ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population. The Korean Heart Rhythm Society organized a Korean AF Management Guideline Committee and analyzed all available studies regarding the management of AF, including studies on Korean patients. This guideline is based on recent data of the Korean population and the recent guidelines of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery, American Heart Association, and Asia Pacific Heart Rhythm Society. Expert consensus or guidelines for the optimal management of Korean patients with AF were achieved after a systematic review with intensive discussion. This article provides general principles for appropriate risk stratification and selection of anticoagulation therapy in Korean patients with AF. This guideline deals with optimal stroke prevention, screening, rate and rhythm control, risk factor management, and integrated management of AF.

Keywords: Atrial fibrillation; Guideline; Anticoagulants; Therapy

PREAMBLE

This guideline is based on recent data of the Korean population and the recent guidelines. The level of evidence and strength of the recommendation of particular management options were weighed and graded according to predefined scales as outlined in Tables 1 and 2. The Korea Heart Rhythm Society (KHRS) Committee for Practice Guidelines supervises and coordinates the preparation of a new guideline produced by task forces, expert groups, or consensus panels. The Committee is also responsible for endorsing this guideline.
INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population. AF increases the risk of mortality and morbidity resulting from stroke, congestive heart failure (HF), and impaired quality of life, explaining its enormous socioeconomic and healthcare implications. The prevalence of AF has been projected to increase to 12 million people in the USA by the year 2050 and 17.9 million in Europe by the year 2060, with more than half of these patients being ≥80 years of age, leading to substantial public health and economic burdens. Consequently, the healthcare burden associated with AF is growing considerably and is mainly driven by hospitalizations. As populations continue to age, AF is likely to become a greater public health burden.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION IN KOREA

Many of the risk factors for developing AF also lead to complications related to AF such as stroke and death. The prediction of incident AF has been the focus of reviews, and risk factors have been used to derive clinical risk scores for incident AF. The largest derivation and validation in an Asian population (including Korea) is the simple C2HEST score: C2HEST: C: coronary artery disease (CAD)/chronic obstructive pulmonary disease (COPD) (1 point each); H: Hypertension; E: Elderly (Age ≥75, doubled); S: Systolic HF (doubled); T: Thyroid disease (hyperthyroidism).

Prevalence and incidence of atrial fibrillation

Reliable prevalence and incidence figures are needed for clinicians and policymakers. The prevalence of AF progressively increased by 2.10-fold from 0.73% in 2006 to 1.53% in 2015 in Korea. The prevalence was significantly greater in men than in women for all years (Figure 1A). The annual trends of AF incidence were stable with the 10-year overall incidence of 1.77 per 1,000 person-years. The 10-year overall incidence in men was 1.89 per 1,000 person-years, 1.16 times higher than 1.65 per 1,000 person-years in women, and the tendency was consistent over the study period (Figure 1B). The prevalence of AF in Korea was similar to the recent prevalence rates of 1.07–1.6% in Asia; 1.07% in 2011 in Taiwan.
1.5% in Singapore,\(^{22}\) and 1.6% in 2006 in Japan.\(^{23}\) Across all age groups, the prevalence consistently increased over the study period, except the prevalence among those aged 20–29 years decreased significantly (Figure 2A). The annual AF incidence in subjects aged ≥80 years increased significantly from 12.1 in 2006 to 14.3 per 1,000 person-years in 2015, while the incidences in all other age groups decreased (Figure 2B).\(^{20}\) Patients with regular hospital visits showed a lower prevalence of AF and an increasing trend of the incidence of AF.\(^{24}\) 25\)

The prevalence of Korean AF is expected to be 5.81% (2,290,591 AF patients) in 2060 (Figure 3), while the prevalence of Taiwan AF is estimated to be 4.01% in 2050.\(^{21}\) Although the prevalence of AF is increasing steeply in Asia, it remains lower in Korea (and many Asian countries) than that of Western populations. Because AF is becoming an important public health burden, regional and socioeconomic inequality of AF patterns and treatment is also important.\(^{26}\) The prevalence of AF differs according to geographical regions and income levels.\(^{27}\)

