of atrial remodeling.[64] Based on this classification, paroxysmal AF was defined as recurrent AF ($>$ 2 episodes) that terminates spontaneously within 7 days. Persistent AF was defined as recurrent AF that has sustained for more than 7 days. Patients with continuous AF who undergo cardioversion within 7 days is classified as either paroxysmal AF if the cardioversion is performed within 48 hours of AF onset, or persistent AF if cardioversion is performed more than 48 hours after onset of AF. Continuous AF with duration $>$ 1 year is defined as longstanding persistent AF. Permanent AF is defined as condition of continuous AF that is accepted by patient and physician and further attempts to restore and/or maintain sinus rhythm are no longer considered.

Recommendation

- Patterns of AF: paroxysmal, persistent, longstanding persistent, and permanent, should be documented for AF patients.

7. Diagnosis and evaluation

A comprehensive clinical evaluation of a patient with AF consists of a detailed history, a thorough physical examination, and diagnostic investigations. Table 4 shows a summary of diagnosis and evaluation of AF. This table is useful for assessing the severity of AF-related symptoms, identifying the potential etiology of AF, classifying the type of AF,

Table 4 Diagnosis and evaluation in patients with atrial fibrillation (AF).

Basic evaluation	
1. History and physical examination	Symptoms associated with AF
	AF type (paroxysmal, persistent, long persistent or permanent)
	Date of the first symptomatic AF and total history of AF (y or mo)
	Frequency, duration, precipitating/relieving factors, and modes of initiation or termination of AF
	Pharmacological or nonpharmacological responses
	Comorbidities or reversible conditions (e.g., hyperthyroidism or alcohol consumption)
2. 12-lead Electrocardiography	Rhythm (confirm AF diagnosis)
	Left ventricular hypertrophy
	P-wave duration and morphology or fibrillatory P waves
	Wolff—Parkinson—White syndrome
	Bundle-branch block
	Old myocardial infarction
	Other atrial or ventricular arrhythmias
	Changes of the R-R, QRS duration, and QT intervals after antiarrhythmic drug therapy
3. Transthoracic echocardiography	Valvular heart disease
	Left atrial and right atrial size
	Left ventricular and right ventricular size and function
	Estimated peak pulmonary artery systolic pressure
	Left ventricular hypertrophy
	Left atrial cavity/appendage thrombus
	Pericardial diseases
4. Blood tests of thyroid, renal, and hepatic function	At the first diagnosis of AF
	When the ventricular rate is difficult to control or suspected antiarrhythmic drugs-related adverse effects
Advanced evaluation (1 or several tests may be necessary)	
1. 6-min walk test	To evaluate the adequacy of rate control
	To reproduce exercise-induced AF
	To exclude myocardial ischemia prior to treatment with a type IC antiarrhythmic drug [a]
2. Exercise testing	To evaluate the adequacy of rate control
	To reproduce exercise-induced AF
	To exclude myocardial ischemia prior to treatment with a type IC antiarrhythmic drug [a]
3. Holter or event monitoring	To enhance AF diagnostic rate
	To evaluate the adequacy of rate control
4. Transesophageal echocardiography	To identify spontaneous echo contrast in atria
	To identify left atrial cavity or appendage thrombus
	To guide cardioversion
5. Electrophysiological study	To confirm the mechanism of wide QRS-complex tachycardia
	To identify and ablate a triggering arrhythmias such as atrial flutter or paroxysmal supraventricular tachycardia
	To perform atrioventricular junction ablation for ventricular rate control
6. Chest radiograph	To assess coexistent pulmonary diseases
	To evaluate cardiac size and presence or absence of pulmonary hypertension

[a] Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs.

predicting prognosis, and choosing therapeutic strategies for rhythm management and thromboembolism prevention.

7.1. History and physical examination

Symptoms associated with AF including palpitations, dyspnea, dizziness, weakness, and chest pain are highly variable.[65] Although some AF patients may present debilitating symptoms, others may follow an asymptomatic period of unknown duration. The impact of these symptoms on quality of life can be evaluated by the EHRA symptom score,[66] which only includes symptoms that are attributable to AF and reversed or attenuated by restoring sinus rhythm or achieving effective rate control.

The physical findings suggestive of AF consist of an irregularly irregular arterial pulse, an irregular jugular

venous pulse without a-wave, and variation in the intensity of the first heart sound. The physical examination may also uncover the underlying etiology of AF or comorbidities including hypertension, heart failure, valvular heart disease, congenital heart disease, or hyperthyroidism.

7.2. Diagnostic investigations

The diagnosis of AF is established by electrocardiography (ECG) showing at least a single-lead recording for $\geq$ 30 seconds during the arrhythmic event.[66] AF is defined by the following ECG characteristics: (1) the surface ECG showing irregularly irregular R-R intervals; (2) there are no distinct P waves on the surface ECG (some regular atrial activity may be seen in several ECG leads, particularly in lead V1); and (3) the interval between two consecutive atrial activations when discernible is usually variable and >300 beats/min (bpm). In patients with implanted pacemakers or defibrillators, AF can be detected automatically via the diagnostic and memory functions of the device.[67] In patients with suspected AF, a 12-lead ECG is recommended as the first step to establish the diagnosis. Clinical symptoms highly suggestive of AF or other arrhythmias, but not detected by a 12-lead ECG, ECG monitoring is need.

Intermittent ECG monitoring devices include Holter (24 hours to 7 days) recording, patient and automatically activated event-recorder, and external loop recorders. Kirchhof et al[66] reported that extending the duration of Holter recording for 24 hours to 7 days or using daily and symptom-activated event recordings may increase the diagnosis rate to 70% in AF patients, with a negative predictive value of 30—50%. An external loop recorder is ideal for capturing brief episodes of arrhythmias not possibly detected by other devices. The external loop recording is triggered automatically according to the implemented arrhythmia detection algorithm or triggered manually by the patient. This device is suitable for highly motivated patients to detect AF within a limited period of time, usually 1—4 weeks.[68]

Continuous ECG monitoring can be obtained from implantable devices capable of recording intracardiac atrial electrograms such as dual-chamber pacemakers and defibrillators, which can detect AF appropriately, particularly when an arrhythmia is $\geq$ 5 minutes in duration.[57] Another approach is to use a leadless implantable loop recorder, which can provide continuous AF monitoring over a 2-year period with automatic AF detection algorithm based on analyzing R-R interval regularity. The clinical data suggest that use of implantable loop recorder has a good sensitivity but less specificity for AF detection. Recently, new devices incorporating wireless, ambulatory, real-time transmission technologies with a built-in auto-detection system have been used to facilitate the diagnosis of AF.[69,70] With continuous technological improvement for both software and hardware designs,[71] we can anticipate that the future device is able to detect AF accurately in a timely manner to allow early therapeutic interventions to prevent and treat AF-related complications.

Since exploring underlying etiology and the associated comorbidities is necessary for making appropriate decisions regarding the use of rate- and rhythm-controlling agents and antithrombotic therapy, a variety of routine investigations are warranted in all patients presenting with a history of AF.[72,73] A chest radiograph is valuable in evaluating pulmonary diseases and the pulmonary vasculature. It is important that thyroid, renal, and hepatic functions, serum electrolytes, and the blood profile with coagulation study should be measured at least once in the course of evaluation. All patients with AF should also undergo two-dimensional and Doppler ECG to assess left atrial (LA) and left ventricular (LV) dimensions and functions and to detect valvular, congenital, and pericardial disease or cardiomyopathy. Thrombus in the LA or LA appendage (LAA) is often detected with transesophageal ECG (TEE). Previous data showed that thrombus, spontaneous echo contrast, reduced LAA flow velocity, and aortic atheroma are important risk factors associated with thromboembolism in patients with nonvalvular AF.[74] Therefore, detection of LA and/or LAA thrombus in the setting of stroke or systemic embolism is highly suggestive of a cardiogenic mechanism.

Additional investigations include exercise testing and invasive electrophysiological studies, which may be considered in specific conditions. For example, exercise testing may supplement Holter monitoring in some patients with exercise-related symptoms and help to determine the ventricular rate during exercise after adopting rate control strategy. Invasive electrophysiological studies and radiofrequency catheter ablation should be considered in AF patients with suspected coexistent atrial flutter (AFL) or paroxysmal supraventricular tachycardia.

Recommendation

- In patients aged $\geq$ 65 years, opportunistic screening by pulse palpation, followed by ECG in those with an irregular pulse, is indicated to detect AF prior to the first stroke.

8. Management algorithm

The overall management algorithm is shown in Figure 2. When encountering patients with AF, hemodynamic status should be checked immediately. In the case of hemodynamically instability, including hypotension, shock, dyspnea, chest tightness, or acute coronary syndrome (ACS), electrical cardioversion (EC; Section 12.1) with concomitant heparin infusion should be undertaken immediately. If there is no evidence of hemodynamic instability, the risk of stroke should be assessed and a documented strategy for stroke prevention should be provided (Section 9). Symptoms should be re-assessed thereafter, and acute rate control (Section 11.1) is advocated if symptoms persist. Otherwise, patients can choose EC (Section 12.1). In patients who do not have symptoms or whose symptoms have been resolved by acute rate control strategy (Section 11.1), subsequent management would depend on type of AF.

For patients with paroxysmal AF, several options are provided, depending on AF burden or frequency of AF. For patients with low AF burden, patients may choose to have

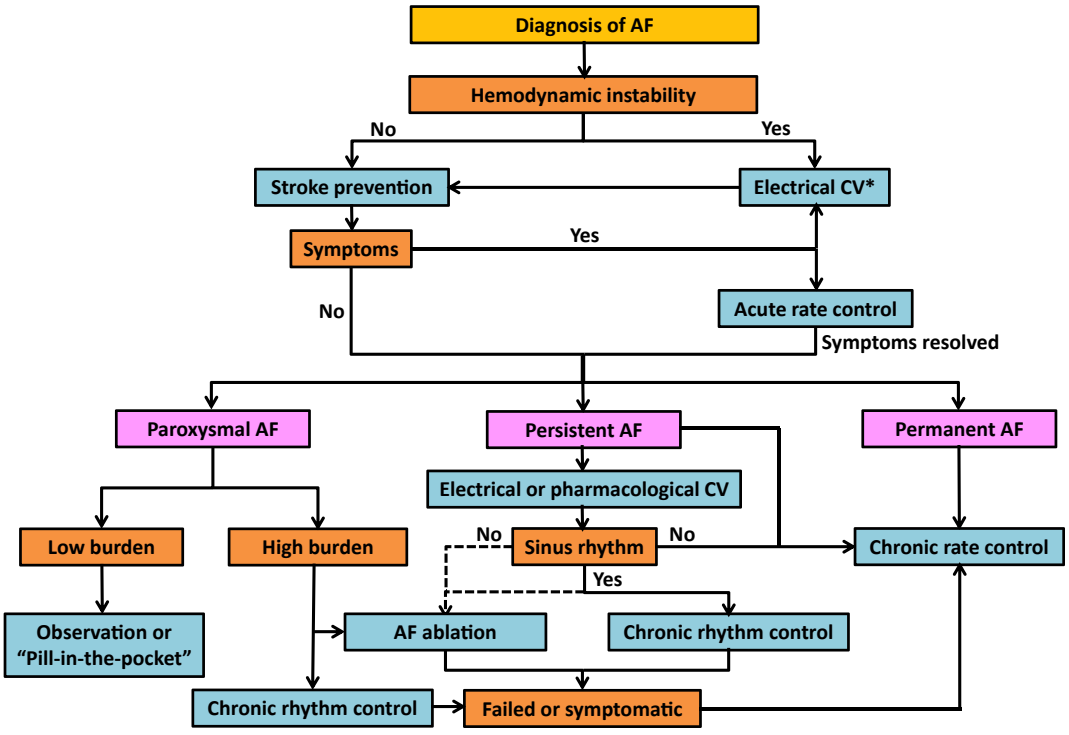

Figure 2 Overall management algorithm of atrial fibrillation. AF = atrial fibrillation; CV = cardioversion.

AF ablation (Section 13), or to be merely observed clinically. "Pill-in-the-pocket" strategy (Section 12.4) can be taken if patients have infrequent, but symptomatic, recurrence of AF. If patients have high AF burden, they can choose AF ablation (Section 13) or chronic rhythm control (Section 12.3).

For patients with persistent AF (including longstanding persistent AF), patients can choose to have a chronic rate-control strategy (Section 11.2), EC (Section 12.1), or pharmacological cardioversion (Section 12.2). If sinus rhythm is restored, patients can be maintained on a chronic rhythm-control strategy (Section12.3), or choose to have AF ablation (Section 13). If sinus rhythm cannot be obtained, patients can choose to have a chronic rate-control strategy (Section 11.2), or to have AF ablation (Section 13). If sinus rhythm cannot be maintained by chronic rhythm-control strategy, nor by AF ablation, or patients are still symptomatic, a chronic rate-control strategy (Section 11.2) should be undertaken.

For patients with permanent AF, therapeutic choice become simpler. A chronic rate control strategy (Section 11.2) and stroke prevention (Section 9) is suggested.

It is important to take stroke prevention measures at every step of therapeutic courses, irrespective of AF type.

9. Stroke prevention

9.1. Atrial fibrillation-associated stroke in Taiwan

In Asia, AF patients had three- to four-fold risk of stroke compared with patients without AF.[17,53–55] The annual risk of AF-associated stroke in Taiwan has recently been explored.[75] Using the National Health Insurance Research Database (NHIRD; 1996–2011) of the whole Taiwanese population, Chao et al[75] studied the annual risk of stroke of 185,570 AF patients who did not receive any antiplatelet or oral anticoagulant (OAC). Figure 3 shows the annual risk of stroke in Taiwanese and in a recent Swedish cohort,[76] according to the CHA_2DS_2-VASc score [Congestive heart failure, Hypertension, Age $\geq$ 75 years (doubled), Diabetes, Stroke (doubled)–Vascular disease, Age 65–74 years, Sex category (female)].[77,78] The risk of stroke was numerically higher in Taiwanese than in Swedish patients, at CHA_2DS_2-VASc scores 0–4. These risks were higher than those from a previous report by Lin et al[79] from Taiwan. Both used NHIRD AF population who were not exposed to any antiplatelet or

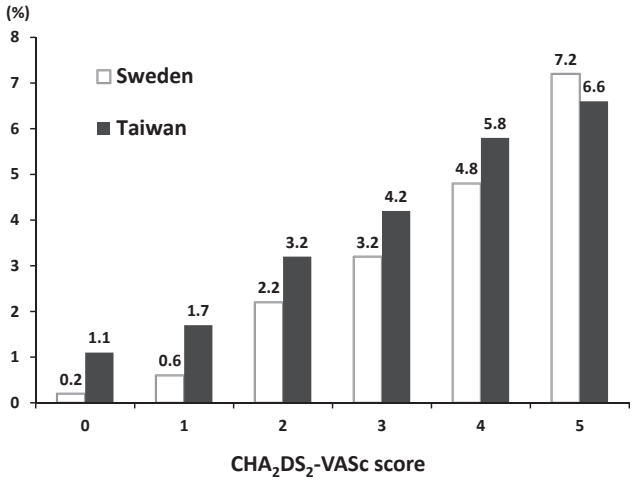

Figure 3 Annual risk of stroke in Taiwanese and Swedish.

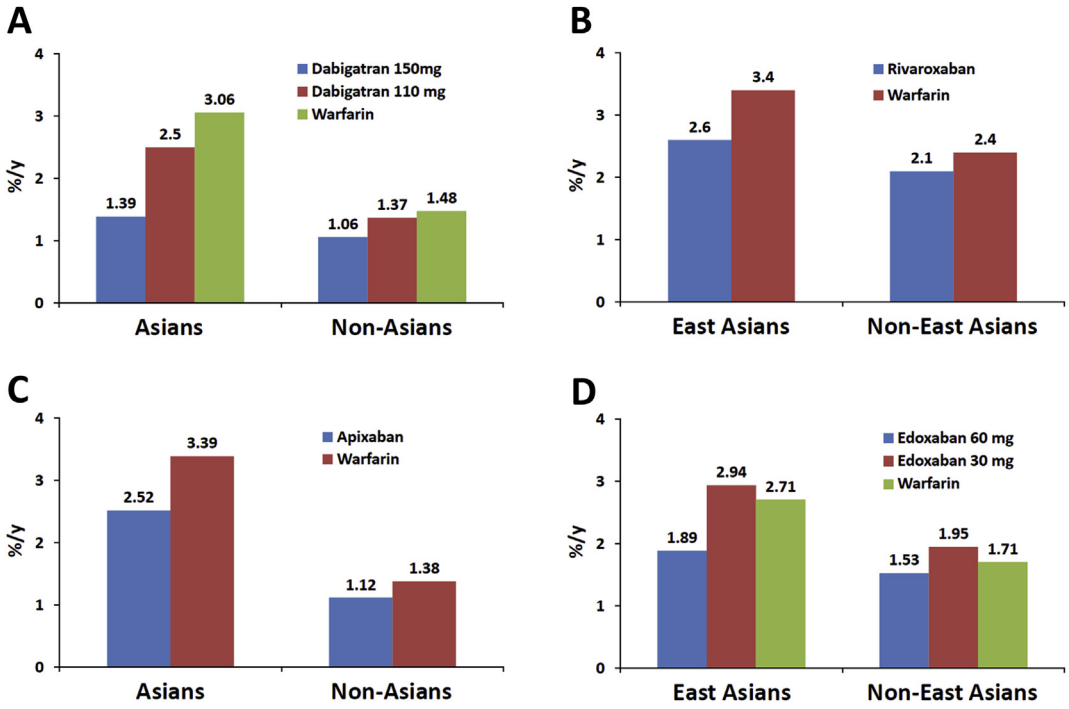

Figure 4 The annual risk of stroke/systemic embolization events in Asians versus non-Asians under either warfarin or non-vitamin K antagonist oral anticoagulant treatment in four major clinical trials. A: RE-LY trial; B: ROCKET AF trial; C: ARISTOTLE trial; D: ENGAGE AF trial. (Modified from Chiang et al.[95] with permission.)

OAC, but only 7920 AF patients from a 1-million population database were analyzed in Lin et al's[79] report. Instead, Chao et al's[75] report took the whole AF population, which included 186,570 AF patients. In parallel to Chao et al's[75] observation, Chang et al[80] showed a four-fold higher stroke risk in AF patients with a CHA2DS2-VASc score of 0 in men and 1 in women compared to the non-AF controls using the NHIRD.

It is difficult to know the risk of AF-associated stroke in drug-naive patients from randomized controlled trials (RCTs), because all patients have to be treated with some forms of OACs due to ethical reasons. It would be possible, however, to examine the risk of stroke whilst taking OAC treatment for Asians versus non-Asians. Four large scaled RCTs (the RE-LY trial, the ROCKET AF trial, the ARISTOTLE trial, and the ENGAGE AF trial) have been done to compare warfarin versus NOACs (previously referred to as new or novel OACs).[81–84] The data for Asians versus non-Asians from these four RCTs have also been published.[85–88] The mean $CHADS_2$ [Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes, Stroke (doubled)][89] scores were very similar among Asians versus non-Asians in each trial (2.2 vs. 2.1 in the RE-LY trial, 3.2 vs. 3.5 in the ROCKET AF trial, 2.1 vs. 2.1 in the ARISTOTLE trial, and 2.9 vs. 2.8 in the ENGAGE AF trial). The annual risk of stroke/systemic embolization events (SEEs) was generally higher in Asians than in non-Asians, whether on warfarin or on NOAC treatment (Figure 4).

The information regarding stroke prevention in this guideline is applied to nonvalvular AF. Patients with moderate or severe rheumatic mitral stenosis or with implantation of mechanical prosthetic valve were not included. Otherwise, patients with mitral or tricuspid insufficiency, and aortic stenosis or insufficiency, can be evaluated and treated according to this guideline.

9.2. $CHADS_2$ and CHA_2DS_2-VASc scores

The $CHADS_2$ score has been used to predict annual stroke risk in patients with nonvalvular AF for more than a decade (Table 5).[89] The $CHADS_2$ score has various limitations,[90] being derived from the historical trial cohorts that only randomized $<$ 10% of patients screened, and many stroke risk factors were not recorded nor consistently defined. Many patients classified as *low-risk* using $CHADS_2$

Table 5 $CHADS_2$ and CHA_2DS_2-VASc score.

	$CHADS_2$	CHA_2DS_2-VASc
Congestive heart failure	1	1
Hypertension	1	1
Age $\geq$ 75 y	1	2
Diabetes mellitus	1	1
Stroke/TIA	2	2
Vascular disease (prior MI, PAD, or aortic plaque)	0	1
Age 65–74 y	0	1
Sex category (i.e., female sex)	0	1
Maximum score	6	9

MI = myocardial infarction; PAD = peripheral artery disease; TIA = transient ischemic attack.

(score = 0) have stroke rates > 1.5%/year, and a $CHADS_2$ score of 0 does not reliably identify AF patients who are *truly* low-risk.

More recently, the CHA_2DS_2-VASc score[77] has been recommended for stroke risk assessment (Table 5), by the latest major guidelines from the European Society of Cardiology (ESC),[78] Asia–Pacific Heart Rhythm Society,[91] American Heart Association/American College of Cardiology/Heart Rhythm Society,[92] and the National Institute for Health and Care Excellence.[93] The CHA_2DS_2-VASc score is more inclusive of common stroke risk factors in AF, and performs best at initially identifying the *low-risk* AF patients (i.e. CHA_2DS_2-VASc score = 0 in men, score = 1 in women) who do not need any antithrombotic therapy.[77,90,94–97] Of note, the CHA_2DS_2-VASc scoring system has been validated and compared with standard $CHADS_2$ criteria in three recent studies from Chinese patients. The first study by Guo et al[35] from China using a hospital-based database suggested a similar stroke risk in nonanticoagulated Chinese AF patients compared to Caucasians. In this study, the c-statistics for predicting stroke/thromboembolism with $CHADS_2$ and CHA_2DS_2-VASc were 0.58 ($p = 0.109$) and 0.72 ($p < 0.001$), respectively. Compared to $CHADS_2$, the use of CHA_2DS_2-VASc would result in a net reclassification improvement of 16.6% ($p = 0.009$) and an integrated discrimination improvement of 1.1% ($p = 0.002$). The CHA_2DS_2-VASc score performed better than $CHADS_2$ in predicting stroke/thromboembolism in this Chinese AF population.[35] The second study by Siu et al[37] from Hong Kong have showed that the CHA_2DS_2-VASc score is superior to the $CHADS_2$ score in terms of stroke risk stratification in 9727 Chinese with AF. The adjusted net clinical benefit favored warfarin over aspirin or no therapy for almost all Chinese AF patients CHA_2DS_2-VASc score ≥ 1.

The third study is the most robust.[75] Chao et al[75] used the NHIRD in Taiwan. A total of 186,570 AF patients without antithrombotic therapy were selected as the study cohort. The clinical endpoint was the occurrence of ischemic stroke. During a mean follow-up of 3.4 years, 23,723 patients (12.7%) experienced ischemic stroke. The CHA_2DS_2-VASc score was compared to the ATRIA score.[98] The CHA_2DS_2-VASc score performed better than ATRIA score in predicting ischemic stroke as assessed by c-indexes (0.698 vs. 0.627, respectively; $p < 0.0001$). The CHA_2DS_2-VASc score also improved the net reclassification index by 11.7% compared with ATRIA score ($p < 0.0001$). Among 73,242 patients categorized as low-risk on the basis of an ATRIA score of 0–5, the CHA_2DS_2-VASc scores ranged from 0 to 7, and annual stroke rates ranged from 1.06% to 13.33% at 1-year follow-up and from 1.15% to 8.00% at 15-year follow-up. The c-index of CHA_2DS_2-VASc score (0.629) was significantly higher than that of the ATRIA score (0.593) in this *low-risk* category ($p < 0.0001$). Chao et al[75] concluded that patients categorized as low-risk by use of the ATRIA score were not necessarily low-risk, and the annual stroke rates can be as high as 2.95% at 1-year follow-up and 2.84% at 15-year follow-up. In contrast, patients with a CHA_2DS_2-VASc score of 0 had a truly low risk of ischemic stroke, with an annual stroke rate of approximately 1%.[75]

The age threshold set in the CHA_2DS_2-VASc score is 65 years. The risk of stroke in Asians is generally higher than that in Caucasians.[99] Therefore the age threshold for AF patients in Asia might be different than that in Caucasians. Recently, Chao et al[100] used the NHIRD in Taiwan to study 186,570 nonanticoagulated AF patients. There were 9416 men with a CHA_2DS_2-VASc score of 0 and 6390 women with a CHA_2DS_2-VASc score of 1. Their risk of ischemic stroke was analyzed with stratification on the basis of age. They found that the annual risks of ischemic stroke for men (score 0) and women (score 1) were 1.15% and 1.12%, respectively, and continuously increased from younger to older age groups, with an increment in stroke risk evident for patients older than 50 years. At a cutoff of 50 years, patients could be further stratified into two subgroups with different stroke risks (age ≥ 50 years: 1.78%/y; vs. < 50 years: 0.53%/y). This observation was consistent for men (1.95%/y vs. 0.46%/y, respectively) and women (1.58%/y vs. 0.64%/y, respectively) with AF. They concluded that for Taiwanese patients aged 50–64 years, the annual stroke risk was 1.78%, which may exceed the threshold for OAC use for stroke prevention. The annual risk of ischemic stroke for AF patients younger than 50 years was 0.53%, which was truly low-risk, and OACs could be omitted. Whether resetting the age threshold to 50 years could refine current clinical risk stratification for Asian AF patients deserves further study.[100]

Since the CHA_2DS_2-VASc score has outperformed other clinical scoring systems in predicting AF-associated stroke, the TSOC/THRS AF guidelines strongly recommend the use of this score. Both cardiologists and general practitioners should be encouraged to use the CHA_2DS_2-VASc score as a basic risk assessment method for selecting better anticoagulation therapy.