The proportion of patients with a congestive HF, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74,
female (CHA₂DS₂-VASc) score ≥2 increased from 68.8% to 81.2% from 2006 to 2015. The proportion of patients with high bleeding risk according to HAS-BLED (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [0.65], drugs/alcohol concomitantly [1 point each]) (score ≥3) increased from 39.3% in 2006 to 59.1% in 2015 (Figure 4).²⁰

Figure 3. The projected prevalence of atrial fibrillation.

Figure 4. Temporal trends of newly diagnosed AF patient by CHA₂DS₂-VASc and HAS-BLED scores, 2006–2015. AF = atrial fibrillation.
Hospital care burden of atrial fibrillation

Overall, hospitalizations for AF increased by 420% from 767 to 3,986 per 1 million Korean population from 2006 to 2015. Most admissions occurred in patients aged ≥70 years, and the most frequent coexisting conditions were hypertension, HF, and COPD. Hospitalizations mainly due to major bleeding and AF control increased, whereas those mainly due to ischemic stroke and myocardial infarction decreased.\(^8\)\(^9\)

The total cost of care increased even after adjustment for inflation from \(₩8.79\) billion (€68.4 million) in 2006 to \(₩49.8\) billion (€388.4 million) in 2015, equivalent to 0.78% of the Korean National Health Insurance Service (NHIS) total expenditure (Figure 5). The total care cost related with AF was estimated as $16–26 billion in the United States, accounting for 1% of the national healthcare budget in the United Kingdom.\(^15\)\(^29\)\(^30\)

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**Figure 5.** Temporal trends of medical costs, 2006–2015. (A) Korean NHIS total expenditures (million €), (B) total AF hospitalization costs (million €), and (C) the proportion of total AF hospitalization costs to Korean NHIS total expenditures (%).

AF = atrial fibrillation; NHIS = National Health Insurance Service.

\(^*\)p value for trends <0.001.
Prognosis of atrial fibrillation

Among prevalent AF patients, annual event rates for all-cause mortality, ischemic stroke, intracranial bleeding, HF admission, and myocardial infarction significantly declined for a decade. In contrast, these events did not change among the non-AF Korean population (Figure 6). Over the last 5 decades, AF-associated mortality decreased by 25% in the Framingham Heart Study.31

In Korea, we observed a 20% reduction in mortality over a decade from 5.0%/year in 2006 to 4.0%/year in 2015.20 Overall in-hospital mortality decreased from 7.5% in 2006 to 4.3% in 2015.28 The in-hospital mortality was highest in patients ≥80 years of age (7.7%) and in those with chronic kidney disease (7.4%). Improved survival after AF onset may arise from: 1) earlier detection (lead time) owing to heightened awareness; 2) changed diagnostic criteria (as described above); 3) enhanced surveillance of AF patients; 4) advances in guideline-recommended treatments for AF including oral anticoagulation (OAC) therapy to reduce the risk of embolization; and 5) more aggressive treatment of complications and comorbidities such as hypertension, ischemic heart disease, HF, and hypercholesterolemia.18

Given the high mortality associated with HF and stroke, the 52% reduction in HF and stroke over the study period and the 9% reduction in risk of ischemic stroke is likely to have contributed substantially to the improved survival. Although our results showing a declining associated risk for HF and stroke following AF are in line with those for other Western populations, the 1-year rates of HF and stroke are 0.2%/year and 1.8%/year, which are still higher than 0.1%/year and 0.6%/year in an age- and sex-matched non-AF population in 2013.

SCREENING FOR ATRIAL FIBRILLATION

The early detection of asymptomatic AF could prevent associated ischemic stroke associated by instituting appropriate anticoagulation.13,14 AF first diagnosed at the event of stroke comprise nearly 10% of total ischemic stroke cases. The incidence of screen-detected AF strongly depends on the population screened and screening duration/intensity.37
Screening for atrial fibrillation by 12-lead electrocardiography

To diagnose AF, its documentation on electrocardiogram (ECG) is mandatory. As the misdiagnosis of AF could cause unnecessary risks and costs for patient management, confirming the diagnosis on ECG is essential. The American College of Cardiology/American Heart Association/Heart Rhythm Society guideline of the management of AF recommends the ECG documentation of AF as a class I indication.2 Moreover, AF is frequently asymptomatic, especially in older people.3 As such, symptom-driven ECG has a substantial limitation for detecting AF. One study revealed that 161 of 476 individuals with new subclinical AF were at an increased risk of cardiovascular and all-cause mortality compared to patients with typical symptoms after the adjustment for age and stroke risk score.3 Another study showed that a single-point screening of a general population ≥ 65 years of age detects subclinical AF in 1.4% of cases and that AF is almost always persistent.4 In the prospective EURObservational Research Programme registry, mortality at 1 year was more than 2-fold higher in asymptomatic than symptomatic patients (9.4% vs. 4.2%, p<0.001) independent of age and comorbidities.4 In the Belgrade AF study including consecutive first-diagnosed AF patients, 10-year survival free of ischemic stroke or AF progression was worse in patients with an asymptomatic presentation.5 The SAFE study6 showed that targeted and total population screening for subclinical AF seems cost-effective in people aged ≥65 years, and similar results were repeatedly reported using intermittent ECG screening in different populations.6 A systemic review showed screening of elderly people revealed a prevalence of 2.3% for persistent AF using short-term ECG monitoring or ECG after pulse palpation.6 These findings encourage the further evaluation of systematic AF screening programs in elderly or increased risk populations, such as stroke survivors or patients with intracardiac devices.

Extended-term screening for atrial fibrillation

As elderly populations continue increasing, the incidence of subclinical AF is also increasing.6 Furthermore, due to recent advances in new technologies, underdiagnosed AF could be detected. Stepwise screening with 12-lead ECG and handheld ECG recordings increased the rate of diagnosis of asymptomatic paroxysmal AF in unselected residents of Halmstad, Sweden aged 75–76 years.6 Long-term monitoring with implantable or wearable devices like smartphones or smart watches has been validated for the detection of short-term asymptomatic AF.

In the REHEARSE-AF study, self-screening using a handheld ECG device once or twice weekly demonstrated a hazard ratio of 3.9 for the detection of AF at 12 months compared with routine care.6 A nongovernmental organization–led community-based screening program based around community centers demonstrated that the prevalence of AF was 2.3% and newly diagnosed AF was 0.69% with a mean CHA2DS2-VASc score of 3.9±1.5.6 The ASSERT-II study investigated the prevalence of subclinical AF among 256 patients with an average left atrial volume of 76.5 mL using implantable loop recorders, and subclinical AF lasting ≥ 5 minutes was detected among 34.4% of patients per year over a mean follow-up of 16 months.6 From these data, the AF-SCREEN group, an international collaboration including more than 100 physicians, nurses, allied health professionals, health economists, and patient advocates, endorsed the use of routine screening of at-risk populations.6

Screening of patients with intracardiac device or previous stroke

A cardiac-implanted electronic device (CIED) could continuously monitor atrial rhythm and detect atrial high-rate episodes (AHRE). However, AHRE has been not used to detect AF. A
minimum 5-minute AHRE duration had clinical relevance in the MOST study.\textsuperscript{51} Alternative arbitrary or data-derived AHRE burden cut points ranging from 5 minutes to 24 hours have been explored over the subsequent 10 years.\textsuperscript{50} The ASSERT study indicated that stroke risk was increased only in patients with AHRE $\geq 24$ hours.\textsuperscript{53} The stroke risk in AHRE patients seemed lower than that in patients with diagnosed AF,\textsuperscript{54} and strokes often occur without AHRE being detected within 30 days before the event.\textsuperscript{55-58} Patients with CIED should be regularly screened for AHRE, while those with AHRE should undergo further assessments for stroke risk factors and overt AF, including ECG monitoring.