Recommendations

- The CHA_2DS_2-VASc score is recommended to assess stroke risk in nonvalvular AF.
- In patients with a 'low risk' CHA_2DS_2-VASc score (i.e. 0 in males or 1 in females), no antithrombotic therapy is recommended.
- In patients with a CHA_2DS_2-VASc score ≥ 1 (beyond female sex alone), antithrombotic therapy should be considered and NOACs are preferred over vitamin K antagonist (VKA).

9.3. HAS-BLED score

The effect of OAC in reducing stroke should be balanced by the bleeding risk, especially intracranial hemorrhage (ICH), with the use of OAC. Many risk factors for bleeding are also risk factors for stroke. While bleeding risk correlates with stroke risk scores (e.g. $CHADS_2$, CHA_2DS_2-VASc), specific bleeding risk scores may perform better than stroke risk scores for predicting bleeding. Various risk scores for predicting bleeding in AF have been proposed,[101,102] but, until recently, uptake has been poor due to their complexity.

More recently, the HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly, Drugs/alcohol concomitantly] score has been proposed as a

Table 6 HAS-BLED score.

Clinical characteristics	Definition	Score
Hypertension	SBP > 160 mmHg	1
Abnormal renal and liver function (1 score each)	Renal: dialysis, transplantation, or creatinine ≥ 2.3 mg/dL Liver: chronic hepatitis, cirrhosis, bilirubin > 2 ULN, with ALT > 3 ULN	1 or 2
Stroke	Previous history, particularly lacunar	1
Bleeding	Bleeding tendency or predisposition (e.g. anemia, recent GI bleed, etc.)	1
Labile INRs	Unstable/high INR, or TTR <60%	1
Elderly	Age > 65 y, frail condition	1
Drugs or alcohol (1 score each)	Drugs: antiplatelet, NSAID Alcohol excess	1 or 2
Maximum score		9

ALT = alanine transaminase; Cr = creatinine; GI = gastrointestinal; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drugs; SBP = systolic blood pressure; TTR = time in therapeutic range; ULN = upper limit of normal.

simple clinical score to predict clinically relevant bleeding in AF patients (Table 6).[103,104] HAS-BLED outperformed all other bleeding risk scores.[76,105,106] Of note, the HAS-BLED score is the only score predictive of ICH[105] and has also been validated in Asian cohorts.[35,97,107,108] The HAS-BLED score has been recommended by the major AF guidelines from the ESC, Canadian Cardiovascular Society and National Institute for Health and Care Excellence.[78,93,109]

The HAS-BLED score has to be used appropriately. A high score is not an excuse to withhold OAC (as such patients derive an even greater net clinical benefit from OAC treatment),[76,94] but to *flag up* patients potentially at risk for bleeding for more careful review and follow-up, and to guide the use of appropriate OAC doses. Furthermore, the HAS-BLED score for an AF patient is not static, but dynamic. It is useful for clinicians to think about the correctable risk factors for bleeding, such as uncontrolled hypertension (the *H* in HAS-BLED), labile INRs (*L*), only applies on a VKA (patient), concomitant drugs such as aspirin or nonsteroidal anti-inflammatory drugs, or alcohol excess/abuse (the *D* in HAS-BLED).

Recommendations

- The HAS-BLED score is recommended to assess bleeding risk in nonvalvular AF.
- A HAS-BLED score ≥ 3 indicates high bleeding risk. Some caution and regular follow-up of these patients is needed.
- The HAS-BLED score is dynamic and some risk factors are modifiable, such as uncontrolled hypertension, labile INRs, concomitant drugs such as aspirin or nonsteroidal anti-inflammatory drugs or alcohol excess/abuse.
- The HAS-BLED score should not be used on its own to exclude patients from OAC therapy.

9.4. Role of aspirin

In a meta-analysis of seven trials comprising 3990 AF patients comparing aspirin versus placebo or no treatment, there was a nonsignificant 19% reduction in stroke incidence.[110] This 19% reduction was driven by the one single positive trial (SPAF-1) which had major internal heterogeneity for the aspirin effect against placebo/control, reducing stroke by 94% in anticoagulation-eligible patients and by only 8% in anticoagulation-ineligible patients.[111] The SPAF-1 trial used aspirin 325 mg daily and had been stopped early hence possibly exaggerating the aspirin efficacy results. Also, aspirin did not reduce strokes in those aged > 75 years, nor did it prevent severe strokes.[111]

Data on the efficacy and safety of aspirin in Asian patients with AF are similarly scarce. In a Japanese trial, aspirin was compared with placebo in the stroke prevention in low-risk AF patients.[112] While there was no effect with the use of aspirin in reducing stroke, the risk of bleeding was increased by aspirin.[112] In a recent Hong Kong cohort, aspirin had a nonsignificant 18.7% reduction in ischemic strokes, compared with no therapy.[37] The overall annual ICH incidence in this Hong Kong cohort, who did not receive antithrombotic therapy, was 0.5% per year, comparable to published rates in Caucasian AF patients (0.6% per year).[113] The rate of ICH increased to 0.77% per year among Hong Kong patients receiving aspirin.[37] This number was higher than that from Caucasians (aspirin 0.6% per year).[113]

The risks of ischemic stroke and ICH in a real-world cohort of Chinese AF patients receiving aspirin or other therapy were reported recently from Hong Kong.[114] The incidence of ischemic stroke on aspirin was 7.95%/y, higher than dabigatran (110 mg) users. The incidence of ICH was lower in dabigatran (110 mg) users (0.32%/y) compared with those on aspirin (0.80%/y).[114] Similarly, In the AVERROES trial, the risk of stroke was significantly lower in apixaban group than in aspirin group (relative risk reduction 45%, $p < 0.001$).[115] The risk of ICH was numerically lower in the apixaban group.[115] These data suggest that there is no role for using aspirin in stroke prevention.

Despite a paucity of data to support the use of aspirin in the stroke prevention in AF, the use of aspirin is highly prevalent in many Asian countries.[41,116] Based on the NHIRD of Taiwan between 2003 and 2004, 70.3% of the AF patients were categorized as high risk group for stroke,[117] according to 2011 American College of Cardiology/American Heart Association recommendations.[118] Among them, 50.6% received aspirin and 15.4% received warfarin. A latest study

using Taiwan NHIRD between 2001 and 2008 showed that the percentage of AF patients who received warfarin, aspirin, or no treatment in Taiwan was 16%, 62%, and 22%, respectively.[119]

Dual antiplatelet therapy including aspirin plus clopidogrel has been tested in the ACTIVE-W and ACTIVE-A trials.[120,121] In the ACTIVE-W trial, aspirin plus clopidogrel was compared with warfarin, and the trial was prematurely terminated due to a 40% reduction ($p < 0.001$) in stroke by warfarin.[120] In the ACTIVE-A trial, aspirin plus clopidogrel was compared to aspirin along. The combination of aspirin and clopidogrel resulted in a 28% risk reduction ($p < 0.0002$) in strokes compared with aspirin alone, but increased major bleeding by 57% ($p < 0.001$).[121] For stroke prevention in AF, it is widely accepted that warfarin is better than aspirin plus clopidogrel, and aspirin plus clopidogrel is better than aspirin alone. The latter benefits are dampened by the significant increase in major bleeding events.[92]

Recommendations

- Aspirin has no role in stroke prevention in patients with nonvalvular AF.
- Dual antiplatelet therapy (DAPT) of aspirin and clopidogrel has no role in the stroke prevention in patients with nonvalvular AF, unless under other therapeutic indications, such as in patients with ACS and receiving stenting therapy.

9.5. Role of vitamin-K antagonists (VKA)

Warfarin is a VKA, inhibiting the formation of factor II, VII, IX, and X in the coagulation cascades. In a meta-analysis of six trials including of 2900 patients, comparing adjusted-dose warfarin versus placebo or no treatment, warfarin significantly reduced stroke by 64%, and total mortality by 26%.[110] When adjusted-dose warfarin were compared with aspirin in a meta-analysis of eight trials of 3647 patients, warfarin reduced risk of stroke by 38%.[110] In the BAFTA trial evaluating the effect of warfarin versus aspirin on the stroke prevention among high-risk elderly patients, warfarin was superior in preventing stroke without a significant increase in bleeding risk.[122] Before the availability of NOACs, warfarin was the treatment of choice for the stroke prevention in AF.

The main problem in the use of warfarin lies in its narrow therapeutic range. An INR of 2.0—3.0 was the optimal range of warfarin use for Caucasians.[123,124] The average individual time in the therapeutic range (TTR) needs to be above 65% to achieve the best safety and efficacy endpoints.[57] However, the TTR was at best 50% in clinic services in the USA, although anticoagulation clinic services were associated with somewhat better TTR compared with standard community care.[125] The TTRs in warfarin users in Asian were generally lower,[36] being attributed to diet, herbal medicines, etc.[126,127] Lack of structured anticoagulation services in many Asian countries may be an added logistic issue that precludes effective VKA management.

Table 7 SAMe-TT_2R_2 score.

Acronym	Definition	Points
S	Sex (female)	1
A	Age (< 60 y)	1
M e	Medical history [a]	1
T	Treatment (interacting drugs, e.g., amiodarone for rhythm control)	1
T	Tobacco use (within 2 years)	2
R	Race (nonwhite)	2
Maximum points		8

[a] More than two of the following: hypertension, diabetes, coronary heart disease/myocardial infarction, peripheral artery disease, congestive heart failure, stroke, pulmonary disease, and hepatic or renal disease.

The recently developed SAMe-TT_2R_2 [Sex female, Age < 60 years, Medical history (more than two comorbidities), Treatment (interacting medications, e.g. amiodarone), Tobacco use (doubled), Race (doubled)] score is useful in predicting those patients who would do well on VKA with a high TTR of >70% (SAME-TT_2R_2 score 0—1) and those who would do less well (SAME-TT_2R_2 score $\geq$ 2; Table 7).[128,129] This score has been validated in Caucasians in predicting not only TTR,[130] but also risk of stroke/thromboembolism (TE), severe bleeding, and death.[131,132] Since nonwhite people would have a score of at least 2, Asian patients are therefore less likely to have a good TTR. In a recent report from Hong Kong, the SAMe-TT_2R_2 score correlates well with TTR in Chinese AF patients, with a score > 2 having high sensitivity and negative predictive values for poor TTR.[133] Ischemic stroke risk increased progressively with increasing SAMe-TT_2R_2 score, consistent with poorer TTRs at high SAMe-TT_2R_2 scores.[133]

Warfarin has not been extensively tested against placebo in large-scaled RCTs in Asians.[134] In a recent prospective cohort study in Hong Kong, warfarin reduced stroke by 53%, compared with no treatment.[37] The main problem when using warfarin in Asians was the risk of ICH. It has been shown that with a similar TTR level Asians had four-fold increase in the risk of ICH, compared with that in white people.[135] Besides, the mortality rate of ICH seems higher than that in white people. In the recently reported data from Hong Kong, the mortality rate of warfarin-induced ICH was 62%,[136] higher than that in white people.[137] The analysis of the effect of warfarin versus NOACs in Asians are discussed in Section 9.6.3.2.

Warfarin has been under-used in the stroke prevention for AF in Taiwan, where only 15% of high risk groups received warfarin.[117] The under-use of warfarin is also common in other Asian countries.[36,41] Moreover, the TTR was generally suboptimal in Asians. In a recent cohort study, the TTRs for Asians including patients from India, China, and other Southeast Asian countries were all below 40%.[36] Thus, there remains a great unmet need for the stroke prevention for AF in Asians.

Recommendations

- Warfarin has not been extensively tested against placebo in large-scaled RCTs in Asians.
- The optimal therapeutic range of INR in the use of warfarin has not been fully established in Asians, although an INR 2.0—3.0 is recommended as the optimal therapeutic range, with attention on the average TTR; ideally >65%.
- The SAMe-TT_2R_2 score can be used to predict the likelihood of achieving a high TTR (e.g. > 70%) in warfarin users.
- In view of the difficulty in maintaining optimal TTR and a significant increase in the risk of ICH, there should be a higher priority to use NOACs rather than warfarin for stroke prevention in Asian patients with AF.

9.6. Non-vitamin K antagonist oral anticoagulants (NOACs)

The availability of NOACs (previously referred to as new or novel OACs) has changed the landscape for stroke prevention in AF.[138,139] The four NOACs—the oral direct thrombin inhibitor, dabigatran, and the oral factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban—have predictable pharmacokinetics, with a stable, dose-related anticoagulant effect and few drug interactions, hence allowing fixed dosing without the need for regular monitoring of anticoagulation status.[140]

9.6.1. Overview

The similarities and differences in the pharmacokinetics of the four NOACs are shown in Table 8.[78,141—143] The time to maximal concentration and half-lives are generally similar for all the four NOACs. The bioavailability is lowest for dabigatran and highest for rivaroxaban. Also, rivaroxaban must be taken with food as there is a 39% in the area under the curve plasma concentrations to a very high bioavailability of almost 100%, whilst there is no such issue for the other NOACs. There are differences in the renal clearance for different NOACs, with the highest for dabigatran (80%), followed by edoxaban (50%), rivaroxaban (35%), and apixaban (27%). Drug—drug interaction through cytochrome P (CYP) 450 is generally not an issue except for rivaroxaban (66% CYP metabolism). All NOACs are excreted, in some part, through P-glycoprotein (P-gp).

9.6.2. Clinical trials

The efficacy and safety of NOACs have been tested in four major RCTs: the RE-LY trial, the ROCKET AF trial, the ARISTOTLE trial, and the ENGAGE AF trial.[81—84] Background characteristics of the four major RCTs are shown in Table 9. The RE-LY trial had a PROBE-design, while others were double-blinded trials. All these trials compared NOACs with dose-adjusted warfarin with target INR of 2.0—3.0, using stroke plus SEEs as primary efficacy endpoints and for most apart from ROCKET AF, major bleeding as the primary safety endpoint. The inclusion criteria were based on $CHADS_2$ score.

The RE-LY trial included patients distributed equally across stroke risk strata ($CHADS_2$ score 0—1 in 31.9% of patients, 2 in 35.6%, and > 2 in 32.5%). The ARISTOTLE trial enrolled patients across stroke risk strata without $CHADS_2$ score 0. Both the ROCKET AF trial and the ENGAGE AF trial enrolled patients with higher risk ($CHADS_2$ score ≥ 2), and lower-risk patients ($CHADS_2$ score = 0 or 1) were not included in these two trials. The mean $CHADS_2$ scores were 2.1 for the RE-LY trial, 3.5 for the ROCKET trial, 2.1 for the ARISTOTLE trial, and 2.8 for the ENGAGE AF trial. The mean $CHADS_2$ scores and distribution of patients in Asian subgroup were similar to those in the global ones.

9.6.2.1. RE-LY trial. Dabigatran is a direct thrombin inhibitor, and was the first NOAC approved by the US Food and Drug Administration (FDA) to reduce the risk of stroke and SEEs in patients with nonvalvular AF. The efficacy and safety of dabigatran was tested in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which was an PROBE-designed trial comparing dabigatran (150 mg or 110 mg twice daily in a blinded fashion) with adjusted-dose warfarin (INR 2.0—3.0) in 18,113 patients over a mean follow-up period of 2 years (Table 9).[81] The mean TTR for warfarin users was 64%. The primary efficacy endpoint was stroke plus SEEs, and the primary safety endpoint was major bleeding.

The efficacy and safety endpoints in the RE-LY trial are shown in Table 10. The efficacy of dabigatran 150 mg twice

Table 8 Pharmacokinetic characteristics of non-vitamin K antagonist oral anticoagulants.

	Direct thrombin inhibitor	Direct factor Xa inhibitors		
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Hours to C_{max}	3	2—4	3	1—2
Half-life (h)	12—17	5—13	9—14	10—14
Bioavailability	6%	80%	60%	62%
Absorption with food	No effect	+39%	No effect	+ (6—22%)
Intake with food recommended	No	Mandatory	No	No
Renal clearance	80%	35%	27%	50%
CYP metabolism	None	66%	15%	<4%
Transporter	P-glycoprotein	P-glycoprotein	P-glycoprotein	P-glycoprotein

Modified from Camm et al,[78] Heidbuchel et al,[141] Eriksson et al,[142] and Lip et al.[143]
C_{max} = maximal concentration; CYP = cytochrome P450.

Table 9 Background characteristics of four major randomized controlled trials.

	RE-LY[81,85]	ROCKET AF[82,86]	ARISTOTLE[83,87]	ENGAGE AF[84,88]
Total patient number	18,113	14,264	18,201	21,105
Asian patient no.	2782	932	1993	1943
Taiwan patient no.	355	159	57	234
Trial design	PROBE	Double-blind	Double-blind	Double-blind
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg twice daily, 110 mg twice daily)	Dose-adjusted warfarin vs. rivaroxaban 20 mg once daily	Dose-adjusted warfarin vs. apixaban 5 mg twice daily	Dose-adjusted warfarin vs. edoxaban (60 mg once daily, 30 mg once daily)
Mean age (y)	71.5	73	70	72
Mean follow-up (y)	2.0	1.9	1.8	2.8
Warfarin naïve	50.4%	37.6%	43%	41%
Inclusion criteria				
$CHADS_2$	≥ 0	≥ 2	≥ 1	≥ 2
CHA_2DS_2-VASc	≥ 1	≥ 2	≥ 1	≥ 2
Global				
$CHADS_2$ (mean)	2.1	3.5	2.1	2.8
Proportions of patients by $CHADS_2$ score				
0	31.9% (0 or 1)	0%	0%	0%
1		0%	34.4%	0%
2	35.6%	13.0%	35.8%	77.4% (2 or 3)
3	32.5% (3–6)	43.6%	30.2% (3–6)	
4		28.7%		22.6% (4–6)
5		12.7%		
6		2.0%		
Asians				
$CHADS_2$ (mean)	2.2	3.2	2.1	2.9
Proportions of patients by $CHADS_2$ score				
0	30.2% (0 or 1)	0%	0%	0%
1		0%	39.3%	0%
2	33.0%	24.0%	28.3%	76.5% (2 or 3)
3	36.8% (3–6)	42.2%	32.4% (3–6)	
4		24.3%		23.5% (4–6)
5		8.3%		
6		1.2%		

$CHADS_2$ = Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes, Stroke (doubled); CHA_2DS_2-VASc score = Congestive heart failure, Hypertension, Age $\geq$ 75 years (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female); PROBE = prospective randomized opened-label blinded endpoint.

daily was superior to warfarin. There was a numerically increased number of MI events amongst dabigatran-treated patients, although absolute events were low (0.8%, 0.8%, and 0.6% per year for patients randomized to dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, and warfarin, respectively).[144] One meta-analysis of dabigatran RCT found a statistically significant increase in the risk of MI,[145] but there was no signal of increased MI in a recent report from FDA-sponsored Medicare analysis.[146] Although there was no difference in the primary safety endpoints for dabigatran 150 mg twice daily dosing compared with warfarin, the risk of ICH and major plus minor bleeding were lower for dabigatran 150 mg twice daily dosing. There is an increased risk of gastrointestinal bleeding with dabigatran 150 mg twice daily, and this finding has been replicated in the recent report from a Medicare database.[146]

For dabigatran 110 mg twice daily dosing, the efficacy was generally similar to warfarin, except that the risk of hemorrhagic stroke was lower for dabigatran (Table 10). Dabigatran 110 mg twice daily dosing was safer than warfarin in the risk of major bleeding, ICH, and major plus minor bleeding.

This guideline does not recommend using dabigatran in patients with a calculated creatinine clearance $<$ 30 mL/min, according to the exclusion criteria of the RE-LY trial.[81]

9.6.2.2. ROCKET AF trial. Rivaroxaban is an oral direct factor Xa inhibitor, and is the second NOAC approved by FDA for reduction of risk of stroke and SEE in patients with nonvalvular AF. The ROCKET AF (The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism, for Prevention of Stroke and Embolism Trial, in Atrial Fibrillation) trial is a double-blind study, comparing rivaroxaban (20 mg/day; 15 mg/d in patients with creatinine clearance 30–49 mL/min) with dose-adjusted warfarin (INR 2.0–3.0) in 14,264 patients

Table 10 Relative risk reduction in the efficacy and safety endpoints of non-vitamin K antagonist oral anticoagulant (NOAC) versus warfarin in four major randomized controlled trials (RCTs).

	RE—LY[81]				ROCKET AF[82]		ARISTOTLE[83]		ENGAGE AF[84]			
	Dabigatran 150 mg		Dabigatran 110 mg		Rivaroxaban		Apixaban		Edoxaban 60 mg		Edoxaban 30 mg	
	RR	*p*	RR	*p*	RR	*p*	RR	*p*	RR	*p*	RR	*p*
Efficacy endpoints												
Stroke + SEE	0.66 (0.53—0.82)	< 0.001	0.91 (0.74—1.11)	0.34	0.88 (0.75—1.03)	0.12	0.79 (0.66—0.95)	0.01	0.87 (0.73—1.04)	0.08	1.13 (0.96—1.34)	0.10
Ischemic stroke	0.76 (0.60—0.98)	0.03	1.11 (0.89—1.40)	0.35	0.94 (0.75—1.17)	0.58	0.92 (0.74—1.13)	0.42	1.00 (0.83—1.19)	0.97	1.41 (1.19—1.67)	< 0.001
Hemorrhagic stroke	0.26 (0.14—0.49)	< 0.001	0.31 (0.17—0.56)	< 0.001	0.59 (0.37—0.93)	0.024	0.51 (0.35—0.75)	< 0.001	0.54 (0.38—0.77)	< 0.001	0.33 (0.22—0.50)	< 0.001
Myocardial infarction	1.27[a] (0.94—1.71)	0.12	1.29[a] (0.96—1.75)	0.09	0.81 (0.63—1.06)	0.121	0.88 (0.66—1.17)	0.37	0.94 (0.74—1.19)	0.60	1.19 (0.95—1.49)	0.13
CV death	0.85 (0.72—0.99)	0.04	0.90 (0.77—1.06)	0.21	0.89 (0.73—1.10)	0.289	0.89 (0.76—1.04)	NA	0.86 (0.77—0.97)	0.013	0.85 (0.76—0.96)	0.008
All-cause death	0.88 (0.77—1.00)	0.051	0.91 (0.80—1.03)	0.13	0.85 (0.70—1.02)	0.073	0.89 (0.80—0.998)	0.047	0.92 (0.83—1.01)	0.08	0.87 (0.79—0.96)	0.006
Safety endpoints												
Major bleeding	0.93 (0.81—1.07)	0.31	0.80 (0.69—0.93)	0.003	1.04 (0.90—1.20)	0.58	0.69 (0.60—0.80)	< 0.001	0.80 (0.71—0.91)	< 0.001	0.47 (0.41—0.55)	< 0.001
Intracranial hemorrhage	0.40 (0.27—0.60)	< 0.001	0.31 (0.20—0.47)	< 0.001	0.67 (0.47—0.93)	0.02	0.42 (0.30—0.58)	< 0.001	0.47 (0.34—0.63)	< 0.001	0.30 (0.21—0.43)	< 0.001
GI bleeding	1.50 (1.19—1.89)	< 0.001	1.10 (0.86—1.41)	0.43	1.39 (1.19—1.61)	NA	0.89 (0.90—1.15)	0.37	1.23 (1.02—1.50)	0.03	0.67 (0.53—0.83)	< 0.001
Bleeding of any cause	0.91[b] (0.86—0.97)	0.002	0.78[b] (0.74—0.83)	< 0.001	1.03[c](0.96—1.11)	0.44	0.71[d] (0.68—0.75)	< 0.001	0.86[c] (0.80—0.92)	< 0.001	0.62[c] (0.57—0.67)	< 0.001

CV = cardiovascular; GI = gastrointestinal; NA = not available; RR = relative risk reduction; SEE = systemic embolic event.

[a] Reference 144.

[b] Major + minor bleeding.

[c] Major and nonmajor clinically relevant bleeding.

[d] Any bleeding.

with AF and a prior history of stroke or at least two other additional risk factors for stroke (Table 9). It is worth noting that the patients enrolled in the ROCKET AF trial had a high risk for stroke, with an average $CHADS_2$ score of 3.5, higher than other NOAC trials. The mean follow-up period was 1.9 years, and the mean TTR for warfarin users was 55%.[82] The primary efficacy endpoint for the intention-to-treat analysis was stroke plus SEE, and the primary safety endpoint was major bleeding.[82]

The efficacy and safety endpoints in the ROCKET AF trial are shown in Table 10. In general, rivaroxaban was noninferior to warfarin for the efficacy endpoints, but the risk of hemorrhagic stroke was significantly lower than warfarin.[82] The risk of major bleeding was similar to warfarin, but the risk of gastrointestinal bleeding was increased. However, the risk of ICH was significantly decreased, a consistent finding for all NOACs.[82]

This guideline does not recommend using rivaroxaban in patients with a calculated creatinine clearance <30 mL/min, according to the exclusion criteria of the ROCKET AF trial.[82]

9.6.2.3. AVERROES and ARISTOTLE trials. Apixaban is another direct factor Xa inhibitor and is the third NOAC approved by the FDA for reduction or risk of stroke and SEE in patients with nonvalvular AF. The efficacy of apixaban has been examined in two RCTs: ARISTOTLE and AVERROES.