Stroke is the first manifestation of AF in >25\% of AF-related stroke cases.\textsuperscript{59} In the Swedish registry of ischemic strokes, approximately 9\% were associated with subclinical AF and 20\% with undertreated AF,\textsuperscript{59,60} whereas in a global registry, 10\% were caused by previously unknown AF.\textsuperscript{61} Sequential ECG monitoring detected AF in 23.7\% of stroke survivors\textsuperscript{52} and in 11.5\% in different meta-analyses of prospective observational studies or randomized controlled trials (RCTs),\textsuperscript{59} with variations depending on optimal timing, methods, and duration of monitoring for the detection of AF. Cryptogenic stroke defined as the cause of ischemic stroke remains uncertain despite a complete diagnostic evaluation.\textsuperscript{63} AF detection is not uncommon in unselected stroke patients (hazard ratio [HR], 6.2; 95\% confidence interval [CI], 4.4–8.3),\textsuperscript{64} but is more likely in patients with cryptogenic stroke with implantable loop recorders or who have undergone prolonged ECG monitoring.\textsuperscript{64-65}

Accordingly, prolonged ECG monitoring seems reasonable in all survivors of ischemic stroke without overt AF.

### Summary of recommendations for AF screening

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients &gt;65 years of age.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with transient ischemic attack (TIA) or ischemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended to interrogate pacemakers and ICDs on a regular basis for AHRE. In cases of AHRE detected by a CIED of at least 5 minutes duration, we suggest that direct analysis of electrograms corresponding to AHRE is clinically indicated to exclude artifacts or other causes of inappropriate detection of atrial tachyarrhythmias or AF (ungraded consensus-based statement).</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In stroke patients, additional ECG monitoring by long-term noninvasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Systematic ECG screening may be considered to detect AF in patients aged &gt;75 years, or those at high stroke risk.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

### DETECTION AND MANAGEMENT OF RISK FACTORS AND CONCOMITANT CARDIOVASCULAR DISEASE

Several concomitant conditions are closely related to AF development, recurrence, and complications. The prevention, detection, and treatment of these conditions are essential to preventing AF and reducing its burden. AF independently increases all-cause mortality, and only 1 in 10 deaths in AF patient are related to stroke, while >7 in 10 are cardiovascular.\textsuperscript{66} Hence, cardiovascular and comorbidity risk management is essential as part of the holistic or integrated care of AF management to reduce deaths and hospitalisations.\textsuperscript{66}
HF and AF coexist in many patients and can exacerbate each other. HF is a risk factor of AF (HR, 1.43; 95% CI, 0.85–2.40).\(^{67,68}\) The principal of AF management in HF patients does not differ from that in patients without HF, and these efforts should be performed regardless of left ventricular ejection fraction (LVEF).\(^{69}\) Appropriate OAC therapy by patient stroke risk is crucial and optimal HF therapy by guideline is also important.\(^{69}\) Angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) with a beta-blocker or eplerenone reduced the risk of new-onset AF in patients with reduced LVEF HF patients.\(^{70-74}\) According to recently published data in the CASTLE-AF trial, catheter ablation of AF reduced the risk of all-cause death (47%) and cardiovascular death (51%) in patients with HF and reduced LVEF.\(^{75}\) Catheter ablation of AF in HF patients could be a treatment option for improvement outcomes in selected patients.