In the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Strokes) trial, 5599 patients with nonvalvular AF and at least one additional stroke risk factor who were unsuitable for VKA therapy were randomized to apixaban 5 mg twice daily or aspirin 81–324 mg once daily.[115] A reduced dose of apixaban 2.5 mg twice daily were used in patients (9.1% in the apixaban group) with at least two of the following criteria: age $\geq$ 80 years; body weight $\leq$ 60 kg; and serum creatinine $\geq$ 1.5 mg/dL (6% in the apixaban group). After a mean follow-up of 1.1 years, the trial was stopped early because of a clear benefit in favor of apixaban.[116] The primary outcome of stroke or SEE was 1.6%/y in patients assigned to apixaban compared with 3.7%/y in patients assigned to aspirin [hazard ratio (HR) 0.45; 95% confidence interval (CI), 0.32–0.62; $p < 0.001$]. The rates of major bleeding were similar with apixaban (1.4%/y) and aspirin (1.2%/y; HR with apixaban, 1.13; 95% CI, 0.74–1.75; $p = 0.57$). The rates of ICH were numerically lower in the apixaban group (HR with apixaban, 0.85; 95% CI, 0.38–1.90; $p = 0.69$). Importantly, the rates of gastrointestinal bleeding were also identical (0.4% per year; HR with apixaban, 0.86; 95% CI, 0.40–1.86; $p = 0.71$). The AVERROES study concluded that in patients with AF for whom VKA was unsuitable, apixaban reduced the risk of stroke or SEE without significantly increasing the risk of major bleeding or ICH.[115]

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, 18,201 patients with nonvalvular AF (excluding patients with moderate/severe mitral stenosis or prosthetic heart valve) and $CHADS_2$ score $\geq$ 1 were randomized to apixaban 5 mg twice daily or adjusted-dose warfarin (Table 9).[83] The mean follow-up period was 1.8 years and the mean TTR was 62%. A reduced dose of apixaban 2.5 mg twice daily were used in patients (9.1% in the apixaban group) with at least two of the following criteria: age $\geq$ 80 years; body weight $\leq$ 60 kg; and serum creatinine $\geq$ 1.5 mg/dL (9.1% in the apixaban group).

The efficacy and safety endpoints in the ARISTOTLE trial are shown in Table 10. Among the efficacy endpoints, apixaban was superior to warfarin in reducing the risk of stroke/SEE, hemorrhagic stroke, and all-cause death.[83] For the safety endpoints, apixaban was better than warfarin in the reduction of major bleeding, ICH, and any bleeding. The ARISTOTLE trial concluded that, in patients with nonvalvular AF, apixaban was superior to warfarin in preventing stroke/SEE, caused less bleeding, and resulted in lower mortality.[83]

Based on new pharmacokinetic profiles in a limited data set,[147] the prescription recommendations of apixaban in USA were changed to "the recommended dose for nonvalvular atrial fibrillation patients with end-stage renal disease maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age $\geq$ 80 years or body weight $\leq$60 kg) is present." These recommendations represent the use of full-dose apixaban in many patients undergoing dialysis and are made with no evidence regarding the clinical impact or safety of continued use of this agent.[147] There are no published data for the use of apixaban in these clinical settings. This guideline, therefore, does not recommend using apixaban in patients with a calculated creatinine clearance $<$ 25 mL/min, according to the exclusion criteria of the ARISTOTLE trial.[83]

9.6.2.4. ENGAGE AF trial. Edoxaban is a direct factor Xa inhibitor and is the fourth NOAC approved by the FDA for reduction or risk of stroke and SEE in patients with nonvalvular AF. In the ENGAGE AF-TIMI 48 (The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) trial, 21,105 patients with nonvalvular AF and a $CHADS_2$ score $\geq$ 2 were randomized to two once-daily regimens of edoxaban (60 mg and 30 mg) or adjusted-dose warfarin (Table 9).[84] The mean follow-up period was 2.8 years and the mean TTR was 65%.

The efficacy and safety endpoints in the ENGAGE trial are shown in Table 10. The efficacy of edoxaban 60 mg once daily was noninferior to warfarin, but the risk of hemorrhagic stroke and CV death was lower with edoxaban 60 mg once daily. The safety endpoints generally favor the use of edoxaban 60 mg once daily, except that the risk of gastrointestinal bleeding was higher with edoxaban.

For edoxaban 30 mg once daily, albeit primary endpoints did not show significant difference when compared with warfarin, the risk of ischemic stroke was higher than warfarin. Consistent to other NOACs, the risk of hemorrhagic stroke was lower with the use of edoxaban 30 mg. Interestingly, CV death and all-cause death were lower for edoxaban 30 mg. All the safety endpoints were in favor of edoxaban 30 mg.

This guideline does not recommend using edoxaban in patients with a calculated creatinine clearance $<$ 30 mL/min, according to the exclusion criteria of the ENGAGE AF trial.[84]

9.6.2.5. Meta-analysis of major trials. The efficacy and safety of four major RCTs of NOACs (the RE-LY trial, the

ROCKET AF trial, the ARISTOTLE trial, and the ENGAGE AF trial)[81–84] were analyzed in a prespecified meta-analysis.[139] There were 71,683 participants included, and the main outcomes were stroke/SEEs, ischemic stroke, hemorrhagic stroke, all-cause mortality, MI, major bleeding, ICH, and gastrointestinal bleeding. Altogether, 42,411 participants received a NOAC and 29,272 participants received warfarin. Standard doses of NOACs (dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily) significantly reduced stroke/SEEs by 19% compared with warfarin (risk ratio 0.81,95% CI 0.73–0.91; $p < 0.0001$), mainly driven by a reduction in hemorrhagic stroke (0.49, 0.38–0.64; $p < 0.0001$). NOACs also significantly reduced all-cause mortality (0.90, 0.85–0.95; $p = 0.0003$) and ICH (0.48, 0.39–0.59; $p < 0.0001$), but increased gastrointestinal bleeding (1.25, 1.01–1.55; $p = 0.04$). There were no heterogeneity for stroke/SEEs in important subgroups, but there was a greater relative reduction in major bleeding with NOACs when the center-based TTR was $<$ 66% than when it was $\geq$ 66% (0.69, 0.59–0.81 vs. 0.93, 0.76–1.13; p for interaction 0.022). Low-dose NOAC regimens (dabigatran 110 mg twice daily, and edoxaban 30 mg once daily) showed similar overall reductions in stroke/SEEs to warfarin (1.03, 0.84–1.27; $p = 0.74$), but a significant reduction in the risk of hemorrhagic stroke (0.33, 0.23–0.46; $p < 0.0001$) and ICH (0.31, 0.24–0.41; $p < 0.0001$). However, there was a significantly increased risk of ischemic stroke (1.28, 1.02–1.60; $p = 0.045$) and MI (1.25, 1.04–1.50; $p = 0.018$).[139]

This meta-analysis is the first to include data for all four NOACs studied in the pivotal phase 3 clinical trials for the prevention of stroke/SEEs in patients with AF. NOACs had a favorable risk–benefit profile, with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of NOACs was consistent across a wide range of patients. One should be careful to integrate this information into patient care in Asia. As mentioned in previous sections, Asians are prone to bleeding due to warfarin use. Therefore, a more detailed examination of the Asian subset in these RCTs is important.

9.6.3. Asian sub-analyses of clinical trials

Although there were no large scaled RCTs to test the efficacy of warfarin in Asians in the stroke prevention in AF, several smaller or cohort studies suggested the superiority of warfarin compared to aspirin or placebo in Asians.[134] Among 71,783 participants in the four major RCTs of NOACs,[81–84] 7650 patients were from Asia. The Asian sub-analyses of all these RCTs have been published or presented.[85–87,148] This information provides a great opportunity for the understanding of both efficacy and safety of the use of NOACs versus warfarin in Asia.

9.6.3.1. Background characteristics. The mean $CHADS_2$ score and other risk factors for stroke in Asians and non-Asians are shown in Table 11. In general, the mean $CHADS_2$ score were similar in Asians and non-Asians across all four trials. The prevalence rate of previous stroke/TIA was numerically higher in Asians than in non-Asians, whilst hypertension and ages were higher in non-Asians.

9.6.3.2. Warfarin in Asians versus non-Asians. In these four large-scale RCTs of NOACs, warfarin was tested against NOACs for stroke prevention. There was a substantial proportion of patients receiving warfarin therapy, and a total of 7650 Asian patients were included. It would be a great opportunity to analyze the safety and efficacy of warfarin in Asians versus non-Asians. Figure 5 shows the TTR (INR 2.0–3.0) and proportions of patients with INR $<$ 2.0 or INR $>$ 3.0 in these RCTs. Apparently, TTR was consistently lower in Asians than in

Table 11 Risk profiles of atrial fibrillation in Asians versus non-Asians in four clinical trials.

	Heart failure (%)	Hypertension (%)	Age $\geq$ 75 y (%)	Diabetes (%)	Stroke/TIA (%)	Mean $CHADS_2$ score
RE-LY[85]						
Asians ($n = 2782$) [a]	36.3	71.2	27.4	25.1	24.2	2.2
Non-Asians ($n = 15,331$)	31.2	80.2	42.2 (mean age)	23.0	10.4	2.1
ROCKET AF[86]						
East Asians ($n = 932$)[b]	38.6	79.9	69.7	36.9	65.0	3.2
Non-East Asians ($n = 13,322$)	64.1	91.3	71.3	40.1	54.0	3.5
ARISTOTLE[87]						
Asians ($n = 1993$)[c]	26.2	82.3	24.4	25.2	28.8	2.1
Non-Asians ($n = 16,202$)	36.6	88.1	32.0	25.0	18.3	2.1
ENGAGE AF[88]						
East Asians ($n = 1943$)[d]	47.3	82.1	37.5	35.0	42.4	2.9
Non-East Asians ($n = 19,162$)	58.5	94.8	40.4	36.2	26.9	2.8

TIA = transient ischemic attack.
[a] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India.
[b] China, South Korea, Taiwan, Hong Kong.
[c] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia.
[d] China, Japan, South Korea, Taiwan.

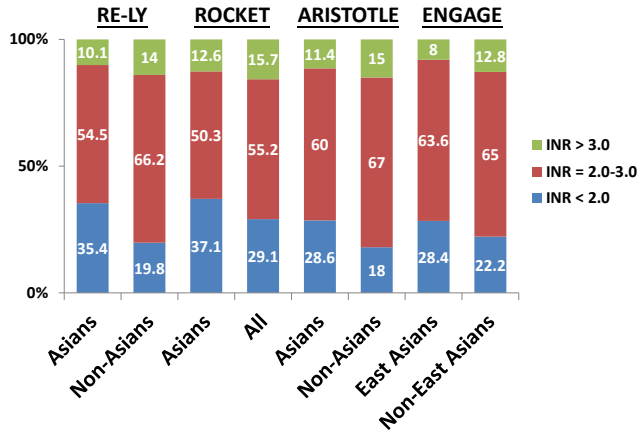

Figure 5 International normalized ratios (INRs) in the randomized trials. Asians in RE-LY included patients from China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, and India.[85] Asians in ROCKET included patients from China, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, and Thailand.[330] Asians in ARISTOTLE included patients from China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, and Malaysia.[87] East Asians in ENGAGE included patients from China, Japan, South Korea, and Taiwan.[88] Modified from Lip et al[149] with permission.

non-Asians.[95] Higher proportions of Asians had an INR of $<$ 2.0, while non-Asians more commonly to have an INR $>$ 3.0. These data suggest that Asians were less intensely anticoagulated with warfarin in these RCTS. Other factors associated with bleeding risk were generally similar among Asians and non-Asians. For instance, the mean HAS-BLED score was 2.9 in Asians and 2.8 in non-Asians in the ROCKET AF trial, and it was 1.7 in Asians and 1.8 in non-Asians in the ARISTOTLE trial.[86,87]

The safety endpoints, including major bleeding (primary safety endpoint), ICH, gastrointestinal bleeding, and bleeding of any cause are shown in Figure 6.[149] Even though Asians were less intensely anticoagulated with warfarin, the bleeding events, except gastrointestinal bleeding, were generally higher in Asians than in non-Asians. The event rates of ICH, the most devastating bleeding event, were much higher in Asians than in non-Asians. These data confirmed the finding from previous report that Asians are prone to bleeding when treated with warfarin.[135]

The efficacy endpoints, including stroke/SEEs (primary efficacy endpoint), ischemic stroke, hemorrhagic stroke, MI, and all-cause mortality are shown in Figure 7.[149] Despite similar $CHADS_2$ score in Asians versus non-Asians in these four RCTs, the event rates of stroke/SEEs, hemorrhagic stroke, and ischemic stroke were higher in Asians, possibly due to inadequate intensity of anticoagulation in Asians

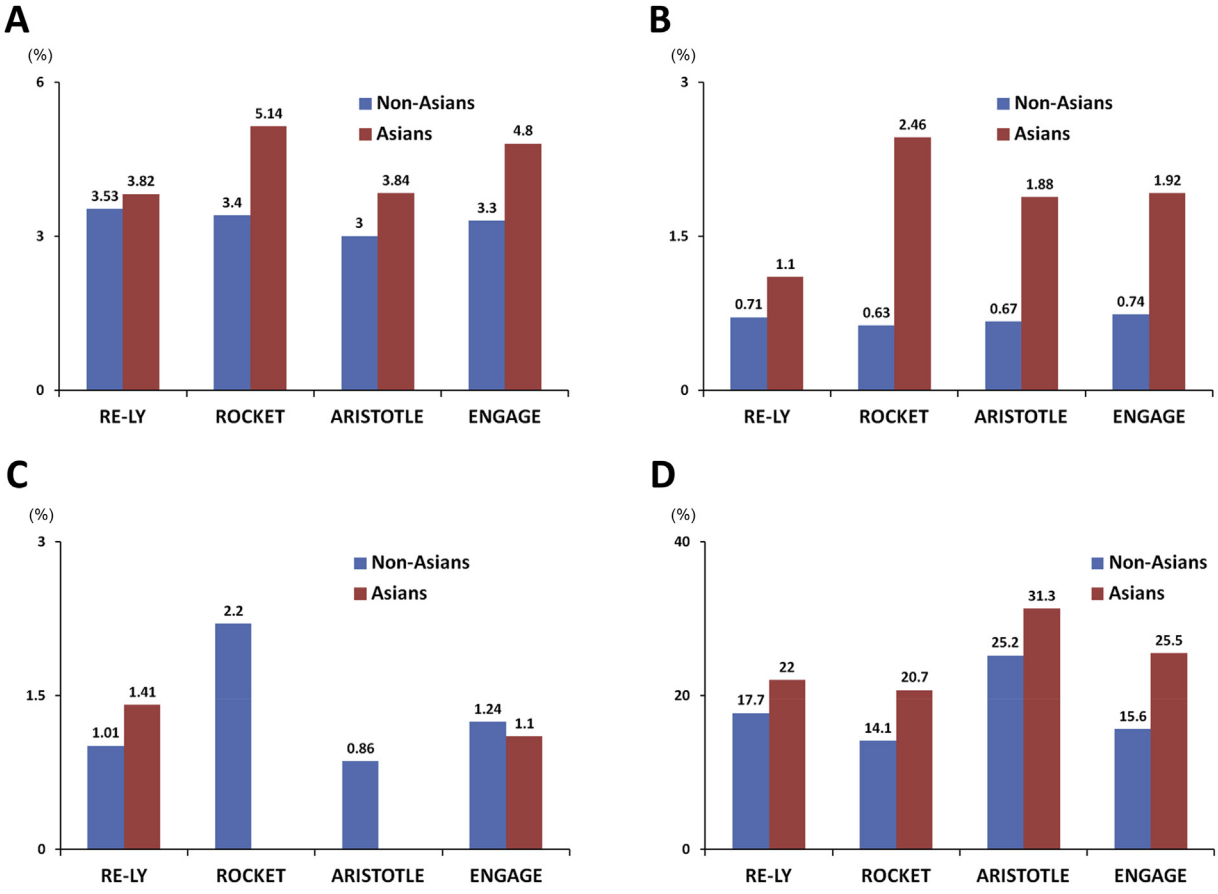

Figure 6 Bleeding events on warfarin in Asians versus non-Asians, from the randomized trials. (A) Major bleeding; (B) intracranial hemorrhage; (C) gastrointestinal bleeding; (D) all (major plus minor) bleeding episodes. Modified from Lip et al[149] with permission.

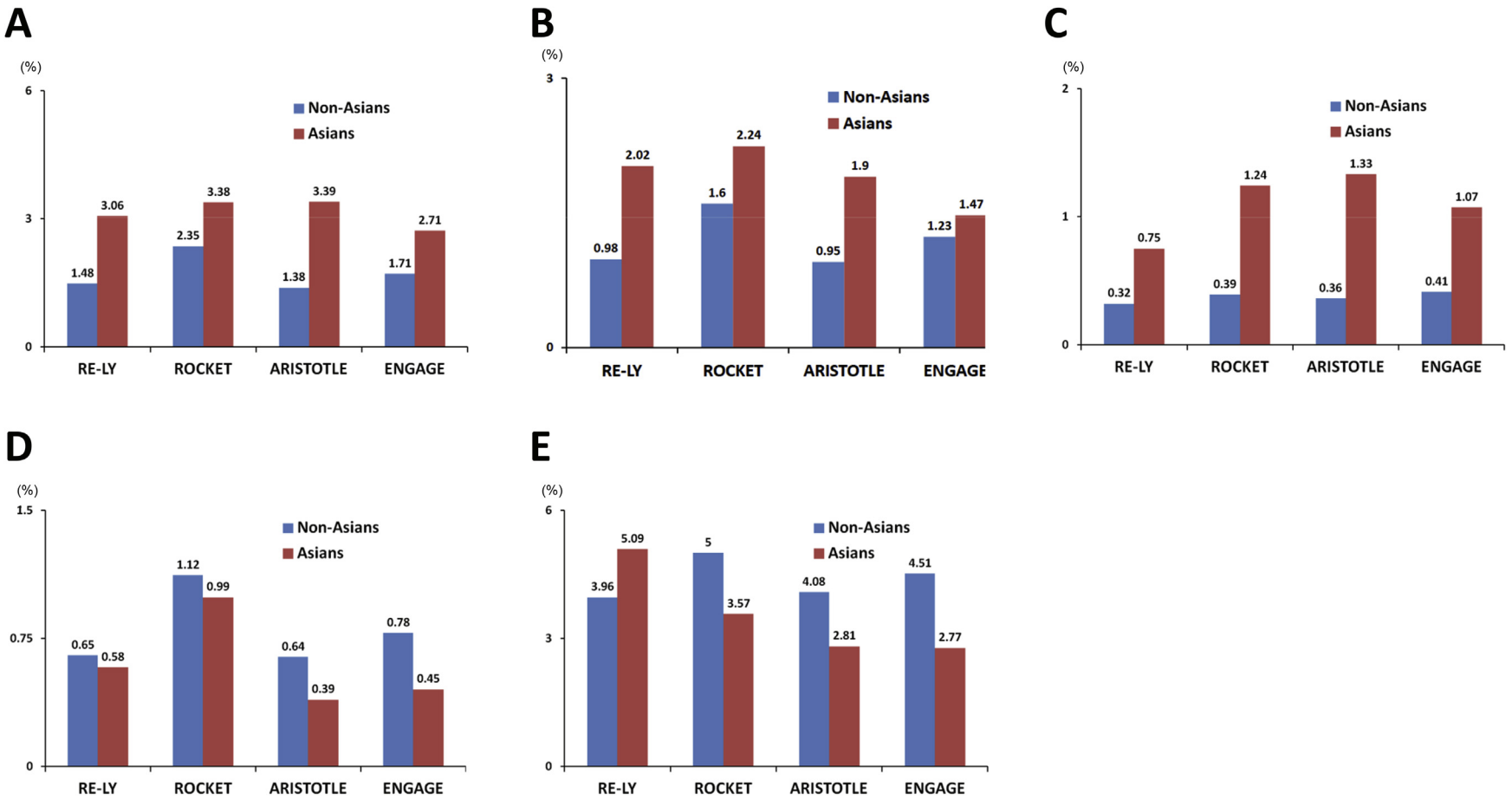

Figure 7 Major cardiovascular events on warfarin in Asians versus non-Asians, from the randomized trials. (A) Stroke and systemic embolization events; (B) ischemic stroke; (C) hemorrhagic stroke; (D) myocardial infarction; (E) all-cause death. Modified from Lip et al[149] with permission.

(more patients with INR <2.0). The risk of MI and all-cause mortality did not differ significantly.

Fact

- When warfarin is used, Asian patients have a higher risk of stroke, major bleeding, and ICH compared with non-Asians, despite the average anti-coagulation intensity of warfarin being lower in Asians.

9.6.3.3. NOACs in Asians versus non-Asians. The differences in efficacy endpoints (stroke/SEEs, ischemic stroke, hemorrhagic stroke, MI, all-cause mortality, and CV mortality) and safety endpoints (major bleeding, ICH, gastrointestinal bleeding, and bleeding of any cause) in the four RCTs have been analyzed and published.[149] Table 12 summarizes the effectiveness and safety of each NOAC comparing with warfarin. These important messages from the Asian subanalyses of the four RCTs of NOACs strongly suggested the great advantages of using NOACs in the stroke prevention in AF patients in Asia. The performance of most NOACs were even better in Asians than in non-Asians. Although these are subgroup analyses, randomization processes were undertaken in Asia, and most of the confounders were randomized and evenly distributed in the NOAC group and the warfarin group.[85–87,148] Moreover, the total number of Asian patients is > 7600, more than any previous study on anticoagulants in Asia. There has been no head-to-head RCT to compare different NOACs. The superiority of one NOAC over the other cannot be stated.

9.6.3.4. Meta-analysis of NOACs in Asia. In a recent meta-analysis, the differences in efficacy and safety outcomes of NOACs in Asian patients were compared with non-Asian patients.[150] The five RCTs included RE-LY, ROCKET AF, J-ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48, comprising of 8928 Asian patients (5250 with NOACs and 3678 with VKAs) and 64,033 non-Asian patients (37,800 with NOACs and 26,233 with VKAs).[81–88,148,151] There were two separate analyses: meta-analysis for standard-dose NOACs (dabigatran 150 mg, edoxaban 60 mg, rivaroxaban 20 mg, and apixaban 5 mg); and meta-analysis for low-dose NOACs (dabigatran 110 mg, edoxaban 30 mg, and rivaroxaban 15 mg).[150]

The efficacy of standard-dose NOACs and VKAs in Asians and in non-Asians is shown in Figure 8.[150] Standard-dose NOACs significantly reduced stroke/SEE both in Asian and non-Asian patients [odds ratio (OR), 0.65; 95% CI, 0.52–0.83; $p < 0.001$ for Asian patients; OR, 0.85; 95% CI, 0.77–0.93; $p < 0.001$ for non-Asian patients].[150] The reduction was more robust in Asian patients than in non-Asian patients (p interaction = 0.045). The effect of standard-dose NOACs on ischemic stroke and MI was similar to VKAs in both Asian and non-Asian patients (p interaction = 0.673 and 0.977, respectively). All-cause mortality was significantly lower in both with standard-dose NOACs than with VKAs (OR, 0.80; 95% CI, 0.65–0.98; $p = 0.030$ for Asian patients; OR, 0.91; 95% CI, 0.86–0.97; $p = 0.003$ for non-Asian patients; p interaction = 0.219).[150]

Figure 9 shows safety outcomes of standard-dose NOACs in Asian versus non-Asian patients.[150] Standard-dose NOACs reduced major bleeding more in Asian than in non-Asian patients (OR, 0.57; 95% CI, 0.44–0.74; $p < 0.001$ for Asian patients; OR, 0.89; 95% CI, 0.76–1.04; $p = 0.143$ for non-Asian patients; p interaction = 0.004). ICH was significantly reduced in both populations with standard-dose NOACs (OR, 0.33; 95% CI, 0.22–0.50; $p < 0.001$ for Asian patients; OR, 0.52; 95% CI, 0.42–0.64; $p < 0.001$ for non-Asian patients; p interaction = 0.059). Standard-dose NOACs had a more significant reduction in hemorrhagic stroke in Asian than in non-Asian patients (OR, 0.32; 95% CI,

Table 12 Efficacy and safety endpoints of different NOACs in Asians.[85–88,148]

	Stroke/ SEE	Ischemic stroke	Hemorrhagic stroke	Myocardial infarction	All-cause death	CV death	Major bleeding	Intracranial hemorrhage	GI bleeding	Bleeding of any cause
Dabigatran [a] 150 mg	V	V	V			NR	V	V		V
Dabigatran [a] 110 mg			V			NR	V	V		V
Rivaroxaban [b]								V	NR	
Apixaban [c]			V			NR	V	V	NR	V
Edoxaban [d] 60 mg			V		V	V	V	V		V
Edoxaban [d] 30 mg			V				V	V		V

GI = gastrointestinal; NOACs = non-vitamin K antagonist oral anticoagulants; NR = not reported; SEE = systemic embolization events; V = p value less than 0.05 when compared with warfarin.

[a] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India.

[b] China, South Korea, Taiwan, Hong Kong.

[c] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia.

[d] China, Japan, South Korea, Taiwan. Modified from Lip et al[149] with permission.