Hypertension is a risk factor of AF development (HR, 1.32; 95% CI, 1.08–1.60) and a risk factor of stroke and bleeding in AF patients. Good blood pressure control should be considered part of the optimal care of AF patients.\(^{68,69,77}\) Several previous reports suggested that ACEIs or ARBs had a beneficial effect on new-onset AF and the prevention of AF recurrence.\(^{70-72,78-82}\)

Diabetes is a commonly prevalent comorbidity with AF sharing common risk factors.\(^{83-86}\) Diabetes is a risk factor of AF (HR, 1.25; 95% CI, 0.98–1.60) and a risk factor of stroke in AF patients, with no profound differences between type I and type II diabetes.\(^{68,87,88}\) Although there is no evidence that intensive glycemic control does not reduce AF development, diabetes severity is associated with an increased risk of AF development (e.g. diabetic retinopathy).\(^{87,89}\)

**INTEGRATED TREATMENTS FOR ATRIAL FIBRILLATION PATIENTS**

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

Use of the ABC pathway of integrated care management is suggested as follows: 1) ‘A’ Avoid stroke with Anticoagulation; 2) ‘B’ Better symptom management (i.e. patient-centered, symptom directed decisions on rate vs. rhythm control); 3) ‘C’ Cardiovascular and comorbidity management, including lifestyle factors (Figure 7).\(^{90}\) Application of the simple ABC pathway allows the streamlining of integrated care for AF patients in a holistic manner and has been reported to be associated with a lower risk of adverse outcomes, including recent data in a Korean cohort.\(^{66}\) An integrated approach for AF management is the basis of consistent guideline-based treatment of AF and such guideline adherence helps improve patient outcomes.\(^{91-94}\)

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

Integrated AF care include patient's active participation, multidisciplinary approach technology use, and all treatment approach (Table 3).

Active patient participation

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

Table 3. Integrated AF treatment

<table>
<thead>
<tr>
<th>Patient's active participation</th>
<th>Multidisciplinary approach</th>
<th>Technology use</th>
<th>All treatment approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients oriented treatment</td>
<td>• Physicians (primary care physicians, cardiologists, cardiovascular surgeons, arrhythmia specialists, and stroke specialists) and allied health professionals</td>
<td>• Technical support for free communication among team members</td>
<td>• Life style modification</td>
</tr>
<tr>
<td>• Patient education by specialists</td>
<td>• Good communication and education between the patient and the physician</td>
<td>• Checklist and communication tools</td>
<td>• Anticoagulation</td>
</tr>
<tr>
<td>• Encouragement for autonomy, self-management</td>
<td>• Monitoring tool on therapy adherence and effectiveness</td>
<td>• Rate control</td>
<td></td>
</tr>
<tr>
<td>• Proper control on related comorbidities</td>
<td>• Treatment of related comorbidities</td>
<td>• Rhythm control by AADs</td>
<td></td>
</tr>
<tr>
<td>• Patient's active participation on decision marking</td>
<td>• Catheter ablation and surgical interventions (ablation, LAA occluder, AF surgery, etc.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AAD = antiarrhythmic drug; AF = atrial fibrillation; LAA = left atrial appendage.
Self-management includes adapting to the treatment process, changing lifestyles, such as smoking cessation and weight control, and requires patients to be aware of the treatment method and goal.\textsuperscript{97,98}

**Multidisciplinary approach**

A multidisciplinary approach involving primary care physicians, cardiologists, cardiovascular surgeons, arrhythmia specialists, and stroke specialists who first encounter the patient can help the patient actively participate in treatment. By engaging the patient in the stage, the patient can adhere to the treatment, which enhances its effect.\textsuperscript{99,100} Thus, a multidisciplinary approach to AF involves not only specialized medical knowledge but also good communication and education between the patient and physician.

**Technological use for smooth communication among medical staff**

For the integrated treatment of AF, it is essential to communicate and exchange smoothly among members. This requires technical support for free communication between patients and physicians, primary care physicians, and arrhythmia specialists. Digital programs and smartphone apps can help with this process.\textsuperscript{101} One pilot study using a smartphone App shows how this can be operationalized.\textsuperscript{102} Because Korea has high rate of smartphone use, a smartphone App can potentially be used for the management of AF.