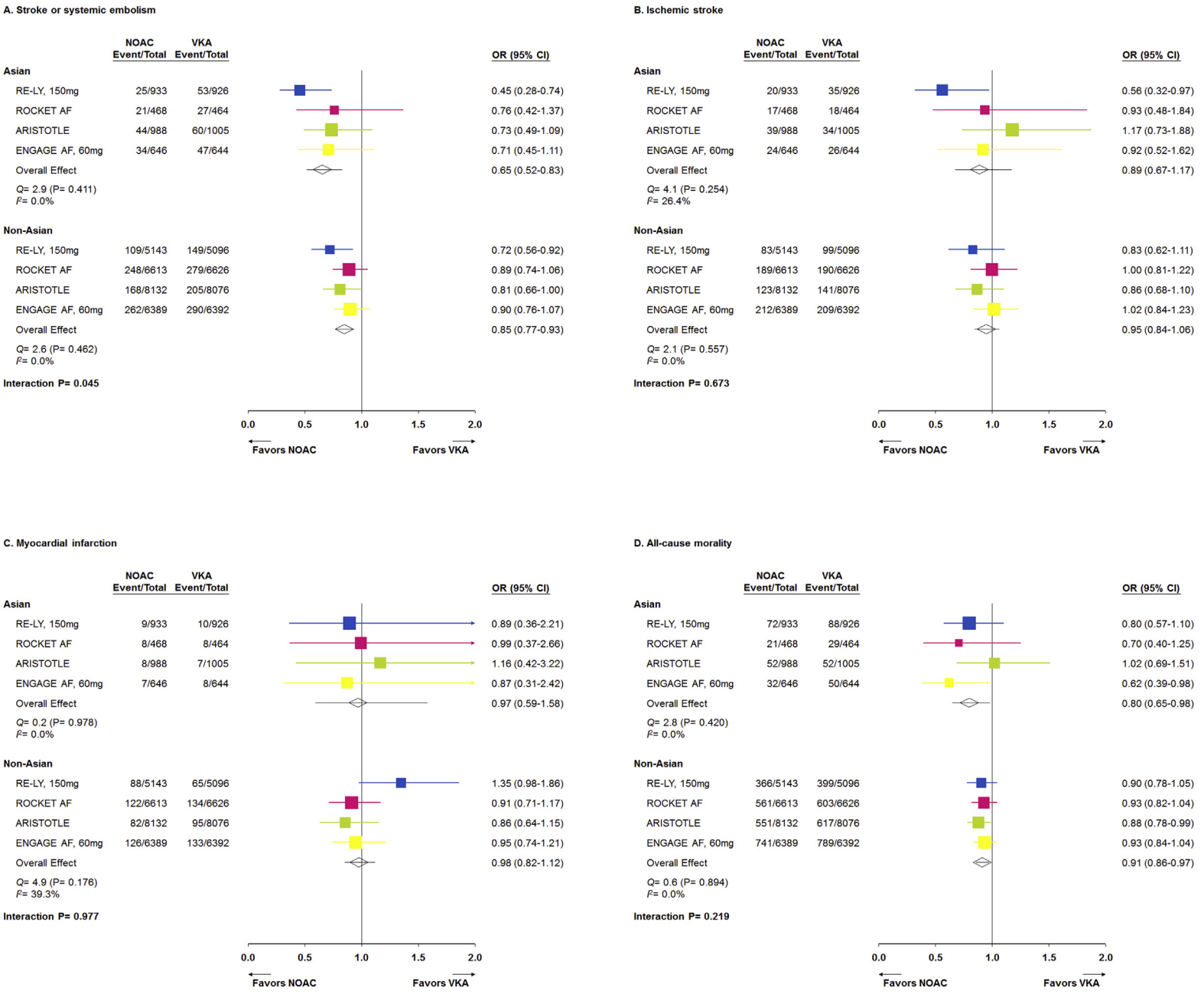

Figure 8 Efficacy outcomes of (A) stroke or systemic embolism, (B) ischemic stroke, (C) myocardial infarction, and (D) all-cause mortality for the standard-dose non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) versus VKAs. Modified from Wang et al[150] with permission. CI = confidence interval; OR = odds ratio.

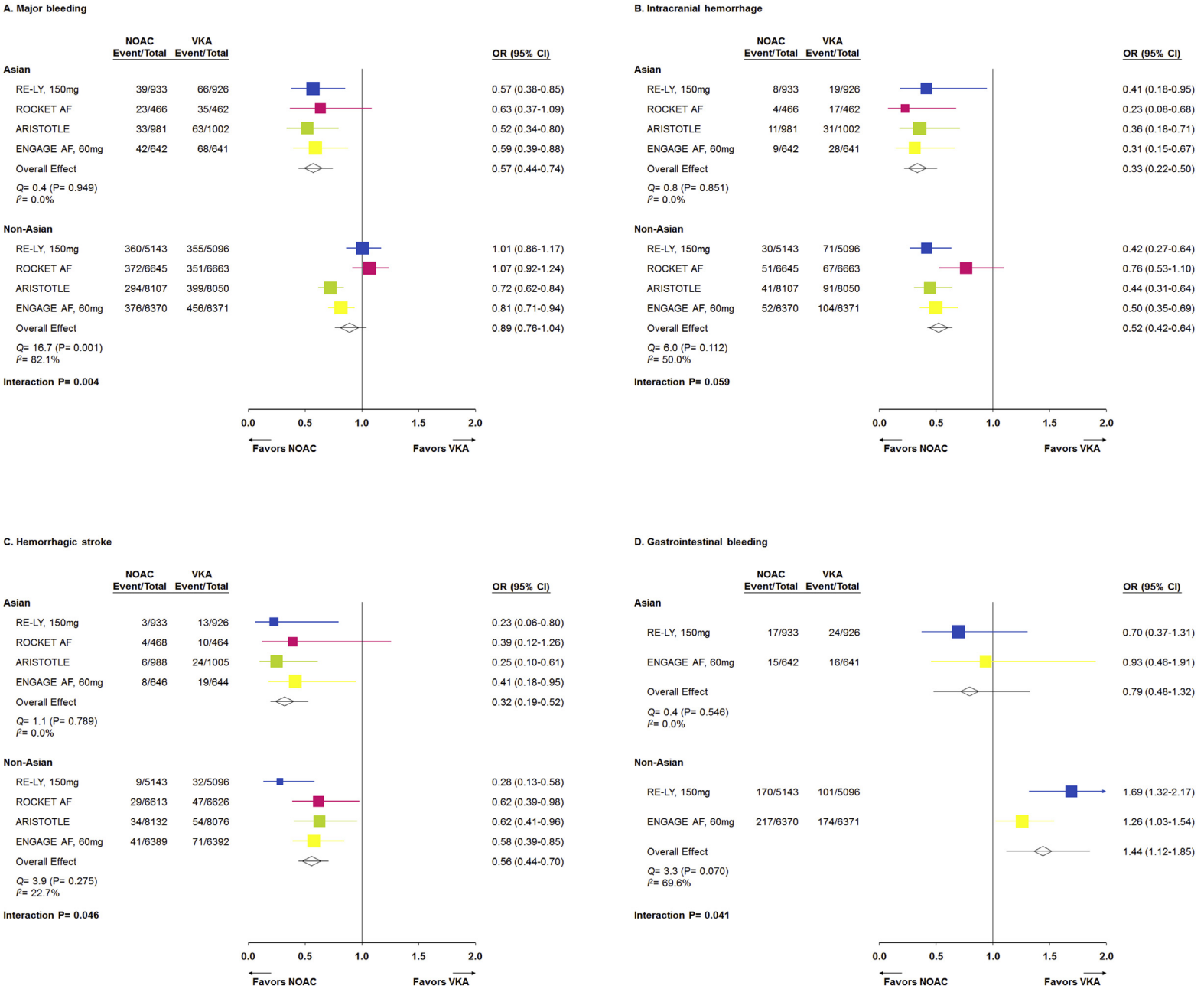

Figure 9 Safety outcomes of (A) major bleeding, (B) intracranial hemorrhage, (C) hemorrhagic stroke, and (D) gastrointestinal bleeding for the standard-dose non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) versus VKAs. Modified from Wang et al[150] with permission. CI = confidence interval; OR = odds ratio.

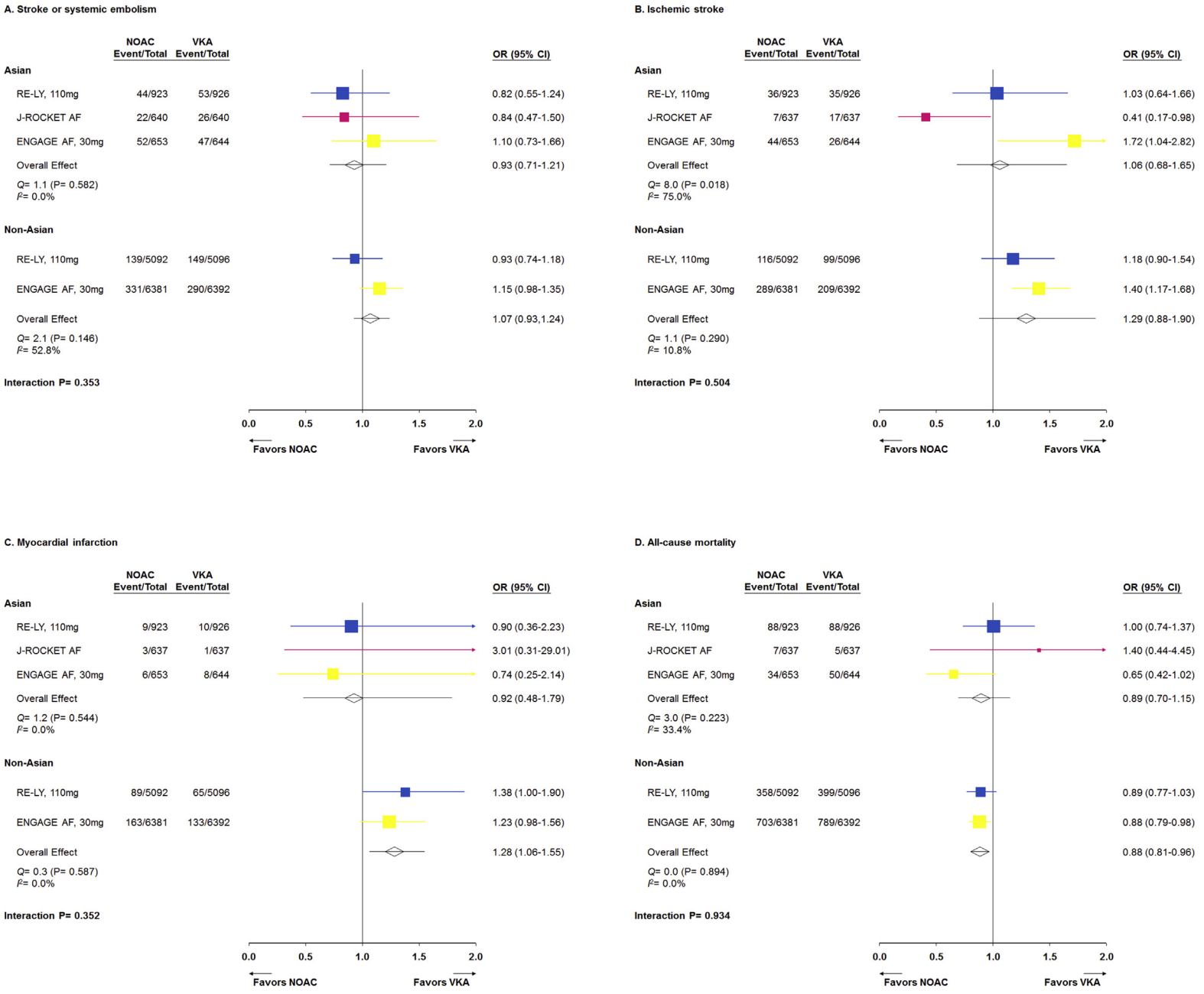

Figure 10 Efficacy outcomes of (A) stroke or systemic embolism, (B) ischemic stroke, (C) myocardial infarction, and (D) all-cause mortality for the low-dose non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) versus VKAs. Modified from Wang et al[150] with permission. CI = confidence interval; OR = odds ratio.

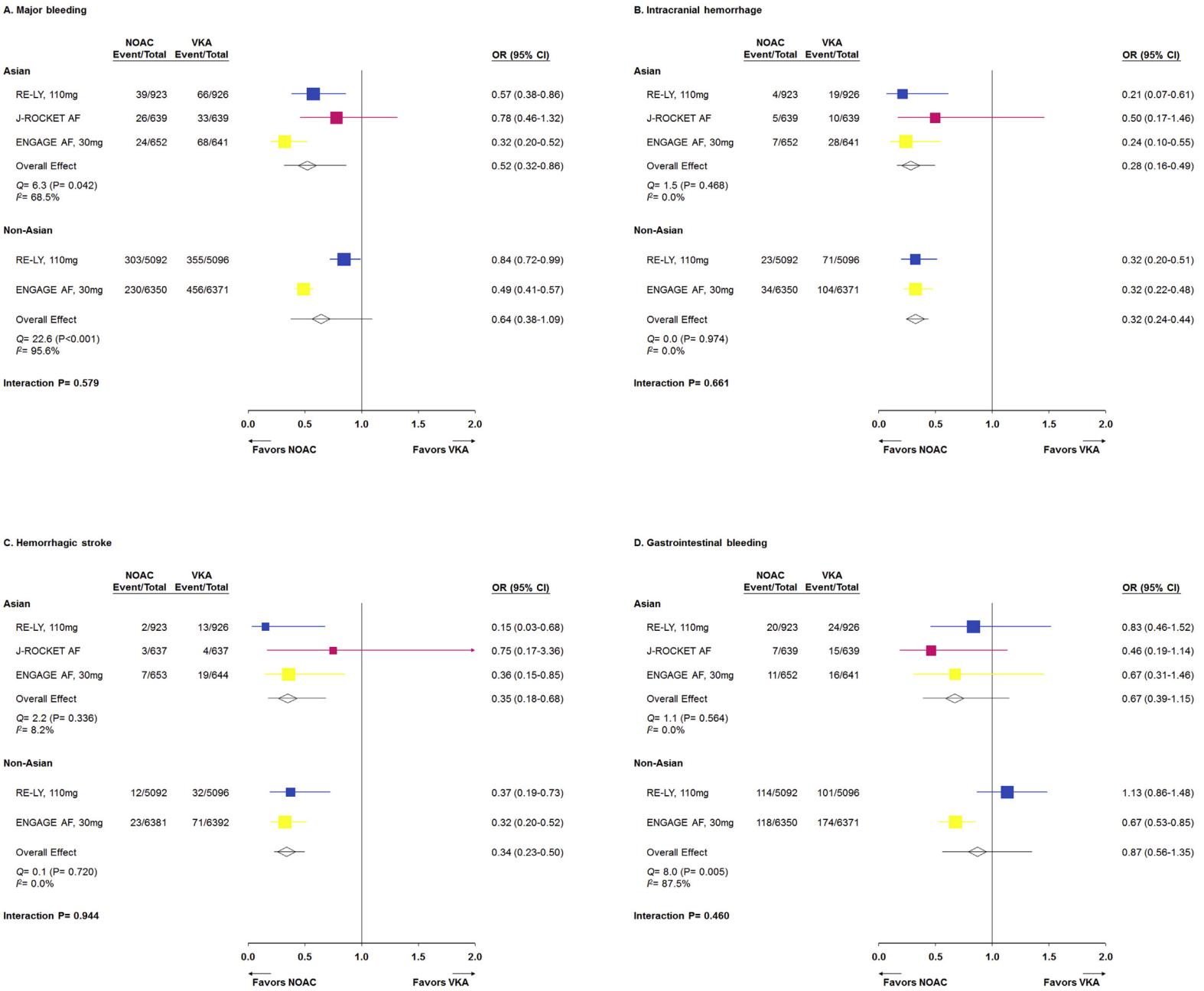

Figure 11 Safety outcomes of (A) major bleeding, (B) intracranial hemorrhage, (C) hemorrhagic stroke, and (D) gastrointestinal bleeding for the low-dose non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) versus VKAs. Modified from Wang et al[150] with permission. CI = confidence interval; OR = odds ratio.

0.19—0.52; $p < 0.001$ for Asian patients; OR, 0.56; 95% CI, 0.44—0.70; $p < 0.001$ for non-Asian patients; p interaction = 0.046) compared with VKAs. Moreover, standard-dose NOACs increased the risk of gastrointestinal bleeding in non-Asian patients but not in Asian patients (OR, 1.44; 95% CI, 1.12—1.85; $p = 0.005$ for non-Asian patients; OR, 0.79; 95% CI, 0.48—1.32; $p = 0.378$ for Asian patients; p interaction = 0.041).

The comparison of low-dose NOACs and VKAs with regard to the various efficacy outcomes is presented in Figure 10.[150] Low-dose NOACs had similar efficacy to VKAs on stroke or SEE and ischemic stroke both in Asian and non-Asian patients (p interaction = 0.353 and 0.504, respectively). With regard to MI, non-Asian patients had more events with low-dose NOACs than with VKAs (OR, 1.28; 95% CI, 1.06—1.55; $p = 0.010$), whereas the effect of low-dose NOACs seemed to be similar to VKAs in Asian patients (OR, 0.92; 95% CI, 0.48—1.79; $p = 0.816$); however, there was no statistical heterogeneity (p interaction = 0.352). Low-dose NOACs were associated with a significant reduction in all-cause mortality in non-Asian patients and a trend for a reduction in Asian patients (p interaction = 0.934).

The safety outcomes of low-dose NOACs are presented in Figure 11.[150] Low-dose NOACs reduced major bleeding, ICH, and hemorrhagic stroke in both Asian and non-Asian patients (p interaction = 0.579, 0.661, and 0.944, respectively). There was no difference in gastrointestinal bleeding in Asians and non-Asians (p interaction = 0.460).

Overall, standard-dose NOACs were more effective and safer in Asians than in non-Asians. The increased risk of GI bleeding was not found in Asians. Low-dose NOACs performed similarly in efficacy in both populations, but the safety was much better than warfarin in both populations. Increased risk of MI was not found in Asians.[150]

Recommendations

- Standard-dose NOACs are more effective and safer than warfarin in Asians, and should be recommended as first choice for the stroke prevention in Asians.
- Low-dose NOACs are equally effective as, but safer than warfarin in Asians, and should be recommended as therapeutic choice when standard-dose NOACs are not appropriate, such as in patients with age $\geq$ 75 years or in those patients with moderate to severe chronic kidney disease [CKD; creatinine clearance rate (CCr) 30—49 mL/min]. For apixaban, the lower dose is used in patients with two or more of the following criteria: age $\geq$ 80 years, body weight $\leq$ 60 kg, or serum creatinine $\geq$ 1.5 mg/dL.

9.6.4. Cost-effectiveness of NOAC in Taiwan

Several cost-effectiveness analyses comparing warfarin with dabigatran have been done in the west and have shown an incremental cost-effectiveness ratio between CAD$9,041 and USD$86,000 per quality-adjusted-life-year (QALY).[152,153] However, results from these studies may not be applicable to Asian countries, where the disease patterns and treatment patterns are different. The low rate of antithrombotic therapy and the low INR maintained with warfarin users in Taiwan suggest that the avoidable morbidity and mortality due to under-utilization could be significant if a more effective and safer medication can be adopted for warfarin-eligible patients.[118] Moreover, the healthcare systems and healthcare cost structures in Taiwan are very different from those in western countries and other Asian countries.

A cost-effectiveness analysis to evaluate the value of dabigatran to prevent stroke and SEE in patients with AF in Taiwan has recently been reported.[117] Dabigatran was given through sequential dosing, where patients aged $<$ 80 years received 150 mg of dabigatran twice a day and the dosage was reduced to 110 mg for patients aged $\geq$ 80 years. Dabigatran was compared with warfarin under two scenarios: the *real-world adjusted-dose* warfarin assuming all AF patients eligible for warfarin were given the medication and maintained at the INR observed in routine clinical practice in Taiwan, and the *real-world prescribing behavior* similar to the treatment with antithrombotics in real-world practice in Taiwan, where eligible patients could receive warfarin, aspirin, or no treatment. It was found that the incremental cost-effectiveness ratio was US$280/QALY in the real-world prescribing scenario and US$10,551/QALY in real-word warfarin use.[117] It is suggested that dabigatran is highly cost-effective in a clinical practice setting where warfarin has been significantly undeused.[117] Cost-effectiveness analysis of other NOACs has not been reported in Taiwan.

Fact

- Dabigatran is highly cost-effective in clinical settings in Taiwan.

9.6.5. Reversal agents

Patients who experienced major bleeding on dabigatran required a shorter stay in intensive care and had a trend to lower mortality compared with those who had major bleeding on warfarin.[154] Nonetheless, it has always been a concern that NOACs do not have reversal agents to normalize the coagulation activity. Idarucizumab, a monoclonal antibody fragment, binds dabigatran with an affinity that is 350 times as high as that observed with thrombin.[155] Consequently, idarucizumab binds free and thrombin-bound dabigatran and neutralizes its activity.[155] The REVERSE AD study was undertaken to examine the efficacy and safety of idarucizumab in dabigatran-treated patients who had serious bleeding or required urgent procedures.[156] In the recent interim analysis of the first 90 patients, idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.[156] Immediately after the administration of idarucizumab, the concentration of unbound dabigatran was reduced to a level at or near the lower limit of quantification in all but one patient.[156] On October 16, 2015, the US FDA granted accelerated approval to idarucizumab (Praxbind) to reverse the blood-thinning effects of dabigatran rapidly.

Andexanet-α (andexanet) is a specific reversal agent that is designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors.[157] Andexanet is a recombinant modified human factor Xa decoy protein that is catalytically inactive but that retains the ability to bind factor Xa inhibitors in the active site with high affinity and a 1:1 stoichiometric ratio. In a recently published clinical trial, healthy older volunteers were given 5 mg of apixaban twice daily or 20 mg of rivaroxaban daily.[158] Among the apixaban-treated participants, anti-factor Xa activity was reduced by 94% among those who received an andexanet bolus, as compared with 21% among those who received placebo ($p < 0.001$), and unbound apixaban concentration was reduced by 9.3 ng/mL versus 1.9 ng/mL ($p < 0.001$); thrombin generation was fully restored in 100% versus 11% of the participants ($p < 0.001$) within 2–5 minutes. Among the rivaroxaban-treated participants, anti-factor Xa activity was reduced by 92% among those who received an andexanet bolus, as compared with 18% among those who received placebo ($p < 0.001$), and unbound rivaroxaban concentration was reduced by 23.4 ng/mL versus 4.2 ng/mL ($p < 0.001$); thrombin generation was fully restored in 96% versus 7% of the participants ($p < 0.001$). These effects were sustained when andexanet was administered as a bolus plus an infusion. It is concluded that andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects.[158] The ongoing ANNEXA-4 phase 3b–4 study (ClinicalTrials.gov number, NCT02329327) is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor–associated acute major bleeding.

9.7. Management algorithm in Asians

In recently updated AF guidelines,[91,93,159] warfarin was still placed as one of the first choices for stroke prevention. In the recent analysis of the Asian data from the four RCTs,[96,150] it is clear that warfarin is difficult to use in Asians, and well-controlled INRs do not preclude the risk of ICH.[160] NOACs are much better than warfarin both in efficacy and the safety endpoints, and thus NOACs should be preferentially indicated for stroke prevention in AF for Asians.[150] Aspirin is ineffective for stroke prevention in Asian AF patients,[112] and antiplatelet therapy should not be used unless both NOACs and warfarin are refused or not tolerated.

Because the CHA_2DS_2-VASc score has outperformed other scoring systems in predicting AF-associated stroke in Asians,[161,162] the TSOC/THRS AF guidelines strongly recommend the use of CHA_2DS_2-VASc score in the prediction of stroke risk in Taiwan.

There is some debate as to whether we should treat patients with a CHA_2DS_2-VASc score ≥ 1 or ≥ 2, but the net clinical benefit is positive in favor of OAC in patients with at least one stroke risk factor, but neutral or negative for aspirin.[163]

In a recent report using the NHIRD in Taiwan,[161] a total of 186,570 AF patients without antithrombotic therapy were analyzed. The annual risk of ischemic stroke in patients with a single additional stroke risk factor [i.e., CHA_2DS_2-VASc score = 1 (men) or 2 (women)] was 2.75% for men and 2.55% for women.[162] These numbers are well above the annual risk of NOAC-induced ICH in Asians, but were not much different from the risk of warfarin-induced ICH in Asians (Figure 12). It would be reasonable to suggest starting the use of NOACs instead of warfarin in Asians with a CHA_2DS_2-VASc score = 1 in men or 2 in women. Since AF patients with a CHA_2DS_2-VASc score = 1 were included in the RE-LY trial and the ARISTOTLE trial but not included in the ROCKET or ENGAGE trials, rivaroxaban and edoxaban are recommended only in patients with a CHA_2DS_2-VASc score ≥ 2.

The CHA_2DS_2-VASc score has been shown to be best to identify low risk patients, even in Asian cohorts.[164] Hence, rather than a categorized approach to stroke risk stratification, the initial management approach should be to initially identify low risk patients (i.e. CHA_2DS_2-VASc score

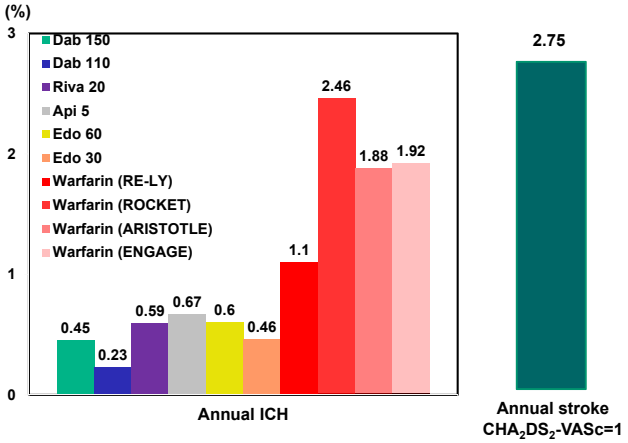

Figure 12 Rationale for using CHA_2DS_2-VASc score = 1 for threshold of using non-vitamin K antagonist oral anticoagulants in Asians. ICH = intracranial hemorrhage.