**All treatments for atrial fibrillation**

The ABC pathway described above includes proactive assessment and management of cardiovascular disease and risk factors (cardiovascular and comorbidity risk reduction).\textsuperscript{90} To this end, the active management of related diseases such as obesity, hypertension, sleep apnea and diabetes should be performed, and lifestyle corrections such as smoking, drinking, and exercise should be corrected.\textsuperscript{90,103,104}

**Diagnostic approach to atrial fibrillation**

**Integrated assessment of patients with atrial fibrillation**

A review of the history of systemic embolism including cardiac infarction and symptoms of AF and causes should be performed. The possible causes of correction should be assessed through interviews regarding lifestyle habits such as diabetes, hypertension, COPD, obesity, and sleep apnea; underlying diseases such as hyperthyroidism; and drinking or smoking.\textsuperscript{103,120} An analysis of standardized Korean NHIS screening data showed that increased blood pressure and fasting blood sugar alone increased the incidence of AF in pre-hypertensive and pre-diabetic patients.\textsuperscript{103} Even in an analysis of Asian patients with relatively low degree of body mass index, the incidence of AF increased and the prognosis was poor when obesity was comorbid.\textsuperscript{104,121} A 12-lead ECG should be used to evaluate the presence of cardiac conduction disturbances, ischemic heart disease, and structural heart disease. Transthoracic echocardiography should be performed on all patients to determine the treatment strategy for AF.

**Additional diagnostic methods for patients with atrial fibrillation**

Twenty-four-hour Holter monitoring is useful for evaluating heart rate and the relationship between symptoms and AF. In particular, information about heart rate during exercise or activity provided by 24-hour Holter monitoring can be used to determine if the goal of heart rate modulation through drug therapy has been achieved. Transesophageal echocardiography (TEE) is useful for evaluating left atrial function and screening for thrombus in the left atrium. Therefore, the evaluation of intracardiac thrombi through TEE is essential in patients who are undergoing invasive sinus rhythm conversion or radiofrequency ablation.\textsuperscript{122,123}
Follow-up of patients with atrial fibrillation

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

STROKE PREVENTION THERAPY IN ATRIAL FIBRILLATION PATIENTS

Prediction of stroke risk

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

The CHA₂DS₂-VASc score is now used in most guidelines for stroke prevention in patients with AF. The adjusted incidence rates (per 100 person-years) of ischemic stroke were 3.79 in Korea, being 0.26 in low-risk patients (CHA₂DS₂-VASc score 0 [male] or 1 [female]), 1.18 in intermediate-risk patients (CHA₂DS₂-VASc score 1 [male]), and 5.30 in high-risk patients (CHA₂DS₂-VASc ≥2). The incidence rates of patients with a CHA₂DS₂-VASc score of 1 (male), 2, 3, 4, 5, 6, and 7 or more were 1.04, 1.91, 2.54, 4.72, 5.79, 8.36, and 8.82, respectively (Table 4). The more recent focus of stroke prevention in patients with non-valvular AF has shifted away from predicting “high-risk” patients toward initially identifying patients at a “truly low risk” of ischemic stroke in whom OAC has no net clinical benefit. Korean patients who were categorized as “low risk” by the CHA₂DS₂-VASc score (i.e. score 0 in males or 1 in females) consistently had an event rate of <1%/year.