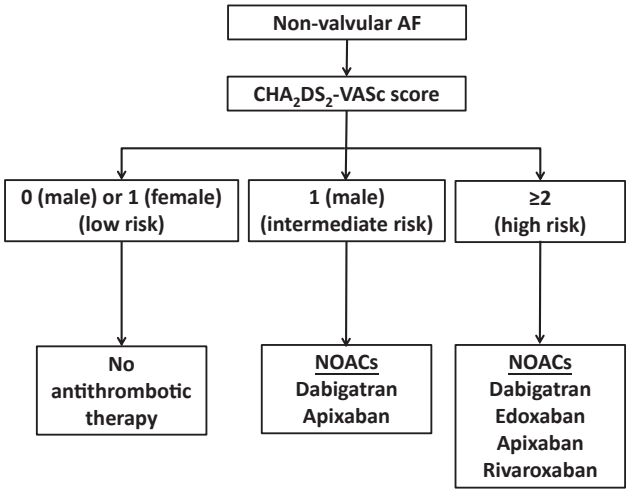

Figure 13 Management algorithm for stroke prevention in Asians. AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant. (Modified from Lip et al.[149] with permission.)

0 in men, 1 in women), no antithrombotic agent is recommended. The next step is to offer stroke prevention (which is OAC) to patients with $\geq$ 1 stroke risk factors. The suggested management algorithm in AF patients in Asia is illustrated in Figure 13.

Recommendations

- NOACs should be preferentially indicated in stroke prevention for AF in Asia.
- The first step is to identify those patients with low risk (i.e. CHA_2DS_2-VASc score 0 in men, 1 in women), no antithrombotic agent is recommended.
- For patients with only one stroke risk factor using CHA_2DS_2-VASc (i.e. score = 1 in men or 2 in women), dabigatran or apixaban are recommended.
- For CHA_2DS_2-VASc score $\geq$ 2 (or $\geq$ 3 in women), any NOAC, including dabigatran, apixaban, rivaroxaban, or edoxaban, is recommended.

9.8. NOACs in clinical practice

9.8.1. Switching of OAC

An algorithm for switching anticoagulants is shown in Figure 14. INR monitoring is needed when switching between NOACs and warfarin. A bridging method (rivaroxaban, apixaban, and edoxaban) or overlapping method (dabigatran and edoxaban) can be used. INR should be checked at least twice weekly. The switching between NOAC and parenteral agents [unfractionated heparin (UFH) or low molecular weight heparin (LMWH)] is much easier.

9.8.2. Measurement of anticoagulation activity

It is not recommended to monitor the coagulation activity routinely. Neither the dose nor the dosing intervals should be altered in response to changes in laboratory coagulation parameters for the current registered indications.[141] In certain emergent conditions, such as serious bleeding and thrombotic events, requirement for urgent surgery, and suspected overdosing, assessment of drug exposure and a qualitative assessment of anticoagulation effect may be needed. Also, this may be needed in NOAC-users suffering from ischemic stroke when thrombolytic therapy is to be considered, to ascertain if there is a systemic anticoagulant effect from the NOAC.

The coagulation activity of NOACs should be checked at the trough level, i.e., 12 hours or 24 hours after ingestion of the same dose. The activated partial thromboplastin time (aPTT) may provide a qualitative assessment of the presence of dabigatran.[141,165] If the aPTT level at trough (i.e. 12–24 hours after ingestion) still exceeds two times the upper limit of normal, this may be associated with a higher risk of bleeding. By contrast, a normal aPTT in dabigatran-treated patients can be used to exclude any relevant remaining anticoagulant activity. The ecarin clotting time assay can provide a direct measurement of the activity of dabigatran, while dilute thrombin time can more accurately predict dabigatran anticoagulation. Both of these tests are not routinely performed. Dabigatran has little effect on the prothrombin time (PT) and INR at clinically relevant plasma concentrations.[141]

Rivaroxaban has a concentration-dependent prolongation of PT, but the prolongation has no known relation with bleeding risk. For apixaban and edoxaban, the PT cannot be used for assessing their anticoagulant effects, and an anti-factor Xa activity assay should be used. One should be careful that conversion of PT to INR is not corrected for the variations and even increases the variability. Therefore,

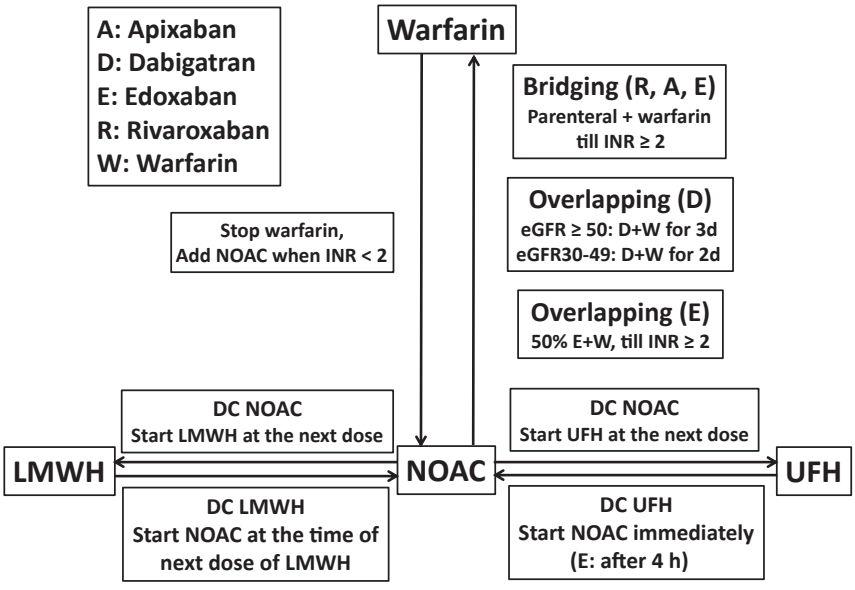

Figure 14 Switching algorithm of anticoagulants. DC = discontinue; eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2); INR = international normalized ratio; LMWH = low molecular weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; UFH = unfractionated heparin.

the INR is completely unreliable for the evaluation of Xa inhibitory activity.[141]

There have been no data on the true cut-off levels of any coagulation test to predict the bleeding risk of NOACs. Moreover, whether measurement of drug levels and dose adjustment based on laboratory parameters can reduce bleeding risk has not been studied.[141]

Recommendations

- Routine measurement of coagulation activity for NOACs is not recommended.
- In rare conditions, such as in NOAC-users suffering from ischemic stroke when thrombolytic therapy is considered, monitoring coagulation activity may be useful.
- aPTT can be used to assess the presence of an anticoagulant effect from dabigatran.
- PT, but not INR, can be used to assess the presence of an anticoagulant effect from rivaroxaban.
- Anti-factor Xa assay can be used to assess the anticoagulant effect of the factor Xa inhibitors (rivaroxaban, apixaban, edoxaban).

9.8.3. Drug—drug interaction

Unlike warfarin, NOACs are mostly free from food—drug interaction. Drug—drug interactions, however, need further address. An important interaction mechanism for all NOACs consists of significant re-secretion via a P-gp transporter after absorption in the gut. An inhibition or induction of P-gp results in significant changes in plasma levels. CYP3A4-type cytochrome P450-dependent elimination plays a more minor role in the interaction. Some important drug—drug interactions for NOACs are shown in Table 13.

9.8.4. Patients with chronic kidney disease

All NOACs are partially eliminated by the kidney (Table 8). Patients with mild-to-moderate CKD (CCr, 30—89 mL/min) have been randomized in RCTs of four NOACs, and the efficacy and safety have been confirmed.[81—84] For patients who have a CCr of 30—49 mL/min dabigatran 110 mg, instead of 150 mg, is recommended by some guidelines,[78,141] although subgroup analysis still favors 150 mg in patients with a CCr of 30—49 mL/min.[166]

There are no efficacy and safety data for NOACs in patients with advanced CKD (CCr $<$ 30 mL/min), and these guidelines recommend against their use in such patients, similar to ESC guidelines.[78,141] For patients with end-stage CKD, neither warfarin nor NOACs have prospective data. Warfarin with high TTR ($>$ 70%) is recommended in patients with end-stage CKD by most guidelines.[141]

Renal function needs to be monitored yearly in patients on NOACs to detect changes in renal function and dose adjust accordingly. For patients with impaired renal function (CCr $<$ 60 mL/min), renal function should be checked every 6 months, especially in patients receiving dabigatran or edoxaban which depend more on renal clearance.[141] The EHRA practical guide suggests that if renal function is impaired (i.e. CCr $\leq$ 60 mL/min, one could specify a recheck interval of a number of months.[142]

Recommendations

- For patients with stage III CKD (CCr 30—49 mL/min), dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily, or edoxaban 30 mg once daily may be considered.
- For patients stage IV or V CKD, including those on hemodialysis, NOACs should not be used. Warfarin with high TTR ($>$ 70%) is recommended.

9.8.5. Patients with coronary heart disease

Both during elective or urgent percutaneous coronary intervention (PCI), NOACs should be preferably be temporarily discontinued in patients with stable CHD or upon presentation of ACS, as what has been followed during all the four RCTs of NOACs.[141] Temporary discontinuation of NOACs allows safe initiation of antiplatelet therapy and standard anticoagulation practices periprocedurally.[141] The use of ticagrelor or prasugrel as part of the triple therapy

Table 13 Drug—drug interaction for NOACs.

	Mechanism	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Amiodarone	P-gp	50% dose If $\geq$ 75 y	50% dose If $\geq$ 75 y	50% dose If $\geq$ 75 y	50% dose If $\geq$ 75 y
Dronedarone	P-gp, CYP3A4	X	No data	No data	50% dose
Verapamil	P-gp	50% dose	No data	No effect	No data
Rifampin	P-gp, CYP3A4	X	X	X	X
HIV protease inhibitor	P-gp, CYP3A4	X	X	X	X
Intraconazole and ketoconazole	P-gp, CYP3A4	X	X	X	50% dose
Carbamazepine, phenobarbital, and phenytoin	P-gp, CYP3A4	X	X	X	X

HIV = human immunodeficiency virus; NOACs; non-vitamin K antagonist oral anticoagulants; P-gp = P-glycoprotein; X = contraindication.

regimen is not recommended, given that their bleeding risk associated with NOACs is unknown.[167] For all stable CHD patients with AF, the rule-of-thumb is to use anticoagulation as monotherapy and to discontinue any antiplatelet agents at 1 year after presentation with their ACS, except for those with a very high risk of coronary events and an acceptably low bleeding risk.[141]

Recommendations

- During both elective or urgent PCI, NOACs should be preferably discontinued in patients with stable CHD or upon presentation of ACS, to allow safe initiation of antiplatelet therapy and standard anticoagulation practices periprocedurally.
- The inclusion of ticagrelor or prasugrel in the triple therapy is not recommended, because their bleeding risk associated with NOACs is unknown.
- Following presentation with an ACS or a PCI/stent procedure, AF patients should be managed with triple therapy (OAC plus aspirin plus clopidogrel), for 3—6 months (shorter duration if high bleeding risk) followed by dual therapy (OAC plus single antiplatelet, preferably clopidogrel) until 1 year, following which the patient should be managed with OAC monotherapy alone. OAC refers to warfarin with TTR $>$ 70% or a NOAC.
- Where an NOAC is used in combination with antiplatelet therapy, the lower tested NOAC dose used for stroke prevention in AF should be used (i.e. dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily, edoxaban 30 mg).

9.8.5.1. Patients with acute coronary syndrome. There has been no RCT comparing VKA and NOACs in patients with AF undergoing PCI for ACSs. Moreover, there are no RCTs to evaluate new antiplatelets, such as prasugrel or ticagrelor, in patients with AF receiving either VKA or NOACs. In general, adding a single antiplatelet therapy drug to any type of oral anticoagulants increases the risk of major bleeding by 60—80%; adding DAPT increases the risk of major bleeding by 130% over anticoagulants alone.[168,169] Therefore, these data indicate that triple therapy should be kept as short as possible. Strategies that reduce the bleeding risk in patients with AF and ACS include: (1) low doses of aspirin (75—100 mg), especially when combined with a P2Y12 inhibitor; (2) new-generation drug-eluting stents (DES) to minimize the duration of triple therapy; (3) a radical approach for interventional procedures to reduce the risk of access site bleeding; and (4) proton-pump inhibitors should be considered in all patients with a combination of antiplatelets and anticoagulants.[141]

In stabilized patients who do not have recurrent ischemia or need for other invasive procedure, OAC can be restarted after parenteral anticoagulation is stopped. The same NOAC that the patient was taking prior to the ACS can be restarted.[141]

In patients with an ACS and treated with medical therapy or PCI, 6 months of triple therapy should be recommended prior to stepping down to double therapy. The duration of triple therapy can be shortened to 1 month or the triple therapy can be replaced with double therapy in patients with an extremely high risk of bleeding. Standard 12-month triple therapy can be considered in patients receiving a first-generation DES or those with a combination of very high atherothrombotic risk and low bleeding risk.[141]

Recommendations

- Strategies that reduce the bleeding risk in patients with AF and ACS include: (1) low doses of aspirin (75—100 mg), especially when combined with a P2Y12 inhibitor; (2) third-generation DESs to minimize the duration of triple therapy; (3) a radical approach for interventional procedures to reduce the risk of access site bleeding; and (4) proton-pump inhibitors should be considered in all patients with a combination of antiplatelets and anticoagulants.
- In patients with an ACS and treated with medical therapy or PCI, 3—6 months of triple therapy should be recommended prior to stepping down to double therapy.
- The duration of triple therapy can be shortened to 1 month or the triple therapy can be replaced with dual therapy (i.e. OAC plus clopidogrel) in patients at extremely high risk of bleeding.
- Standard triple therapy for 12 months can be considered in patients receiving a first-generation DES or those with a combination of very high atherothrombotic risk and low bleeding risk.

9.8.5.2. Patients with elective PCI. In stabilized patients who do not have recurrent ischemia or need for other invasive procedure, OAC can be restarted after parenteral anticoagulation is stopped. The same NOAC that the patient was taking prior to the ACS can be re-started.[141]

All phase III trials of NOACs allowed the concomitant use of aspirin ($\leq$ 100 mg/d) for patients undergoing PCI, but only the RE-LY trial included a substantial number of patients on concomitant clopidogrel with or without aspirin.[170] Several RCTs were ongoing to test NOACs versus warfarin in combination with aspirin and/or P2Y12 inhibitors (RE-DUAL-PCI for dabigatran NCT 02164864, PIONEER-AF-PCI for rivaroxaban NCT 01830543, and AUGUSTUS for apixaban NCT 02415400).

AF patients should be managed with triple therapy (OAC plus aspirin plus clopidogrel), for 3—6 months (shorter duration if high bleeding risk) followed by dual therapy (OAC plus single antiplatelet, preferably clopidogrel) until 1 year, following which the patient should be managed with OAC monotherapy alone. OAC refers to warfarin with TTR $>$ 70% or a NOAC.[141] In patients with a high bleeding risk or a low atherothrombotic risk, the duration of triple therapy can be shortened and the duration of combination therapy can be abbreviated to 3—6 months. By contrast, longer duration of triple therapy (3—6 months) may be considered

in patients receiving first-generation DES, or in patients with high atherothrombotic risk and low bleeding risk.

Recommendations

- For patients receiving elective PCI, triple therapy [OAC plus low dose aspirin (75—100 mg) plus clopidogrel] 1 month (for a bare metal stent or newer DES) is recommended, thereafter stepping down to double therapy (OAC and clopidogrel) until 1 year. OAC alone is adequate after 1 year.
- In patients with a high bleeding risk or a low atherothrombotic risk, the duration of triple therapy (for a bare metal stent or newer DES) can be shortened and the duration of dual therapy (with OAC and clopidogrel) can be abbreviated to 3—6 months. OAC alone is adequate thereafter.
- Longer duration triple therapy (3—6 months) may be considered in patients receiving first-generation DES, or in patients with high atherothrombotic risk and low bleeding risk, thereafter stepping down to double therapy (with OAC and clopidogrel) until 1 year. OAC alone is adequate after 1 year.
- When VKA is combined with DAPT, the preferred INR is 2.0—2.5.
- When an NOAC is combined with DAPT, lower doses of NOACs are preferred, such as dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily, or edoxaban 30 mg once daily.
- There is no preference for one NOAC over another.

9.8.5.3. Patients with chronic stable coronary heart disease. Combining single antiplatelet therapy or DAPT with chronic NOAC or VKA significantly increases bleeding risk.[170—172] There is no RCT comparing VKA and NOAC in this setting. Patients with stable CHD who have AF should receive anticoagulation, depending on their CHA_2DS_2-VASc score. Anticoagulation alone without additional antiplatelet is recommended for most AF patients who have stable CHD.[141,167,173] A recent Danish registry showed that adding an antiplatelet agent to VKA in stable CHD patients increased bleeding risk without any benefits in atherothrombotic or thromboembolic events.[172] In Asian patients, NOACs are preferred over warfarin for patients with AF and stable CHD.[149]

Recommendations

- Monotherapy with an NOAC is preferable for patients with AF and stable CHD. This suggestion is applicable to all NOACs.
- In the absence of direct comparative studies, no particular NOAC can be favored over another.

9.8.6. Patients with stroke

Warfarin is superior to aspirin and placebo in the prevention of recurrent stroke after TIA or stroke in patients with AF.[174,175] All RCTs comparing NOACs versus warfarin had subgroups of patients with prior stroke or TIA. In a meta-analysis of 14,527 patients with prior stroke or TIA from the RE-LY trial, the ROCKET AF trial, and the ARISTOTLE trial, NOACs were associated with a significant reduction in the incidence of recurrent stroke and SEEs compared with warfarin (OR 0.85, CI 0.74—0.99).[176] The risk of major bleeding was also decreased (OR 0.86, CI 0.75—0.99), mainly due to a significant reduction in the incidence of hemorrhagic stroke (OR 0.44, CI 0.32—0.62).

Use of combination therapy with an OAC and an antiplatelet after TIA or stroke is not suggested, because combination therapy did not prevent ischemic events, but increased the risk of major bleeding.[174,175,177] In patients suffering from stroke or TIA during well-treated warfarin therapy, substitution with a NOAC is reasonable.[174,175]

Recommendations

- NOACs as a group are superior to warfarin for secondary prevention stroke prevention.
- The combination of aspirin plus OAC does not prevent ischemic stroke better than OAC alone, and should be restricted to specific high-risk periods.

9.8.6.1. Patients with acute hemorrhagic stroke. Hemorrhagic stroke is a complication of anticoagulant therapy. VKA accounts for 12—14% of patients with ICH,[178] a risk that is even greater in Asian patients.[95] In the RE-LY trial, patients with ICH on dabigatran had the same poor prognosis as patients on warfarin.[179] The first step when encountering OAC-related ICH is discontinuation of the drug and supportive therapy. The coagulation status of patients under NOAC should be corrected as soon as possible, by using prothrombin complex concentrate (PCC), activated PCC (aPCC), and activated factor VII. In patients on dabigatran, the specific reversal agent, idarucizumab (a humanized antibody fragment that specifically binds dabigatran), can be used. Its effect has been supported by a recent clinical study.[156]

Recommendations

- The first step when encountering OAC-related ICH is discontinuation of the drug and supportive therapy.
- PCC, aPCC, and activated factor VII can be used to correct coagulation status.
- Idarucizumab can be used as a reversal agent in patients receiving dabigatran.

9.8.6.2. Patients with acute ischemic stroke. In patients on NOACs presenting with acute ischemic stroke, thrombolytic therapy should not be undertaken within 48 hours after the last administration of NOAC.[141] In case of uncertainty concerning last NOAC dosage time, a

prolonged aPTT (for dabigatran) or prolonged PT (for rivaroxaban) indicates that the patient is anticoagulated and thrombolysis should not be given. In patients treated with warfarin, the risk of ICH with use of thrombolytic agents appears to be low when the INR is $\leq$ 1.7.[180] We do not recommend the use of thrombolytics in situations with uncertainty about the anticoagulation status. In this situation, mechanical recanalization of occluded vessels with stent retrievers may be considered as an alternative treatment option.[141]

Decision on timing to start NOACs after acute ischemic stroke depends on infarct size and stroke severity.[141] Recommendations on the initiation of anticoagulation are based on consensus opinion,[141] in what is known as the *1-3-6-12 day rule*: in patients with TIA, NOAC can be initiated at Day 1. In patients with mild stroke [National Institute of Health Stroke Scale (NIHSS) $<$ 8], NOAC can be initiated after 3 days, or after ICH is excluded by imaging modality [computed tomography (CT) or magnetic resonance imaging (MRI)]. In patients with moderate stroke (NIHSS 8–16), NOAC can be initiated after 5–7 days, and in severe stroke (NIHSS $>$ 16) after 12–14 days.[141]

Recommendations

- In patients on NOACs presenting with acute ischemic stroke, thrombolytic therapy should not be undertaken within 48 hours after the last administration of NOAC, unless coagulation tests specific for the individual NOAC reveal low or absent anticoagulant effect.
- In patients on warfarin presenting with acute ischemic stroke, thrombolytic therapy can be given if INR is $\leq$ 1.7.
- Mechanical recanalization of occluded vessels with stent retrievers may be considered as an alternative treatment option for patients with acute ischemic stroke with proximal intracranial artery occlusion who are effectively anticoagulated with a NOAC.
- Reinitiation of anticoagulation can be based on the *1-3-6-12 day rule*: in patients with TIA, NOAC can be initiated at Day 1. In patients with mild stroke (NIHSS $<$ 8), NOAC can be initiated after 3 days, or after ICH is excluded by imaging modality (CT or MRI). In patients with moderate stroke (NIHSS 8–16), NOAC can be initiated after 5–7 days, and in severe stroke (NIHSS $>$ 16) after 12–14 days.

9.8.6.3. Patients with a history of hemorrhagic stroke. It is always a difficult decision on whether to initiate OAC in patients with a history of ICH. A recent Danish cohort study showed that in patients with a history of ICH OAC treatment was associated with a significant reduction in ischemic stroke/all-cause mortality rates (0.55, CI 0.39–0.78) in patients on oral anticoagulant treatment in comparison with no treatment.[181] Survival benefit was also reported from a recent cohort study from Germany.[182] OAC resumption showed fewer ischemic complications [OAC: 9/172 (5.2%) vs. no OAC: 82/547 (15.0%); $p < 0.001$] and not significantly different hemorrhagic complications [OAC: 14/172 (8.1%) vs. no OAC: 36/547 (6.6%); $p = 0.48$]. Propensity-matched survival analysis in patients with AF who restarted OAC showed a decreased HR of 0.258 (95%CI, 0.125–0.534; $p < 0.001$) for long-term mortality.[182] In a recent report from Taiwan NHIRD, warfarin use may be beneficial for AF patients with prior ICH having a CHA_2DS_2-VASc score $\geq$ 6.[183] Whether the use of NOACs can lower the threshold for treatment deserves further study.[183]

For patients with low cardioembolic risk and high ICH risk, the indication for OAC should be re-evaluated. Risk factors for increasing the risk of recurrence of ICH include: older age, persistent uncontrolled hypertension, lobal bleeds, cortical bleeds, amyloid angiopathy, severe white matter lesions, multiple microbleeds on MRI, chronic alcoholism, and need for DAPT after PCI.[141] On the other hand, NOAC can be restarted after 4–8 weeks if cardioembolic risk is high and the risk of new ICH is low. To decrease the risk of second episode ICH, unnecessary antiplatelet should be discontinued,[170] and the blood pressure (BP) should be controlled to $<$ 130/80 mmHg.[184]

One should know that in all the RCTs of NOACs, a history of spontaneous ICH was an exclusion criteria, unless the causes of the bleeding have been reversed. These reversible causes include uncontrolled hypertension, triple therapy, and INR $>$ 4–5 in patients on VKAs.[141] The subtypes of ICH are also related to the strategy of anticoagulation. In patients with epidural (always traumatic) and traumatic subdural hematoma, NOAC can be given after 4 weeks. For nontraumatic subdural hematoma (unless due to uncontrolled INR in patients with VKA), NOAC is contraindicated.[141] Otherwise NOAC can be used after 4 weeks.

Recommendations

- The use of NOAC in patients with a history of ICH should be individualized.
- NOAC can be restarted after 4–8 weeks if cardioembolic risk is high and the risk of new ICH is low.
- For patients with low cardioembolic risk and high ICH risk, the following risk factors for increasing risk of ICH should be evaluated prior to decision of using NOACs: lobar bleeds, cortical bleeds, amyloid angiopathy, severe white matter lesions, multiple microbleeds on MRI, chronic alcoholism, and need for DAPT after PCI.
- In patients with epidural and traumatic subdural hematoma, NOAC can be given after 4 weeks.
- For nontraumatic subdural (unless due to uncontrolled INR in patients with VKA), NOAC is contraindicated.

9.8.7. Perioperative use

For AF patients with higher thromboembolic risk treated with VKAs, bridging with LMWH or heparin was a generally accepted strategy. However, in a large systemic review and

meta-analysis of 34 observational studies of bridging anticoagulation,[185] Siegal et al[185] found an odds ratio of 3.6 (CI 1.52—8.50) for major bleeding with bridging vs. nonbridging, and no significant difference in thromboembolism or mortality. Therefore, the role of bridging strategy has been questioned.[186] The recent published BRIDGE trial provided the most compelling evidence that routine bridging in moderate-risk patients is harmful.[187] In the BRIDGE trial—a randomized, double-blinded, placebo controlled noninferiority study—1884 AF patients (valvular and nonvalvular) who were undergoing a procedure with planned warfarin interruption were randomized to anticoagulation bridging with the low molecular-weight heparin, dalteparin, or placebo. The average $CHADS_2$ score was 2.3, making the study population largely moderate risk for TE. The primary endpoints were arterial TE and major bleeding. The rate of arterial TE in the placebo group was noninferior to the bridging group (0.4% vs. 0.3%; $p = 0.01$ for noninferiority). Major and minor bleeding in the placebo group was significantly less than that in the bridging group (1.3% vs. 3.2%; $p = 0.005$; 12% vs. 20.9%; $p = 0.001$; respectively). There was no measurable difference among MI, deep vein thrombosis, pulmonary embolism, or death. This study confirms that no bridging is noninferior to bridging for preventing TE and is superior for reducing bleeding events.[187]

Unlike warfarin, NOACs are all rapidly absorbed after oral intake and reach maximal plasma concentration within 2—4 hours. After discontinuation, their anticoagulant effects diminish quickly because of short half-lives. These features of NOACs facilitate rapid interruption and reintroduction around the time of surgery. Therefore, bridging therapy with intravenous infusion of heparin or subcutaneous injection of LMWH is generally not necessary in NOAC-treated patients. The decision about the strategy of NOACs during the perioperative period should be made balancing the risk of bleeding against the risk of thromboembolism. Importantly, physicians and surgeons should try their best in technical aspects to reduce the bleeding complications of interventions, which may require prolonged interruption of NOACs and therefore expose patients to a higher risk of thromboembolic events.

For interventions that cause nonclinically important bleeding risk and/or when complete local hemostasis can be achieved easily, it may not be necessary to stop NOACs during the perioperative period (Table 14).[141,188,189] These interventions include dental procedures (such as tooth extraction and abscess incision), cataract or glaucoma surgery and endoscopy examination without tissue biopsy. Practically, these procedures can be scheduled at the trough concentration of the NOACs (12 hours after the last intake of dabigatran/apixaban; 24 hours after the last dosage of rivaroxaban and edoxaban). NOACs could be prescribed 4—6 hours postprocedures if complete hemostasis is achieved. In this way, patients just delay the scheduled dosage of NOACs for several hours without miss any dosage. However, patients should be informed about the potential risk of bleeding, and they should contact the physicians if the bleeding does not stop or recur.

Although there are no universal definitions to classify procedures as *minor (low)* or *major (high)* bleeding risk, the classifications for some procedures are proposed based on the recommendations of some available literature (Table 14).[141,188,189] Generally, a reasonable estimate of perioperative major bleeding with the use of periprocedural anticoagulants is 2—4% for major surgery (major bleeding risk) and 0—2% for nonmajor surgery or minor procedures (minor bleeding risk).[188] The time from the interruption of NOACs to the surgical procedures depends on the risk of bleeding and the renal function (Tables 14 and 15). Because the dabigatran is mainly metabolized through the kidney (~80%), a more graded preintervention termination depending on kidney function has been proposed.

Currently, there are no data regarding when to restart NOACs after surgical interventions. Generally, NOACs could be restarted 24 hours post procedures with low-bleeding risk, and 48—72 hours after procedures with high-bleeding risk.[141,188,189] However, for procedures in which immediate and complete hemostasis can be achieved (e.g. pacemaker implantations and skin surgery), NOACs can be resumed 6—8 hours after the interventions.[141,188,189] The strategy should be individualized for each patient because the surgical process can be very different from one patient to another, and only the surgeon responsible for the intervention is able to weigh the risk of bleeding and thromboembolic events accurately.

Table 14 Elective surgical interventions with low and high bleeding risk.

Not clinically important bleeding risk
Superficial surgery (abscess incision, small excisions, etc.)
Dental procedures
Ophthalmic procedures (cataract or glaucoma)
Endoscopy without biopsy
Minor bleeding risk
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation for right-sided SVT
Coronary angiography
Pacemaker/CRT device/ICD implantations
Hemorrhoidal surgery
Cholecystectomy
Abdominal hernia repair
Arthroscopy
Major bleeding risk
Catheter ablation of left-sided SVT
Liver biopsy
Kidney biopsy
Transurethral prostate resection
Spinal or epidural anesthesia, lumbar puncture
Neurosurgery
Cardiovascular and thoracic surgery
Abdominal surgery
Major orthopedic surgery
Extracorporeal shockwave lithotripsy

Adapted from Spyropoulos et al[188] and Heidbuchel et al.[141,189].
CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; SCT = supraventricular tachycardia.

Table 15 Last intake of non-vitamin K antagonist oral anticoagulants prior to elective surgical intervention.

	Dabigatran		Rivaroxaban, apixaban, edoxaban	
	Low bleeding risk	High bleeding risk	Low bleeding risk	High bleeding risk
CCr $\geq$ 80 mL/min	$\geq$ 24 hours	$\geq$ 48 hours	$\geq$ 24 hours	$\geq$ 48 hours
CCr 50—80 mL/min	$\geq$ 24 hours	$\geq$ 48 hours	$\geq$ 24 hours	$\geq$ 48 hours
CCr 30—50 mL/min	$\geq$ 48 hours	$\geq$ 96 hours	$\geq$ 24 hours	$\geq$ 48 hours

Adapted from Heidbuchel et al[141] and Schulman et al.[331].
CCr = creatinine clearance rate.

Recommendations

- Bridging with LMWH or UFH is not necessarily for warfarin-treated patients undergoing planned surgical intervention.
- Bridging with LMWH or UFH is not necessarily for NOAC-treated patients undergoing planned surgical intervention.
- When surgical procedures carry *no clinically important bleeding risk*, these procedures can be scheduled at the trough concentration of the NOACs without interruption, and NOACs could be prescribed 4—6 hours postprocedure if complete hemostasis is achieved.
- When surgical procedures carry *minor (low)* or *major (high)* bleeding risk, the time from the interruption of NOACs to the surgical procedures depends on the risk of bleeding and the renal function.
- Generally, NOACs can be restarted 24 hours postprocedure with low-bleeding risk, and 48—72 hours postprocedure with high-bleeding risk.
- For procedures in which immediate and complete hemostasis can be achieved (e.g. pacemaker implantations and skin surgery), NOACs can be resumed 6—8 hours after the interventions.

9.8.8. Cardioversion

In patients who have been treated with NOAC for at least 3 weeks, EC can be performed in a similar way as under warfarin. This is based on the subgroup analyses from NOAC trials,[190—192] and the recent X-VeRT trial.[193] If the compliance of patients on NOAC is in doubt, TEE can be performed prior to cardioversion. After cardioversion, continuous NOAC is mandatory for at least another 4 weeks, irrespective of CHA_2DS_2-VASc score.[141]

In OAC-naive patients who have an AF duration of $\leq$ 48 hours, there are insufficient data on safe substitution of LMWH/UFH with NOACs. Therefore, LMWH/UFH should be given and followed by TEE. If no thrombus is found in the atria, cardioversion can be done and NOAC should be given for another 4 weeks. In OAC-naive patients who have an AF duration $>$ 48 hours, two strategies can be chosen. If early cardioversion is attempted, NOACs should be started for 4 hours prior to cardioversion, followed by TEE to exclude atrial thrombus. If late cardioversion is attempted, NOACs can be given for 3 weeks with ensured compliance, and followed by cardioversion. Similarly, continuous NOAC after cardioversion is mandatory for at least another 4 weeks, irrespective of CHA_2DS_2-VASc score.[141] Long-term use of NOACs depends on the CHA_2DS_2-VASc score.

Recommendations

- In patients who have been treated with NOAC for at least 3 weeks, electrical or pharmacological cardioversion can be performed in a similar way as under warfarin. After cardioversion, continuous NOAC is mandatory for at least another 4 weeks, irrespective of CHA_2DS_2-VASc score.
- In OAC-naive patients who have an AF duration of $\leq$ 48 hours, there are insufficient data on safe substitution of LMWH/UFH with NOACs. Therefore, LMWH/UFH should be given and followed by TEE to exclude atrial thrombus.
- In OAC-naive patients who have an AF duration $>$ 48 hours, 2 strategies can be chosen. If early cardioversion is attempted, NOACs should be started for 4 hours prior to cardioversion, followed by TEE to exclude atrial thrombus. If late cardioversion is attempted, NOACs can be given for 3 weeks with ensured compliance, and followed by cardioversion.
- After cardioversion, continuous NOAC is mandatory for at least another 4 weeks, irrespective of CHA_2DS_2-VASc score. Long-term use of NOACs depends on the CHA_2DS_2-VASc score.

9.8.9. Periablation procedure

Because catheter manipulation during ablation may dislodge preexisting thrombi, it is important to minimize the risk of LA thrombus formation prior to the procedure.[194] International guidelines recommend at least 3 weeks of therapeutic anticoagulation prior to ablation in all except the lowest-risk AF patients.[195] By contrast, PV isolation (PVI) constitutes an intervention with a risk of serious bleeding. Tamponade or hemothorax was reported to be around 1.3% in the worldwide AF ablation registry.[196]

All patients undergoing AF ablation who present in AF for the procedure should be anticoagulated for at least 3 weeks prior to AF ablation.[197] If they have not been anticoagulated prior to ablation, a TEE should be performed.[197] International consensus or guidelines recommend performing PVI in VKA-treated patients without VKA interruption.[57,195] This recommendation was supported by a recent

RCT.[198] We recommend uninterrupted warfarin use with a target INR of 2.0—2.5 in these guidelines.

There are many reports on outcomes of PVI patients under NOAC therapy.[141] Meta-analyses of three NOACs have demonstrated similar thromboembolic and bleeding rates compared with uninterrupted VKAs.[199—201] The first RCT on this aspect, the Venture-AF trial, showed similar event rates in patients on uninterrupted rivaroxaban compared with uninterrupted VKA.[202] We recommended that a last intake of NOACs be 24 hours prior to the procedure, although a continued intake until the evening prior to the procedure or even the morning of the procedure seems to be equally safe, especially in experiences centers.[141]

During the PVI procedure, all patients should receive full anticoagulation with intravenous heparin, and an activated clotting time of 300—350 seconds is recommended.[197]

After the ablation procedure, anticoagulants should be initiated. In those patients who discontinued a VKA or had a low INR at the time of ablation, LMWH should be administered at 4—6 hours once hemostasis has been achieved, along with reinitiating VKA, maintaining the administration of LMWH until INR reach 2.0—3.0.[197] In those patients in who the procedure has been performed with brief interruption of a NOAC, the next dose should be administered after 3—4 hours once hemostasis has been achieved.[197] Oral OAC, either a VKA or a NOAC, should be continued for at least 2 months after ablation, because the vast majority of thromboembolic events occurs in the first 4 weeks after ablation.[203]

Recommendations

- All patients undergoing AF ablation who present in AF for the procedure should be anticoagulated for at least 3 weeks prior to AF ablation. If they have not been anticoagulated prior to ablation, a TEE should be performed to exclude atrial thrombus.
- In warfarin-treated patients, we recommend uninterrupted warfarin use with a target INR of 2.0—2.5 prior to PVI.
- In NOAC-treated patients, we recommend uninterrupted NOAC use prior to PVI.
- During the PVI procedure, all patients should receive full anticoagulation with intravenous heparin, and an activated clotting time of 300—350 seconds is recommended.
- Oral OAC, either warfarin or a NOAC, should be continued for at least 2 months after ablation. Long-term use of NOACs depends on the CHA_2DS_2-VASc score.

9.8.10. Management of bleeding complications

It has been shown that the use of NOACs in Asians is more effective and much safer than warfarin.[149,150] The more serious bleeding events, such as ICH and hemorrhagic stroke, were much less common in patients on NOACs than in patients on warfarin.[150] Even in patients with anticoagulant-related ICH, the hematoma volume was much smaller and the prognosis was much better in the NOAC-users compared with warfarin users.[204] As more patients start using NOACs, the number of bleeding events is expected to increase.

A proposed management strategy of bleeding in patients on NOACs was shown in Table 16.[165] The first thing is to stop NOACs immediately and follow the strategy. Since the elimination half-lives of most NOACs are relatively short, time is the most important antidote of NOACs. After cessation of treatment, restoration of hemostasis is to be expected within 12—24 hours after the last taken dose, given plasma half-life of around 12 hours for most NOACs.[141] The drug history should be evaluated in every patient, as increased medication number was associated with the risk of bleeding.[103,104,205] In patients with non—life-threatening bleeding, standard supportive care will be enough. In case of bleeding in patients on dabigatran, adequate diuresis must be maintained. Although dabigatran can be dialyzed, there is limited clinical experience in using dialysis in this setting.[141] Dialysis is not expected to significantly reduce the plasma level of factor X inhibitors due to their high plasma binding and limited renal excretion.[141]

In patients encountering life-threatening bleeding, more aggressive management is suggested. In patients treated with dabigatran, idarucizumab is the preferred reversal agent.[156] The efficacy of PCC and aPCC in patients who are actively bleeding has not been firmly established, although animal studies have shown their efficacy in normalizing anticoagulation parameters.[141] Nevertheless, the

Table 16 Management strategy of bleeding on non—vitamin K antagonist oral anticoagulant (NOAC).

Review	1. Stop NOAC and antiplatelets, review history of last dose of NOAC 2. Review drug history: NSAID, COX-2 inhibitors, P-gp inhibitors, CYP3A4 inhibitors 3. Check vital signs and maintain organ perfusion 4. Check baseline laboratory data, including CBC, platelet count, renal and liver function, PT, aPTT 5. Check source of bleeding
Remove	1. Gastric lavage 2. Oral charcoal 3. Dialysis (only for dabigatran)
Repair	1. Assess the need for surgery to stop bleeding
Reverse	1. Idarucizumab (for dabigatran) 2. 4-factor PCC 3. Platelet transfusion (for thrombocytopenia)

Modified from Kovacs et al[165] with permission.
aPTT = activated partial thromboplastin time; CBC = complete blood count; COX-2 = cyclooxygenase-2; CYP = cytochrome P450; NSAID = non-steroidal anti-inflammatory drugs; PCC = prothrombin complex concentrate; P-gp = P-glycoprotein; PT = prothrombin time.

administration of PCC or aPCC can be considered in patients with life-threatening bleeding if immediately hemostasis is required.[141] Fresh frozen plasma cannot reverse anticoagulation in patients on NOACs, but may be used to expand plasma volume as a supportive care. Vitamin K administration has no role in the management of bleeding event due to NOACs.[141]

Recommendations

- When encountering bleeding events, the first thing is to stop NOACs immediately. After cessation of NOAC, restoration of hemostasis is to be expected within 12—24 hours after the last taken dose.
- In patients with non—life-threatening bleeding, standard supportive care will suffice.
- In patients encountering life-threatening bleeding with the use of dabigatran, idarucizumab is the preferred reversal agent.
- The administration of PCC or aPCC can be considered in patients with life-threatening bleeding if immediate hemostasis is required.
- Fresh frozen plasma cannot reverse anticoagulation in patients on NOACs, but may be used to expand plasma volume as a supportive care.
- Vitamin K administration has no role in the management of bleeding event under NOACs.

9.9. Left atrial appendage closure

It is generally believed that the LAA is the main (but not the only) source of thrombi formation that induce ischemic stroke in AF patients.[92,206] Observational studies have shown inconsistent results of surgical LAA excision or occlusion.[207] Two self-expanding devices, the WATCHMAN and the Amplatzer Cardiac Plug, which are trans-septally placed in the LAA, are available for clinical use. The PROTECT AF trial randomized 707 patients either to percutaneous closure of the LAA, using the WATCHMAN devices, or to OAC (INR range 2.0.3.0).[208] Patients randomized to LAA occlusion were treated with OAC for 45 days after the procedure, followed by DAPT for 6 months and aspirin alone as chronic therapy. The early findings for the WATCHMAN device suggested noninferiority to warfarin for the composite endpoint of stroke, SEE, and CV death; however, early adverse events occurred in about 10% of patients.[208] The Continued Access to PROTECT AF registry was following patient outcomes beyond the end of enrolment and demonstrated a *learning curve effect* with reduced complication rates after the end of the trial.[209] Data from the PREVAIL trial found that the earlier device-related complications were mitigated with increasing operator experience.[210] In 2015, US FDA approved the use of the WATCHMAN device for the prevention of stroke in patients with AF.

The initial experience with the Amplatzer Cardiac Plug appears promising, with 97% acute obliteration of the LAA.[211] The long-term outcomes of the use of this device, requiring RCTs to study reduced stroke risk and safety, are not yet defined.

Recommendation

- Percutaneous LAA closure may be considered in patients with a very high stroke risk and absolutely contraindicated for long-term OAC.

10. Rate versus rhythm control

It is generally believed that AF patients have deleterious outcomes compared with those in sinus rhythm and sinus rhythm maintenance should be better. On one hand, outcomes of virtually all *rate versus rhythm* trials have shown no such advantage (Figure 15). A recent meta-analysis of five clinical trials suggests a trend towards increased mortality and stroke with rhythm control.[212] A *post hoc* analysis of the AFFIRM database showed a 47% reduction in mortality among patients who remained in sinus rhythm during the study, but this benefit was possibly nullified by the 49% increase in mortality conferred by antiarrhythmic drugs (AADs).[213] Furthermore, when applied in patients who were candidates for both treatment strategies, a rhythm-control strategy resulted in more hospitalizations.[214] Therefore, a routine use of rhythm strategy is not warranted for some patients. On the other hand, rhythm-control strategy is associated with improvements in symptoms and quality of life in some patients,[215,216] while persistent symptoms remain the most compelling indication for a rhythm-control strategy.[92] Early initiation of rhythm-control strategy can also prevent progression of AF.[56,217,218]

The only randomized trial comparing rhythm versus rate control in an eastern population is the J-Rhythm trial.[219] In this trial, although the rhythm-control strategy was superior to rate control where the primary endpoints were concerned, there was no difference when hard endpoints, such as mortality, embolization, bleeding, and heart failure were taken into account. Furthermore, J-Rhythm included low-risk patients: only 42.8% of the population had hypertension, 7.4% had coronary artery disease, and 3.6% had heart failure. The vast majority, 78.1%, had a $CHADS_2$ score of 0 or 1. This does not reflect the complicated AF patients seen in daily practice.[32,214]

Since there is no evidence suggesting a preferred strategy, the management of AF should be individualized. The initial therapy after onset of AF should always include adequate antithrombotic treatment and control of the ventricular rate (Figure 2). If the ultimate goal is restoration and maintenance of sinus rhythm, rate-control medication should be continued throughout follow-up, unless continuous sinus rhythm is present.[57] The goal is to control the ventricular rate adequately whenever recurrent AF occurs.[57] Symptoms related to AF are an important determinant in making the decision to choose for rate or rhythm control. Rhythm-control strategy is recommended in patients with symptomatic (EHRA $\geq$ 2) AF despite adequate rate control. Other factors that may favor attempts at

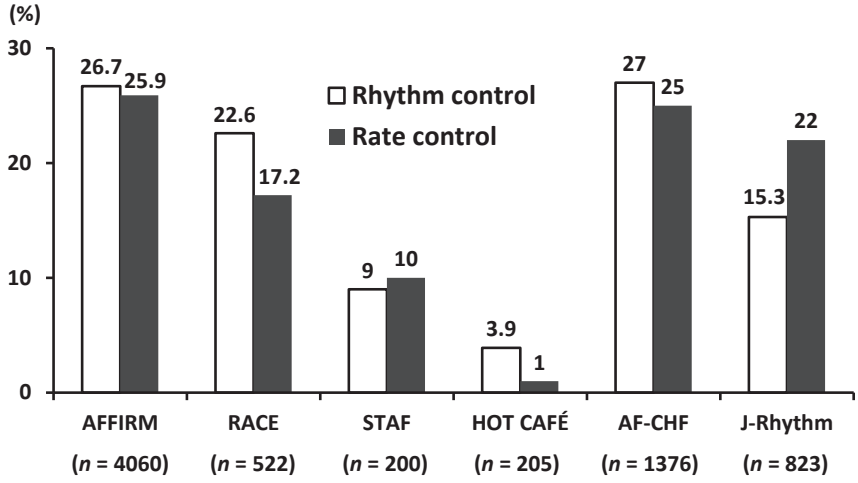

Figure 15 Cardiovascular outcomes of randomized controlled trials of comparing rhythm- versus rate-control strategies.

rhythm-control strategy include difficulty in achieving adequate rate control, younger patients, tachycardia-mediated cardiomyopathy, first episode of AF, AF precipitated by an acute illness, and patient preference.[92]

Recommendations

- Rate-control strategy can be applied in patients with minor symptoms (EHRA score I).
- Rate-control strategy should be continued throughout a rhythm-control strategy to ensure adequate control of ventricular rate during recurrences of AF.
- Rhythm-control strategy is recommended in patients with symptomatic (EHRA $\geq$ 2) AF despite adequate rate control.
- Some factors may favor attempts at rhythm-control strategy, such as difficulty in achieving adequate rate control, younger patients, tachycardia-mediated cardiomyopathy, first episode of AF, AF precipitated by an acute illness, and patient preference.

11. Rate-control strategy

11.1. Acute rate control

The acute management of patients with AF is driven by relief of symptoms and acute improvement of cardiac function. The initial assessment should include a careful clinical and medicinal history. Comorbidity and LV function should be noticed in the initial pharmacological management of AF. AF occurring in a patient with Wolff—Parkinson—White syndrome is a dangerous situation because rapid atrioventricular (AV) conduction through the accessory pathway may precipitate ventricular fibrillation. Identification of pre-excited AF is critical and should be considered with any rapid (200—300 bpm) sustained, highly irregular wide QRS-complex tachycardia. In these patients, drugs that block AV conduction (digoxin, β-blockers, calcium-channel blockers, and adenosine) are contraindicated because they do not slow conduction through the accessory pathway and may precipitate VF.

The severity of AF-related symptoms will decide the acute restoration of sinus rhythm (if symptomatic hypotension, angina, or heart failure is present) or acute control of the ventricular rate. The duration of AF and risk of thromboembolic events are other important initial concerns. The initial management of symptomatic AF may differ from one patient to another. For patients with symptomatic AF lasting many weeks, initial therapy may be anticoagulation and rate control. For patients with new-onset AF for $<$ 48 hours, initial therapy may be pharmacological cardioversion or EC,[220] combined with antithrombotic therapy if indicated.

The 2010 European guidelines suggest the target ventricular rate should usually be 80—100 bpm in the acute setting.[57] The Canadian guidelines suggest physician should attempt to reduce the heart rate prior to discharge from the emergency department to target rates of $<$ 100 bpm at rest[159] and $<$ 110 bpm during moderate exercise (such as walk test).[221] However, there is no prospective, randomized, placebo-control study solving this issue, and the optimal level of ventricular rate in the acute rate control of AF remains unknown and deserves further study.

An inappropriate ventricular rate and irregularity of the rhythm can cause symptoms and compromise hemodynamic conditions in AF patients. Patients with rapid ventricular response usually need acute control of their ventricular rate. Recommended intravenous drugs for acute rate control are shown in Table 17. In stable patients, this can be achieved by oral administration of β-blockers or non-dihydropyridine (non-DHP) calcium-channel antagonists. Verapamil should not be used in patients with decompensated heart failure as it may lead to further hemodynamic compromise. In selected patients, intravenous amiodarone or digoxin may be used, especially in those with severely depressed LV function, heart failure, or hypotension.[92,222] However, intravenous amiodarone should not be used in the case of pre-excited AF.[92,223,224]

Table 17 Recommended intravenous drugs for acute rate control of atrial fibrillation.

Drug	Dose	Adverse effects
Diltiazem[a]	0.25 mg/kg IV bolus over 2 min; a second dose in 15 min if necessary	Hypotension, bradycardia, AV block, asystole
Verapamil[a]	0.075–0.15 mg/kg over 2 min; a second dose may be given 30 min later if necessary	Hypotension, bradycardia, AV block, asystole
Propranolol	0.25–1 mg IV every 5 min; no more than 0.2 mg/kg in total	Hypotension, bradycardia, AV block, asystole, congestive heart failure
Esmolol	50–250 μg/kg/min IV infusion	Hypotension, bradycardia, congestive heart failure
Landiolol	1–10 μg/kg/min	Hypotension, bradycardia, congestive heart failure
Amiodarone	15 mg/min for 10 min; then 1 mg/min for 6 h, and 0.5 mg/min thereafter	Hypotension, bradycardia, congestive heart failure
Digoxin	0.25 mg IV every 2 h; up to 1 mg	Bradycardia, AV block, digitalis toxicity

AV = atrioventricular; IV = intravenous.
[a] Calcium-channel blockers or propranolol should not be used in patients with heart failure or left ventricular dysfunction.

Combination therapy may be necessary in some intractable patients. Acute initiation of rate control therapy should usually be followed by a long-term rate or rhythm control strategy.

Most patients with recent-onset AF may be stabilized in a few hours when adequate rate or rhythm control has been achieved. Symptomatic patients with decompensated heart failure or angina pectoris should be hospitalized. Occasionally, admission may be required for highly symptomatic patients in whom adequate rate or rhythm control cannot be reached.

Recommendations

- Intravenous use of β-blockers or non-DHP calcium-channel blockers is recommended to slow ventricular rate in the acute setting in patients without pre-excitation.
- Verapamil should not be used in patients with decompensated heart failure as it may lead to further hemodynamic compromise.
- In selected patients, intravenous amiodarone or digoxin may be used, especially in those with severely depressed LV function, heart failure, or hypotension.
- In patients with pre-excitation and AF, β-blockers, digoxin, non-DHP calcium-channel blockers, and intravenous amiodarone should not be used as they may increase ventricular rate and result in ventricular fibrillation.

11.2. Chronic rate control

Beta-blockers, non-DHP calcium-channel blockers (diltiazem, verapamil), and digitalis are the primary drugs used for ventricular rate control during AF. The choice of drugs for rate control depends on age, underlying heart disease, and the goal of treatment (Figure 16). In patients who remain symptomatic on strict rate-control therapy, rhythm-control therapy may be considered. Table 18 shows the drugs and their dosages for rate control. All these drugs act by slowing AV nodal conduction and prolonging AV nodal refractoriness. Non-DHP calcium-channel antagonists should not be used in decompensated heart failure. With pre-excitation and AF, digoxin, non-DHP calcium-channel antagonists, or intravenous amiodarone, should not be administered.[92,223–225] The safety of oral amiodarone in pre-excitation AF has not been determined.