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc score</th>
<th>Number of patients</th>
<th>Ischemic stroke</th>
<th>Ischemic stroke/systemic embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted for aspirin*</td>
</tr>
<tr>
<td>0 (male) or 1 (female)</td>
<td>860</td>
<td>0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>1 (male)</td>
<td>550</td>
<td>1.04</td>
<td>1.18</td>
</tr>
<tr>
<td>2</td>
<td>975</td>
<td>1.91</td>
<td>2.21</td>
</tr>
<tr>
<td>3</td>
<td>911</td>
<td>2.54</td>
<td>2.88</td>
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<tr>
<td>4</td>
<td>836</td>
<td>4.72</td>
<td>5.34</td>
</tr>
<tr>
<td>5</td>
<td>770</td>
<td>5.79</td>
<td>6.54</td>
</tr>
<tr>
<td>6</td>
<td>513</td>
<td>8.36</td>
<td>9.50</td>
</tr>
<tr>
<td>7 or more</td>
<td>440</td>
<td>8.82</td>
<td>9.97</td>
</tr>
<tr>
<td>Total</td>
<td>5,855</td>
<td>3.32</td>
<td>3.79</td>
</tr>
</tbody>
</table>

TE = thromboembolic event.
*Adjustment made for exposure to aspirin treatment, assuming that aspirin provides a 19% reduction in TE risk, to give an indication of ‘untreated’ rates.
85.7% in CHADS2 and 74.8% in the ATRIA study) and negative predictive value (98.8% vs. 95.3% for CHADS2 and 93.7% for the ATRIA study) for the prediction of stroke incidence and was best for predicting the absence of ischemic stroke during 5 years of follow-up (odds ratio, 16.4; 95% CI, 8.8–30.8). However, the CHA2DS2-VASc score had lower net reclassification improvement and c-index suggesting that it is specifically better to discriminate true low-risk AF for stroke.  

Individual stroke risk factors: sex, age, and hypertension

On multivariate analysis, significant associations between CHA2DS2-VASc risk factors and ischemic stroke were observed. The significance of vascular disease or diabetes mellitus were attenuated after multivariate adjustment, and female sex (HR, 0.73; 95% CI, 0.64–0.84) had a lower risk of ischemic stroke than male sex in Korean NHIS sample cohort (Table 5). Coronary and peripheral artery disease have been reported to be important independent risks for stroke in AF. Several cohort studies have shown that female sex is a risk factor for stroke, although this is dependent on age and the presence of other non-sex risk factors. Recently, female sex was suggested as a risk modifier for stroke in patients with AF, rather than a risk factor. Several Asian cohort studies from Hong Kong, China, Taiwan, and Japan have suggested that female sex was not an independent risk factor for ischemic stroke, again suggesting some potential ethnic differences in the risk of stroke between Asian and non-Asian populations. Consistent with previous Asian studies, female sex was not a risk factor for stroke in a Korean cohort; instead, it was associated with a lower stroke risk of ischemic stroke than male sex. Other risk factors in our population such as older age, previous stroke or TIA history, HF, and hypertension remained independent stroke risk factors consistent with findings in western cohorts.

Older age is the most important predictor of ischemic stroke in Korean and Taiwan patients with AF. Patients aged 65–74 years without other risk factors showed a significantly higher risk of stroke than those with one risk factor other than age. Lowering the current age threshold (age ≥65 years) in the CHA2DS2-VASc score to age ≥55 years might be appropriate among Asian patients with AF. Two recent Korean studies suggested that blood pressure should be controlled more strictly in AF patients.

<table>
<thead>
<tr>
<th>Table 5. Associations between baseline factors and ischemic stroke in patients without anticoagulant treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>65–74</td>
</tr>
<tr>
<td>75</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Ischemic stroke/TIA</td>
</tr>
<tr>
<td>Atherosclerotic disease</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>Vascular disease*</td>
</tr>
<tr>
<td>HF</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>ESRD</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Aspirin use</td>
</tr>
</tbody>
</table>

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; HF = heart failure; HR = hazard ratio; TIA = transient ischemic attack.
*Vascular disease includes previous myocardial infarction, peripheral arterial disease, or aortic plaque.
Recommended anticoagulation for Korean patients.