The adequacy of heart rate control should be assessed during exertion, adjusting drug treatment as necessary to keep ventricular rate within the physiological range. In small, mostly blinded randomized trials, β-blockers led to lower heart rates at rest and exercise but no change or a decrease in exercise capacity.[226] Calcium-channel blockers were less effective at heart rate lowering on exercise but led to an increase or no change in exercise capacity. In one study, β-blockers added to digoxin did not result in improved quality of life, whereas calcium-channel blockers resulted in small improvements in physical and emotional function.[227] Digitalis prolongs AV nodal refractoriness by enhancing vagal tone. During exercise, vagal tone is withdrawn, and therefore digitalis controls the heart rate less effectively than β-blockers or calcium-channel blockers. Digitalis should thus be avoided as the sole agent in active patients.[228,229] Digoxin is generally combined with another rate-slowing drug. Drug combinations are frequently effective when treatment with a single agent fails. Amiodarone has significant rate-controlling properties in addition to its antiarrhythmic actions and may be used in refractory patients. However, because of the risk of toxicity associated with long-term use, it should be used only when other rate control strategies are not feasible or are insufficient.

Long-term CV outcome trials comparing of different rate control drugs are not available. A recent cohort study from Taiwan NHIRD, using data of whole country AF population, may provide some evidence for choice of different rate control agent.[230] There were 43,879, 18,466, and 38,898 patients with AF enrolled in the groups receiving β-blockers, calcium-channel blockers, and digoxin,

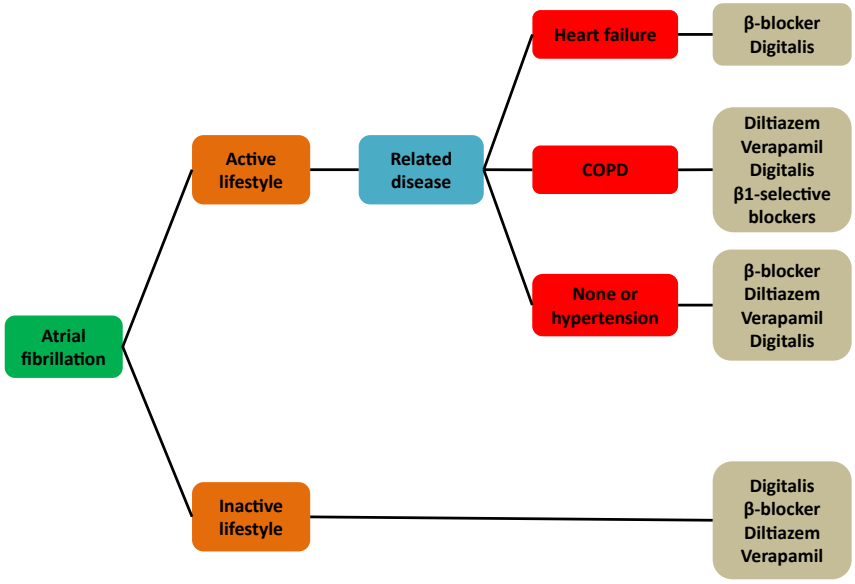

Figure 16 Choice of drugs for chronic rate control. COPD = chronic obstructive pulmonary disease.

respectively. The reference group consisted of 168,678 patients who did not receive any rate-control drug. The clinical end point was all-cause mortality. During a follow-up of 4.9 ± 3.7 years, mortality occurred in 88,263 patients (32.7%). After adjustment for baseline differences, the risk of mortality was lower in patients receiving β-blockers (adjusted HR = 0.76; 95% CI = 0.74—0.78) and calcium-channel blockers (adjusted HR = 0.93; 95% CI = 0.90—0.96) compared with those who did not receive rate-control medications. On the contrary, the digoxin group had a higher risk of mortality with an adjusted hazard ratio of 1.12 (95% CI = 1.10—1.14). The results were observed consistently in subgroup analyses and among the cohorts after propensity matching. In this nationwide AF cohort, the risk of mortality was lower in patients receiving rate-control treatment with β-blockers or calcium-channel blockers, and the use of β-blockers was associated with the largest risk reduction. Digoxin use was associated with greater mortality. Prospective, randomized trials are necessary to confirm these findings.

The negative information about the use of digoxin has increasingly been reported. Two separate papers from Taiwan described an increased risk of ischemic stroke in digoxin users versus nondigoxin users.[231,232] One of them found an increased risk of total mortality.[231] In a retrospective analysis of the ROCKET AF trial, the use of digoxin was associated with a significant increase in all-cause mortality, vascular death, and sudden death in patients with AF.[233] Increased mortality was also found in a retrospective analysis of the AFFIRM trial,[234] and an updated meta-analysis.[235] It is generally accepted that the priority of the use of digoxin in rate control of AF should follow β-blockers and calcium-channel blockers.

Table 18 Drugs for chronic rate control.

	Usual oral maintenance dose
β-blockers	
Metoprolol CR/XL	100—200 mg once daily (ER)
Bisoprolol	2.5—10 mg once daily
Atenolol	25—100 mg once daily
Esmolol	N/A
Propranolol	10—40 mg three times daily
Carvedilol	3.125—25 mg twice daily
Nondihydropyridine calcium-channel blockers	
Verapamil	40 mg twice daily to 360 mg (ER) once daily
Diltiazem	60 mg three times daily to 360 mg (ER) once daily
Digitalis glycosides	
Digoxin	0.125 mg—0.5 mg once daily
Digitoxin	0.05 mg—0.1 mg once daily
Others	
Amiodarone	100 mg—200 mg once daily

CR/XL = controlled release/extended release; ER = extended release; N/A = not applicable.

Recommendations

- The adequacy of heart rate control should be assessed during exertion, allowing adjustment of drug treatment as necessary to keep ventricular rate within the physiological range.
- For rate-controlling agents, β-blockers are preferable in terms of long-term CV outcomes, followed by non-DHP calcium-channel blockers, and digoxin.
- Drug combinations are frequently effective when treatment with a single agent fails.
- In patients with pre-excitation and AF, β-blockers, digoxin, non-DHP calcium-channel blockers, and intravenous amiodarone should not be used as they may increase ventricular rate and result in ventricular fibrillation.

11.3. Endpoints of rate control

Rate control is an important part of therapy for all patients with AF or AFL. An irregular rhythm and a rapid ventricular rate in AF can cause symptoms including palpitations, dyspnea, fatigue, and dizziness. Adequate control of the ventricular rate may reduce symptoms and improve hemodynamics, by allowing enough time for ventricular filling, increases in ventricular regularity, avoiding rate-related ischemia, enhancement of intraventricular conduction with rate reduction, and prevention of tachycardia-mediated cardiomyopathy. The primary goal of rate control is to improve symptoms and prevent deterioration of cardiac function during AF or AFL. Tachycardia-mediated cardiomyopathy refers to a condition characterized by LV systolic dysfunction occurring in patients with sustained rapid heart rates. This complication can occur in some patients with AF or AFL and very rapid ventricular rates (e.g. $>$ 120/min for most of the time) and is totally or partially reversible and preventable with adequate rate control.[236,237]

The optimal level of ventricular rate control with respect to morbidity, mortality, and quality of life remains unclear. In the past, adequate ventricular rate control was empirically defined as $<$ 80 bpm at rest.[72,214] Strict rate-control therapy may result in implantation of a pacemaker for symptomatic bradycardia in 7.3% of patients in the AFFIRM trial, while *post hoc* analyses of the AFFIRM and RACE (rate control vs. EC) studies showed higher resting heart rates were not associated with an adverse outcome.[238] The RACE II (RAte Control Efficacy in permanent AF) trial randomized patients to strict ($<$ 80 bpm at rest and $<$ 110 bpm during moderate exercise) or lenient ($<$ 110 bpm at rest) rate-control strategies.[239] No difference in the primary outcome (composite of CV death, heart failure hospitalization, stroke, systemic embolism, bleeding, and arrhythmic events) was found between these two strategies. Patients assigned to lenient rate control achieved the goal of rate control in a larger proportion of patients with lower drug doses and fewer combinations of drugs, and had fewer hospital visits. Further analysis of RACE II data, even in patients with successful strict rate control, strict rate control still cannot identify a benefit in outcomes over lenient rate-control therapy.[240] Therefore, in patients without severe symptoms due to a high ventricular rate, lenient rate control might be frontline strategy. Relatively few patients randomized to lenient rate control had resting heart rates $>$ 100–110 bpm. Furthermore, at the end of the first year, average resting heart rates were 85 $\pm$ 13 bpm, 78 $\pm$ 12 bpm, and 75 $\pm$ 14 bpm in the lenient, failed strict rate control and successful strict rate control arms, respectively. Since few patients had resting heart rates $>$ 100 bpm in the RACE II trial, and previous studies cannot conclusively show the safety of resting heart rates $>$100 bpm, we recommend that a heart rate target of $<$100 bpm at rest is appropriate for most patients.

Lenient rate control (resting heart rate $<$ 100 bpm) should be the initial approach in patients with AF and minor symptoms. Rate control should continue throughout a rhythm control therapy to ensure adequate ventricular rate during recurrences of AF. Rhythm control should be considered in patients with symptomatic AF despite of adequate rate control.[241] A strict rate-control (resting heart rate $<$ 80 bpm) strategy is reasonable when symptoms persist or tachycardia-mediated cardiomyopathy occurs. After achieving the strict heart rate target, a exercise test and/or 24-hour Holter ECG are recommended to assess the chronotropic response during exertion and to avoid bradycardia. AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological management is inadequate and rhythm control is not achievable. AV nodal ablation should not be performed without prior attempts to achieve rate control with medications. A flow chart of the recommended approach to long-term rate control is shown in Figure 17.

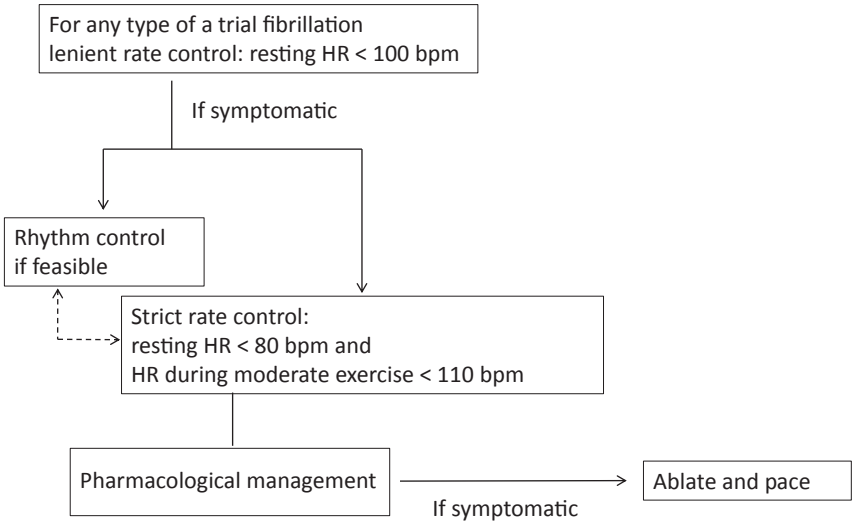

Figure 17 Flow chart of chronic rate control. HR = heart rate (beats/min, bpm).

Recommendations

- Lenient rate control (resting heart rate $<$ 100 bpm) should be the initial approach in patients with AF and minor symptoms.
- A strict rate control (resting heart rate $<$ 80 bpm) strategy is reasonable when symptoms persist or tachycardia-mediated cardiomyopathy occurs.
- After achieving the strict heart rate target, an exercise test and/or 24 hour Holter ECG are recommended to assess the chronotropic response during exertion and to avoid bradycardia.

12. Rhythm-control strategy

12.1. Electric cardioversion

EC is an alternative strategy for the management of patients with AF when rhythm control is appreciated. According to a real-world survey conducted by the EHRA, 67.9% of the study sites preferred EC.[242] Randomized studies support the efficacy and safety of EC such as RACE,[243] STAF,[244] and HOT CAFE.[245] However, this method is performed most frequently in patients with symptomatic or newly diagnosed AF.

Conversion of AF to sinus rhythm could result in transient mechanical stunning of the LA and LAA that could have a risk of thromboembolism. Based on the Finnish CardioVersion Study,[246] the thromboembolic events are $<$ 1% within 30 days after cardioversion of acute AF, even without periprocedural anticoagulation. However, the thromboembolic risk increased to 9.8% among patients with heart failure and diabetes. Under this context, anticoagulation is mandatory in cardioversion of AF if AF duration is $>$ 48 hours or unknown.[57,72] VKA treatment to keep INR 2.0—3.0, or a NOAC should be given for at least 3 weeks prior to EC and the VKA or NOAC should be continued for a minimum of 4 weeks after EC. In patients with risk factors for stroke or AF recurrence, VKA or NOAC treatment should be continued lifelong irrespective of sinus rhythm restoration after EC. A management algorithm was shown in Figure 18.

TEE-guided cardioversion is an alternative method to 3 weeks' precardioversion anticoagulation when early cardioversion is needed. If no LA or LAA thrombus was detected on TEE, heparin or a NOAC should be started prior to the EC and continued after the procedure. If TEE found thrombus in LA or LAA, VKA treatment to keep INR at 2.0—3.0 or a NOAC are required for at least 3 weeks and TEE should be repeated and EC could be performed if the thrombus resolution is completed. If thrombus is still present, the rate control strategy should be considered.

In hemodynamic instability, immediate EC should be performed, and heparinization (UFH or LMWH) should be administered prior to EC. After that, heparin should be continued, combined with VKA, until the INR is at the therapeutic level (2.0—3.0). A NOAC can be used too. If AF duration is $<$ 48 hours, EC can be performed directly under the cover of intravenous UFH, followed by infusion or subcutaneous LMWH. In patients with a CHA_2DS_2-VACs $\geq$ 1, VKA or NOAC should be continued indefinitely.

The immediate success rate varied from 70% to 99% and the complete shock failure or immediate recurrence occurred in approximately 25% of patients undergoing EC of AF. Many randomized studies support that pretreatment with AADs such as amiodarone, ibutilide, sotalol, flecainide, and propafenone could increase the success rate.[247]

Recent evidence supports the use of biphasic external defibrillators for AF cardioversion because of their lower energy requirement and greater efficacy compared to monophasic defibrillators.[248] An initial energy of 200 J or greater is recommended for conversion of AF with

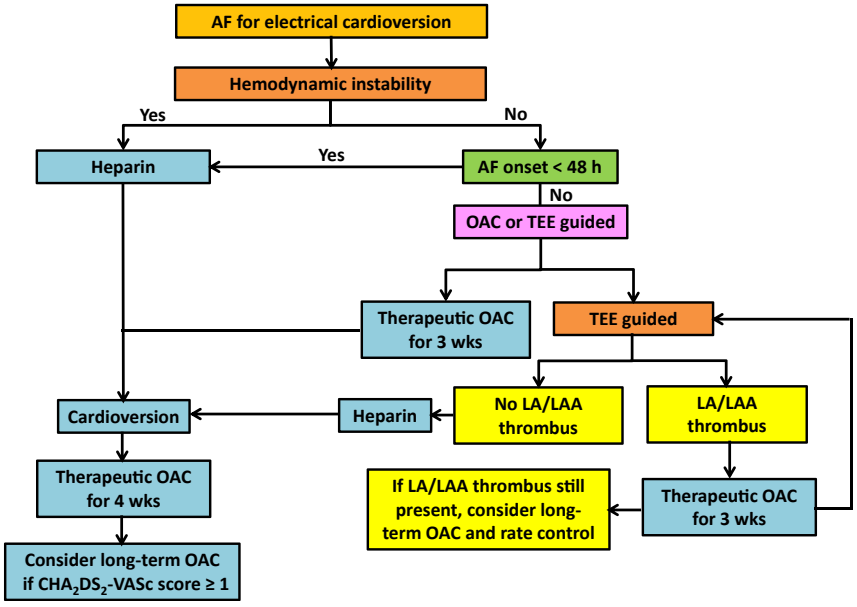

Figure 18 Management algorithm of electrical cardioversion. AF = atrial fibrillation; LA = left atrium; LAA = left atrial appendage; OAC = oral anticoagulant; TEE = transesophageal echocardiography.

monophasic waveform and a similar recommendation to start with 200 J using biphasic waveforms.

The anterior—posterior paddle position was associated with a significantly higher successful conversion rate and lower cumulative energy requirement as compared with anterior—lateral position.[249] Short-acting anesthesia agents, such as midazolam, fentanyl, and propofol, are frequently used due to their rapid onset and short half-life. The shocks should be delivered in a synchronized fashion in order to avoid shock during the vulnerable phase of cardiac cycle (shock on T wave) and subsequent ventricular fibrillation. For patients with an implanted device, the anterior—posterior paddle position is recommended and the paddle should be placed as far as possible and at least 8 cm from the pacemaker battery to reduce the potential risk.

The major risks and complications of cardioversion are: (1) risks associated with sedation; (2) thromboembolic events; and (3) postcardioversion arrhythmias. The procedure is associated with 1—5% risk of thromboembolism and could be reduced by adequate anticoagulation. Serious arrhythmias such as ventricular tachycardia and fibrillation may occur in the presence of hypokalemia, digitalis intoxication, or improper synchronization.

Recommendations

- In AF duration is $>$ 48 hours or unknown, warfarin treatment to keep INR 2.0—3.0, or a NOAC, should be given for at least 3 weeks prior to EC.
- The TEE-guided cardioversion is an alternative method to 3 weeks' precardioversion anticoagulation when early cardioversion is needed.
- If AF duration is $<$ 48 hours, EC can be performed directly under the cover of intravenous UFH, followed by infusion or subcutaneous LMWH.
- Warfarin or NOAC should be continued for a minimum of 4 weeks after EC.
- In patients with a CHA_2DS_2-VACs $\geq$ 2, warfarin or NOAC should be continued indefinitely, irrespective of sinus rhythm restoration after EC.

12.2. Acute pharmacological cardioversion

Pharmacological cardioversion is most likely successful when initiated within 7 days after onset of an episode of AF. Although there are several drugs available for this purpose, only three AADs are available in Taiwan: amiodarone, propafenone, and flecainide. Intravenous amiodarone has more potent β-blocking effect than its Class III drug effect. Therefore, its effect in converting AF to sinus rhythm is usually delayed, slower than oral loading of Class IC drugs, such as propafenone or flecainide.[250,251] In the SAFE-T trial,[215] only 25% of patients with persistent AF were converted by oral amiodarone. Oral propafenone (600 mg) or flecainide (300 mg) are more effective than amiodarone in conversion of AF to sinus rhythm,[251] but this should be done in a monitored condition in the first attempt, since bradycardia or other proarrhythmia may occur. A β-blocker and/or non-DHP calcium-channel blocker should be administered at least 30 minutes prior to the loading of these Class IC AADs to avoid catastrophic AFL with 1:1 AV conduction.[92] In patients with severe structural heart diseases, such as history of MI, CHD, heart failure, severe LV hypertrophy, and hemodynamically significant valvular diseases, Class IC AADs cannot be used.[72]

Recommendations

- In patients without structural heart diseases, Class IC drugs, such as propafenone and flecainide, can be used for pharmacological cardioversion of recent-onset AF.
- In patients with severe structural heart diseases, such as history of MI, CHD, heart failure, severe LV hypertrophy, and hemodynamically significant valvular diseases, Class IC AADs cannot be used.
- In patients with recent-onset AF and structural heart disease, intravenous amiodarone is recommended for pharmacological cardioversion.

12.3. Chronic rhythm control

When a rhythm-control strategy is undertaken, AADs should be selected to reduce the frequency and duration of AF and improve quality of life. Once AAD is initiated, patients' symptoms may improve without complete suppression of AF. Well-tolerated recurrence of AF is a reasonable outcome and should not be called treatment failure.[72]

In the choice of AADs for rhythm control, safety concern seems more important than drug efficacy. A notorious side effect of AADs is the proarrhythmic effect: the exacerbation of a previous arrhythmia or the onset of a new, more serious (or even lethal) arrhythmia caused by the use of an individual AAD.[31] Because proarrhythmias can occur at serum levels below or within the therapeutic range, they cannot be accurately predicted by blood sampling.[31] Two important proarrhythmia effects are ventricular tachycardia/ventricular fibrillation, and drug-induced long QT syndrome/*torsade de pointes*.[31] In the Cardiac Arrhythmia Suppression Trial (CAST), the use of Class IC drugs including flecainide and encainide in patients in the convalescent state of MI resulted in a 2.5-fold increase in mortality compared with placebo.[252] Thereafter, Class IC drugs were contraindicated in patients with acute MI, and also contraindicated in moderate to severe structural heart diseases, such as ischemic heart disease, heart failure, valvular heart disease, cardiomyopathy, and hypertension with severe LV hypertrophy.[57] Long QT syndrome can be caused by Class IA and Class III AADs. In a meta-analysis of 44 trials, AADs significantly reduced recurrence of AF, but all increased proarrhythmias, except amiodarone and propafenone.[253] Class IA AADs were associated with

increased mortality compared with controls, similar to a previous report.[254]

Most AADs, including Class IA, Class IC, and Class III agents, can reduce the risk of recurrence by 50—70% in 1 year.[255] The efficacy of sotalol in the prevention of recurrence of AF is similar to that of propafenone.[256] In the Sotalol Amiodarone atrial Fibrillation Efficacy Trial (SAFE-T), the efficacy of sotalol in maintaining sinus rhythm was not inferior to that of amiodarone in the subgroup of patients with ischemic heart disease.[215]

12.3.1. Amiodarone

When it comes to preventing the recurrence of AF, amiodarone is the most effective drug; better than sotalol and propafenone.[215,256] In a mixed treatment comparison of amiodarone, dronedarone, sotalol, propafenone, and flecainide, amiodarone was the most effective to reduce recurrence of AF.[257] Nevertheless, amiodarone has not been shown to decrease mortality or stroke compared with other treatments or with placebo,[215,256] and it has not been shown to reduce the risk of hospitalization.[258] Patients with New York Heart Association Functional Class III heart failure who received amiodarone had a 44% increase in mortality comparing with those receiving placebo in the SCD-HeFT trial[259]; however, amiodarone can generally be safely used in patients with structural heart disease.[260] Because of multichannel blocking activity, the risk of *torsade de pointes* associated with amiodarone is lower than that with *pure* potassium channel blockers. In patients with LV hypertrophy, heart failure, CHD, previous MI, amiodarone is associated with a low risk of proarrhythmias, making it an appropriate initial choice to prevent AF recurrence in these clinical settings.[92]

12.3.2. Dronedarone

Dronedarone is a benzofuran derivative, structurally related to amiodarone. It is structurally different from amiodarone in two key ways: the two iodine atoms have been deleted and aliphatic side chains have been added. These structural changes have markedly decreased the thyroid toxicity and shortened its half-life. As with amiodarone, dronedarone is a multichannel blocker and has a very low risk for *torsade de pointes*, probably due to three mechanisms: the reduction of dispersion in transmural repolarization; the lack of reverse use-dependent effect; and the ability to abolish early afterdepolarizations.[31]

Dronedarone is more effective in maintaining sinus rhythm than placebo,[261] but is inferior to amiodarone in that aspect.[262] The efficacy of dronedarone in reducing CV outcomes was demonstrated in the ATHENA trial, in which 4628 high-risk patients with paroxysmal or persistent AF were randomized to dronedarone 400 mg twice a day or placebo.[263] After a mean follow-up of 21 months, patients taking dronedarone experienced a 24% reduction ($p < 0.001$) in the combined primary endpoints, which included CV hospitalization and total death. The three secondary endpoints were also reduced: there was a 26% reduction in CV admission ($p < 0.001$), a 29% reduction in CV mortality ($p = 0.03$), and a 16% reduction in all-cause mortality ($p = 0.18$). The *post hoc* analysis also revealed a 34% reduction in stroke ($p = 0.027$).[264] Serious adverse events were similar in both groups.[263] The ATHENA trial has established the preferential role of dronedarone in the treatment of AF, but dronedarone should not be used in patients with New York Heart Association Functional Class II to IV heart failure who have had recent decompensation. In the ANDROMEDA trial, when such patients received dronedarone, the rate of total mortality increased roughly two-fold in just 2 months, resulting in premature termination of the trial.[265]

The effect of dronedarone has also been tested in patients with permanent AF. In the PALLAS trial, patients with permanent AF and CV risk factor were randomized to dronedarone 400 mg twice daily and matching placebo.[266] The trial was prematurely terminated due to an increase in CV events, including CV death, in the dronedarone arm compared with the placebo arm. Stroke and hospitalization for heart failure were also increased. The reason for the results of the PALLAS trial being completely opposite to those in the ATHENA trial was not entirely clear. The PALLAS trial enrolled a high proportion of patients with heart failure and a high percentage of patients taking digoxin. Therefore, AF patients with permanent form or with a history of heart failure should not be given dronedarone. The combined use of dronedarone with digoxin is not recommended. A flowchart of the selection of the rhythm control drugs is shown in Figure 19.

12.4. "Pill-in-the-pocket" strategy

Another way to pharmacological cardioversion for patients with infrequent but symptomatic attack is the "pill-in-the-pocket" strategy.[267,268] Oral flecainide (300 mg) or propafenone (600 mg) were given to restore sinus rhythm in 268 patients with mild heart disease or none who came to the emergency room with AF of recent onset that was hemodynamically well tolerated.[267] Out-of-hospital self-administration of flecainide or propafenone—the "pill-in-the-pocket" approach—after the onset of heart palpitations was evaluated. Treatment was successful in 94% in a mean follow-up of 15 months. The time to resolution of symptoms was 113 minutes. The numbers of monthly visits to the emergency room and hospitalizations were significantly lower during follow-up than during the year prior to the target episode. Only one patient had AFL with a rapid ventricular rate. This study suggested that in a selected population of patients with recurrent AF, "pill-in-the-pocket" treatment is feasible and safe, with a high rate of compliance by patients, a low rate of adverse events, and a marked reduction in emergency room visits and hospital admissions. The initial attempt should be in a monitored condition before this approach is used in the unmonitored outpatient setting.[92] A β-blocker or non-DHP calcium-channel blocker should be administered $\geq$ 30 minutes prior to these Class IC drugs to prevent a rapid ventricular response due to 1:1 AV conduction during AFL.[92]

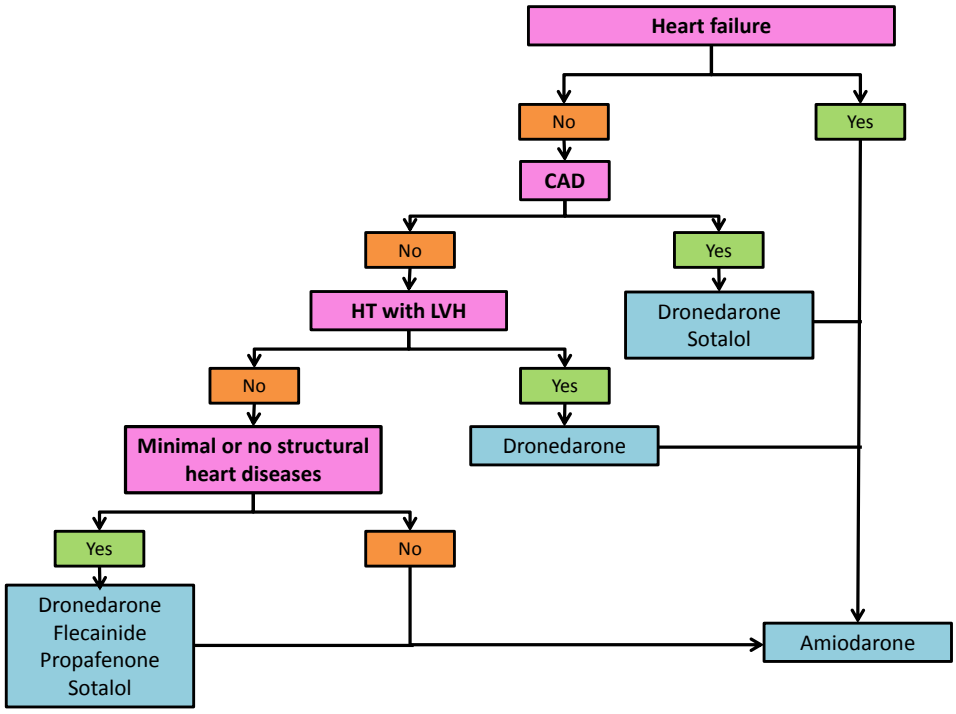

Figure 19 Flow chart of the selection of the rhythm control drugs. CAD = coronary artery disease; HT = hypertension; LVH = left ventricular hypertrophy. (Modified from Chiang et al.[31] with permission.)

Recommendations

- Amiodarone is more effective in maintaining sinus rhythm than propafenone, flecainide, sotalol, and dronedarone.
- For patients with heart failure, amiodarone is the drug of choice for maintaining sinus rhythm.
- In patients with severe structural heart diseases, such as history of MI, CHD, heart failure, several LV hypertrophy, and hemodynamically significant valvular diseases, Class IC AADs cannot be used.
- In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.
- Dronedarone should be considered in patients with nonpermanent AF and CV risk factors to reduce CV hospitalizations and total mortality.
- Dronedarone should not be used in patients with heart failure.
- Dronedarone should not be used in patients with permanent AF.
- Dronedarone should not be combined with digoxin.

12.5. Upstream therapy

Upstream therapy refers to the use of non—ion-channel antiarrhythmic drugs that modify the atrial substrate to prevent the occurrence of new onset AF (primary prevention) or recurrence of the arrhythmia (secondary prevention). Potential intervention mainly includes angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), statins, and fish oil.

Recommendations

- In selected patients without significant structural heart disease, a single high oral dose of flecainide or propafenone (the "pill-in-the-pocket" approach) can be considered for infrequent but symptomatic attack of AF, provided this treatment has proven safe during previous testing in a medically secure environment.
- A β-blocker or non-DHP calcium-channel blocker should be administered ≥ 30 minutes prior to the "pill-in-the-pocket" approach to prevent a rapid ventricular response due to 1:1 AV conduction during AFL.

12.5.1. ACEIs and ARBs

Several retrospective *post hoc* analyses from large RCTs have reported a sustained reduction in new-onset AF (i.e. primary prevention) with ACEIs and ARBs in patients with significant underlying heart disease (e.g. LV dysfunction and hypertrophy).[269] Recently published meta-analyses driven by these studies[270] demonstrates substantial benefits from ACEIs and ARBs in the primary prevention of AF,[271] supporting the concept of RAS

inhibition as an emerging treatment option for the prevention of AF in patients with heart failure and those with hypertension and LV hypertrophy.[270] No definitive evidence favoring one class of RAS inhibitors over the other is available. More information on the effects of ACEIs and ARBs from RCTs is needed for the primary prevention of AF.

For secondary prevention, three larger prospective RCTs have yielded negative results, although hypothesis-generating small clinical studies or retrospective analyses in selected patient categories have been positive. The largest secondary prevention study, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac Atrial Fibrillation (GISSI-AF) enrolling 1442 patients with CV risk factors (mainly hypertension, 85%) and paroxysmal or recently cardioverted persistent AF, demonstrated no effect of valsartan added on top of optimal medical therapy on the primary endpoint of time to first AF recurrence (HR 0.99; 95% CI 0.85—1.15; $p = 0.84$) compared with placebo at 1-year follow-up.[272] The Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) II study in 318 patients with paroxysmal AF and hypertension showed no benefit of treatment of hypertension by candesartan compared with amlodipine, in the reduction in the frequency of paroxysmal AF during 1 year of follow-up.[273] The ANgiotensin II anTagonists In Paroxysmal Atrial Fibrillation (ANTIPAF) study in 425 patients with paroxysmal AF without structural heart disease demonstrated no effect of olmesartan (40 mg/d) compared with placebo on the primary endpoint of AF burden, detected by telemonitoring at 1-year follow-up.[274] In light of currently available data, there is no evidence to make any recommendation for the use of ACEIs and ARBs for secondary prevention of AF.

12.5.2. Statins

Retrospective, observational, and randomized controlled studies have reported a lower incidence of postoperative AF in patients receiving statin therapy. The Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery (ARMYDA-3) trial, the first properly designed RCT, demonstrate that pretreatment with atorvastatin 40 mg/d starting 7 days prior to elective coronary artery bypass surgery was associated with a significant reduction in the incidence of postoperative AF.[275] With all studies in the surgical setting pooled together, the odds ratio for any AF was 0.78 (95% CI, 0.67—0.90; $p < 0.001$), and for new onset AF, it was 0.66 (95% CI, 0.51—0.84).[276] In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca (GISSI-HF) trial, 2285 patients randomized to rosuvastatin (10 mg/d) had a nonsignificant reduction of AF by only 13% during a median follow-up period of 3.7 years.[277] The difference with placebo became statistically significant only after adjustment for clinical variables and concomitant therapy.[277] Clinical data on the primary preventative effects of statins in AF in other settings were inconsistent, depending on underlying disease, duration of follow-up, and the history of AF. While retrospective analysis from epidemiological studies and RCTs in patients with LV dysfunction and heart failure have shown a 20—50% reduction in the incidence of new-onset AF, reports in patients with hypertension, coronary artery disease, ACSs were less consistent.[278]

There is limited evidence of the efficacy of statins in secondary prevention of AF in different clinical settings, and the results are controversial. The only exception is the postoperative AF. Several prospective randomized controlled trials have been underway to assess the antiarrhythmic value of statins. At present, there is no robust evidence to make any recommendation for the use of statins for primary or secondary prevention of AF, except for AF after coronary artery surgery.

12.5.3. Fish oils

Several mechanisms have been implicated in the antiarrhythmic action of Ω-3 fatty acid. In experimental AF, induced by ventricular tachypacing,[279] and vagal stimulation,[280] Ω-3 fatty acid alleviated shortening of atrial effective refractory periods, prevented inducibility of AF, and attenuated structural changes in the atrial myocardium. However, in most of the RCTs in preventing recurrence of symptomatic AF, or in the reduction of postoperative AF, Ω-3 generally failed.[281—283] In a recent meta-analysis, Ω-3 fatty acid was unable to decrease AF recurrence.[284]

Recommendations

- An ACEI or ARB can be used for primary prevention for AF in patients with heart failure with reduced ejection fraction.
- ACEI or ARB can be used for primary prevention for AF in patients with hypertension and LV hypertrophy.
- ACEI or ARB have no role in secondary prevention for AF.
- Statin therapy can be used for primary prevention for AF after coronary artery surgery.
- Therapy with an ACEI, ARB, or statin is not beneficial for primary prevention of AF in patients without CV disease.
- Fish oil has no role in primary or secondary prevention of AF.

12.6. Lifestyle modification

Obesity has been associated with diastolic dysfunction,[285] systemic proinflammatory state,[286] and atrial enlargement.[287] Fat stores have also been shown to correlate with incident AF.[288] In a single-center, partially blinded, clinical trial, 150 AF patients were randomized to weight management (intervention) or general lifestyle advice (control).[289] Both groups underwent intensive management of cardiometabolic risk factors. The intervention group showed a significantly greater reduction, compared with the control group, in weight (14.3 kg and 3.6 kg, respectively; $p < 0.001$) and in AF symptom burden scores (11.8 and 2.6 points, $p < 0.001$), symptom severity scores (8.4 and 1.7 points, $p < 0.001$), number of episodes (2.5 and no change, $p = 0.01$), and cumulative duration (692-minute decline and 419-minute increase,

$p = 0.002$). Additionally, there was a reduction in interventricular septal thickness in the intervention and control groups (1.1 and 0.6 mm, $p = 0.02$) and LA area (3.5 and 1.9 cm^2, $p = 0.02$). These findings support therapy directed at weight and risk factors in the management of AF.[289] A long-term study (LEGACY trial) found a dose effect of weight loss, and weight fluctuation was related to burden of AF.[290] A weight loss $\geq$ 10% resulted in a six-fold greater probability of arrhythmia-free survival compared with a weight loss of $<$ 10%. Weight fluctuation $>$ 5% partially offset this benefit, with a two-fold increased risk of arrhythmia recurrence. Therefore, long-term sustained weight loss is associated with significant reduction of AF burden and maintenance of sinus rhythm.[290]

In the ARREST-AF cohort study, the impact of risk factor and weight management on AF ablation outcomes was evaluated.[291] Of 281 consecutive patients undergoing AF ablation, 149 with a body mass index (BMI) $\geq$ 27 kg/m^2 and at least one cardiac risk factor were offered risk factor management (RFM), including BMI $<$ 25 kg/m^2, BP $<$ 130/80 mmHg, low-density lipoprotein—cholesterol $<$ 100 mg/dL, triglycerides $<$ 200 mg/dL, and glycated hemoglobin $<$ 7%. After AF ablation, all 61 patients who opted for RFM and 88 control individuals were assessed every 3—6 months by clinic review and 7-day Holter monitoring. RFM resulted in greater reductions in weight ($p = 0.002$) and BP ($p = 0.006$), and better glycemic control ($p = 0.001$) and lipid profiles ($p = 0.01$). At follow-up, AF frequency, duration, symptoms, and symptom severity decreased more in the RFM group compared with the control group (all $p < 0.001$). Drug-unassisted arrhythmia-free survival was greater in RFM patients compared with control individuals ($p < 0.001$). On multivariate analysis, type of AF ($p < 0.001$) and RFM (HR 4.8; 95% CI: 2.04—11.4; $p < 0.001$) were independent predictors of arrhythmia-free survival. This study confirmed that aggressive RFM improved the long-term success of AF ablation, and underscored the importance of therapy directed at the primary promoters of the AF substrate to facilitate rhythm control strategies.[291]

Cardiorespiratory fitness is an independent predictor of CV outcome and mortality.[292] Recent studies have found an inverse relationship between increased physical activity and the risk of incident AF.[293] In the CARDIO-FIT study, the role of cardiorespiratory fitness and the incremental benefit of cardiorespiratory fitness improvement on rhythm control was evaluated in obese individuals with AF.[294] Arrhythmia-free survival with and without rhythm control strategies was greatest in patients with high cardiorespiratory fitness compared to adequate or low cardiorespiratory fitness ($p < 0.001$ for both). AF burden and symptom severity decreased significantly in the group with cardiorespiratory fitness gain $\geq$ 2 metabolic equivalents (METs) as compared to $<$ 2 METs group ($p < 0.001$ for all). Arrhythmia-free survival with and without rhythm control strategies was greatest in those with METs gain $\geq$ 2 compared to those with METs gain $<$ 2 in cardiorespiratory fitness ($p < 0.001$ for both). It is concluded that cardiorespiratory fitness predicts arrhythmia recurrence in obese individuals with symptomatic AF. Improvement in cardiorespiratory fitness augments the beneficial effects of weight loss.[294] The association of cardiorespiratory fitness and incident AF in a primary prevention setting was tested in a large, multiracial cohort that underwent graded exercise treadmill testing.[295] A total of 64,561 adults without AF underwent exercise treadmill testing at a tertiary care center. During a median follow-up of 5.4 years (interquartile range, 3—9 years), 4616 new cases of AF were diagnosed. After adjustment for potential confounders, one higher metabolic equivalent achieved during treadmill testing was associated with a 7% lower risk of incident AF (HR, 0.93; 95% CI, 0.92—0.94; $p < 0.001$). The magnitude of the inverse association between cardiorespiratory and incident AF was greater among obese compared with non-obese individuals (p for interaction = 0.02). Therefore, there is a graded, inverse relationship between cardiorespiratory fitness and incident AF, especially among obese patients.[295]

Facts and recommendations

- Long-term sustained weight loss is associated with significant reduction of AF burden and maintenance of sinus rhythm.
- RFM, including BMI $<$ 25 kg/m^2, BP $<$ 130/80 mmHg, low-density lipoprotein—cholesterol $<$ 100 mg/dL, triglycerides $<$ 200 mg/dL, and glycated hemoglobin $<$ 7%, can decrease AF recurrence and symptoms after AF ablation.
- Cardiopulmonary fitness improvement is effective for both primary and secondary prevention of AF.

13. Ablation therapy

During the past decade, catheter ablation of AF has developed rapidly from an experimental unproven procedure to a commonly performed ablation procedure in the majority of electrophysiological laboratories throughout the world. The main objective of this section is to provide foundation of knowledge and literature review for those involved with catheter ablation of AF.

13.1. Rationale for eliminating AF with catheter ablation

Most current available RCTs regarding rhythm control versus rate control of AF were based on the strategy. These clinical trials clearly show that the strategy of rhythm control does not achieve the potential benefits.[296] However, there are some studies suggesting that the clinical benefit of maintenance of sinus rhythm (SR) may be preferred if achieved other than through drug therapy. There are several reasons to perform the ablation procedure for treatment of AF. In recent years, several randomized trials have demonstrated that catheter ablation (including paroxysmal and persistent) was superior to antiarrhythmic therapy in the prevention of recurrent and symptomatic AF.[297—303] The primary justification for an AF ablation is the presence of symptomatic AF with a goal to improve the quality of life of patients.[58,301] Thus, the primary selection criterion for

catheter ablation should be the presence of symptomatic AF. The benefit of AF ablation has not been demonstrated in asymptomatic patients. Second, the transport function of the LA improved after ablation.[304] Last, there is an association between AF and increase risk of cerebral thromboembolism, developing heart failure and increased mortality. The risk of stroke was low after catheter ablation.[305,306] However, large prospective multicenter RCTs are needed to compare with rate control strategy.[307]

13.2. Outcomes of catheter ablation and complications

Catheter ablation is usually performed in patients with symptomatic paroxysmal or persistent AF that is resistant to at least one AAD, irrespective of the presence of structural heart disease. This is supported by the results of multiple randomized trials by comparing AAD treatment with catheter ablation (Table 19).[297–303] Data on direct comparison of catheter ablation as first ablation therapy were available in one randomized trial.[297] Considering the potential AF catheter ablation in paroxysmal AF in patients with minimal or no heart disease, and the relative safety of the technique in the experienced centers, ablation could be considered as an initial therapy in selected patients. For patients with long-standing persistent AF, the treatment strategies and the benefit–risk ratio of catheter ablation are less well established, because extensive ablation and multiple procedures are usually required.[308] Consideration of different types of antiarrhythmic medication should be individualized prior to ablation.

A world survey on the efficacy and safety of catheter ablation of AF has been published.[196] The efficacy rate of free from AADs in patients previously refractory to drugs was 70%, and an additional 10% efficacy rate in the presence of the previously ineffective drug. More than one procedure was required in 27% of patients. According to the survey, catheter ablation is associated with significant complications. The incidence of major complications was 4.5% and the overall mortality was 0.7%. Rarer complications may result in permanent injury, requiring intervention and prolonged hospitalization.

13.3. Pre-ablation assessment

Prior to an ablation procedure, all patients should undergo: (1) 12-lead ECG and/or Holter recording to document AF; (2) a transthoracic ECG to identify/exclude underlying structural heart disease; (3) additional imaging, e.g. CT or MRI, demonstrates individual three-dimensional geometry and provides quantification of atrial fibrosis; (4) exclusion of LA thrombosis by TEE prior to the procedure (usually within 48 hours) or during the procedure. Appropriate anticoagulation should be considered to bridge the time of TEE and the procedure itself. LA venography was recommended to exclude the heavy smoke or thrombus immediately prior to the procedure; and (5) barium esophagogram prior to ablation to demonstrate the location of esophagus, and avoid injury.

13.4. Catheter ablation strategy

Identification of initiating triggers allows prevention of AF recurrence by ablation at the sites of the triggers. It is well known that PV is the major site of ectopic foci initiating paroxysmal AF.[22,309] PV ablation is considered the primary choice for first-time ablation in paroxysmal AF, and even in persistent, and long-lasting AF patients.[310] The end-points for different PV isolation approach is either elimination of amplitude reduction of the ablation sites, elimination of PV potentials recorded from circular catheter (or dissociation), and/or exit block from the PVs.[311] A randomized trial showed that isolation of larger circumferential lesion is more effective than segmental ablation,[312] owing to the elimination of non-PV ectopies near the PV ostium.[313] Non-PV triggers initiating AF can be identified in up to one-third of AF patients. Elimination of the non-PV ectopies resulted in elimination of AF.[314] The sites of non-PV triggers include superior vena cava, crista terminalis, coronary sinus, posterior wall of LA, and ligament of Marshall. Furthermore, non-PV reentrant sources of AF could be identified in the RA and LA, which were identified by frequency analysis and/or high density mapping technique.[315,316] Some patients with paroxysmal AF with extensive atrial modeling (or positive inducibility)

Table 19 Randomized controlled study comparing catheter ablation and antiarrhythmic therapy as rhythm control therapy.

Study	PAF/Per AF	Patients (ablation/AAD)	Ablation	AF freedom ablation	AF freedom AAD	Follow-up duration
Wazni 2005[297]	96% PAF (primary therapy)	33/37	PVI	85%	21%	9 mo
Oral 2006[298]	100% Per AF	77 (32 re-do)/69 (77% cross-over)	PVI+LA lines	74% (Multi)	58%	12 mo
Pappone 2006[299]	100% PAF	99/99	PVI + Mitral line + CTI	85%	35%	12 mo
Stabile 2006[300]	67% PAF	68/69	PVI + mitral lines	65%	8.7%	12 mo
Jais 2008[301]	100% PAF	53/59	PVI + non-PV	89% (Multi)	23%	12 mo
Wilber 2010[302]	100% PAF	106/61	PVI ± line, CFEs	66% (combined end-points)	16%	9 mo
Mont 2014[303]	100% Per AF	98/48	PVI ± line, CFEs	70.4%	43.79%	12 mo

AAD = antiarrhythmic drug; CFE = complex fractionated atrial electrograms, CTI = cavotricuspid isthmus; PAF = paroxysmal AF; Per AF = persistent atrial fibrillation; PVI = pulmonary vein isolation.

and nearly all patients with nonparoxysmal AF may require substrate modification to improve the outcome in addition to elimination the triggers.[317] Substrate modification included: (1) linear ablation of the LA and/or RA; (2) complex fractionated atrial electrograms[318–320]; and (3) elimination of small-radius reentry as rotors.[320] However, recent study showed that no reduction in the rate of recurrent AF when either linear ablation or ablation of complex fractionated electrograms was performed in addition to PV isolation.[321] The wide variation in the use of additional techniques and in the choice of endpoints reflects the uncertainties and lack of guidance in additional to PV ablation in persistent AF.

In the right atrium, cavotricuspid isthmus linear ablation is required for isthmus dependent AFL, paroxysmal AF with inducible isthmus dependent AFL and in all patients with nonparoxysmal AF. The efficacy of cavotricuspid isthmus ablation was high, with acute success rate of 97%. Ablation could be considered as the first line therapy compared to antiarrhythmic medication in patients with sustained symptomatic typical AFL with high efficacy and a positive impact of quality of life, low complication and lower comorbidity.[322,323]

13.5. Follow-up considerations

Regarding the anticoagulation use following catheter ablation, anticoagulant is recommended to be prescribed for a minimum of 2 months after the catheter ablation in high-risk patients. Individual stroke risk of patients shall be considered to determine whether oral anticoagulation should be continued. Although recent cohort studies demonstrated that the patients without symptomatic AF had a lower risk of vascular events or death, discontinuation of warfarin therapy postablation is generally not recommended in patients with high risk of stroke ($CHA_2DS_2VASc \geq 2$), as multiple comorbidity exist in these patients.[306] The usefulness of the CHA_2DS_2VASc score in the prediction of adverse events after catheter ablations has been proved and validated.[324]

Symptom-based follow-up may be sufficient, as symptom relief is the main aim of AF ablation. To obtain information to compare success rates following different procedures and to improve ablation techniques, systematic, standardized ECG monitoring is needed. Expert consensus recommends an initial follow-up visit at 3 months, with 6-monthly intervals thereafter for at least 2 years. The true AF recurrence rate will be markedly underestimated by a longer recording duration.

13.6. Atrioventricular node ablation and modification

Atrioventricular node (AVN) ablation provides highly effective control of ventricular rate in patients with AF. Complete heart block is achieved by selective catheter-mediated destruction of the AVN or His bundle, with radiofrequency current serving as the predominant source of ablation energy. Ablation of the AVN is a palliative rate control therapy but irreversible procedure and is therefore reasonable in patients in whom pharmacological rate control or rhythm control with drugs and/or ablation has failed. In such patients, AVN ablation improves quality of life and renders mortality similar to death rates in the general population. It is reasonable to assume that patients with reduced LV function may require biventricular pacing after AVN ablation to prevent deterioration of LV function. In patients without LV dysfunction, it is not established at present whether biventricular pacing is needed: some data suggest that biventricular pacing may be beneficial, and LV failure should be considered in patients with right ventricular pacing.

13.7. Surgical AF ablation

The Maze procedure was the first surgical technique developed to ablate AF and was developed before PV ablation strategy. Currently the conventional Cox III Maze procedure with cut-and-saw remains the cold standard of surgical ablation, even though many energy source including cryoablation, bipolar ablation, and microwave are evolving in clinical service. Based on the reports from major centers, the efficacy of AF prevention is high, with potential sinus node injury/permanent pacemaker implantation, recurrence of organized AF/AFL and reconnection of PV (Table 20).[325–329]

Many studies have demonstrated that treating AF results in an improved quality of life, fewer long-term strokes and improved long-term survival while adding no risk to the overall surgical procedure. Moreover, the major cardiology and surgery societies recommend that concomitant AF surgery be performed in all cases when feasible. Patients undergoing coronary artery bypass graft and mitral/aortic valve surgery who have symptomatic paroxysmal AF may consider concomitant surgical PV ablation, while those with long-standing persistent AF, right atrial linear ablation should include a Maze procedure.

Ablation strategies have been deployed with the intention of *curing* AF in several patient populations. Long-term

Table 20 Summary of surgical ablation efficacy and outcome.

Study	Per AF	Number	Long AF	Mortality	PPM	Efficacy
Izumoto 2000[325]	100%	104	0%	4.9% (1 y)	6%	65% (3 y)
McCarthy 2000[326]	78%	100	23%	1% (periop), 5% (late)	6%	90% (3 y)
Schaff 2000[327]	80%	221	25%	1.4% (early)	3.2%	70% (3 y)
Je 2009[328]	87%	550	—	1.6% (early), 4.2% (3 y)	2.3%	82.2% (5 y)
Weimar 2012[329]	52%	212	100%	1.3% (30 d), 2.6% (late)	8%	90% (2 y)

Per AF = persistent atrial fibrillation; periop = perioperative; PPM = permanent pacemaker.

follow-up of these patients suggests that sinus rhythm is better preserved than with AADs. The majority of studies have recruited patients with symptomatic paroxysmal AF and no or minimal structural heart disease. In general, catheter ablation should be reserved for patients with AF that remains symptomatic despite optimal medical therapy, including rate and rhythm control (Figure 2).

Recommendations

- Catheter ablation is usually performed in patients with symptomatic paroxysmal or persistent AF that is resistant to at least one antiarrhythmic drug, irrespective of the presence of structural heart disease.
- Stand-alone PV ablation is the primary choice of ablation strategy for first-time ablation, even in patients with persistent AF.
- The usefulness of the CHA_2DS_2-VASc score in the prediction of adverse events after catheter ablations has been proven and validated.
- Ablation of the AVN is a palliative rate control therapy.
- Concomitant surgical PV ablation should be considered in all AF patients undergoing coronary artery bypass graft and mitral/aortic valve surgery.

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