The performance of CHA₂DS₂-VASc score in Korean populations is comparable with that seen in Western populations. For patients with AF without valvular heart disease, including those with paroxysmal AF, who are at low risk of stroke (e.g., CHA₂DS₂-VASc score of 0 in males or 1 in females), we suggest no antithrombotic therapy (class III). The next step is to consider stroke prevention (i.e., OAC therapy) for patients with 1 or more non-sex CHA₂DS₂-VASc stroke risk factors. For patients with a single non-sex CHA₂DS₂-VASc stroke risk factor, we suggest OAC rather than no therapy, aspirin, or combination therapy with aspirin and clopidogrel (class IIa); and for those at high risk of stroke (e.g., CHA₂DS₂ ≥2 in males or ≥3 in females), we recommend OAC rather than no therapy, aspirin, or combination therapy with aspirin and clopidogrel (class I) (Figure 8).

Where we recommend or suggest in favor of OAC, we suggest using a NOAC rather than adjusted-dose vitamin K antagonist therapy. With the latter, it is important to aim for good quality anticoagulation control with a time in therapeutic range (TTR) >70%. Attention to modifiable bleeding risk factors (e.g., uncontrolled blood pressure [BP], labile INRs, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in an anticoagulated patient, alcohol excess) should be made at each patient contact, and the HAS-BLED score used to assess the risk of bleeding whereby ‘high risk’ patients (score ≥3) should be reviewed and followed up more frequently. While NOACs are increasingly the preferred option, warfarin is still widely used and the SAMe-TTTR₂ score (which has been validated even in Asian cohorts)¹⁴⁰ can help identify patients less likely to do well on warfarin, so as to arrange more frequent INR checks, education and counselling – or to consider a NOAC instead of warfarin (Figure 9).⁵

Dynamic adjustment of stroke and bleeding risk

Many clinical variables of stroke and bleeding risk score have “dynamic” variation through follow-up.¹⁴¹⁻¹⁴³ Age increases annually in all patients, and incident hypertension, diabetes mellitus, vascular disease, congestive HF, and prior stroke or transient ischemic attack may become evident in some patients. These dynamic changes in risk factors may increase the

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**Figure 8.** Stroke prevention strategy in patients with AF. AF = atrial fibrillation; HF = heart failure; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulation. *CHA₂DS₂-VASc score: a congestive HF, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74, female.

---
CHA<sub>2</sub>DS<sub>2</sub>-VASc score, stroke risk category, and absolute ischemic stroke rate. Despite using only baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc score to predict the risk of ischemic stroke in AF patients, a time-dependent CHA<sub>2</sub>DS<sub>2</sub>-VASc score and “delta CHA<sub>2</sub>DS<sub>2</sub>-VASc score” (follow-up minus baseline) improved the prediction of ischemic stroke in Korean and Taiwan AF populations (Figure 10).<sup>141,142</sup>

Figure 9. Practical management algorithm in light of the 2018 American College of Chest Physicians guidelines, which are evidence based and GRADE.
AF = atrial fibrillation; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation therapy.
*HAS-BLED: hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (0.65), drugs/alcohol concomitantly (1 point each).

CHA<sub>2</sub>DS<sub>2</sub>-VASc score, stroke risk category, and absolute ischemic stroke rate. Despite using only baseline CHA<sub>2</sub>DS<sub>2</sub>-VASc score to predict the risk of ischemic stroke in AF patients, a time-dependent CHA<sub>2</sub>DS<sub>2</sub>-VASc score and “delta CHA<sub>2</sub>DS<sub>2</sub>-VASc score” (follow-up minus baseline) improved the prediction of ischemic stroke in Korean and Taiwan AF populations (Figure 10).<sup>141,142</sup>

Figure 10. Receiver operating characteristic curves of Δ CHA<sub>2</sub>DS<sub>2</sub>-VASc score for predicting ischemic stroke during the entire second follow-up period. AUC = area under the curve; CI = confidence interval; SE = standard error.
 Recommended non-vitamin K oral anticoagulants dose regimen for Korean patients
The benefits of NOAC was more profound in Asian population than non-Asian population. Based on the standard dose group, NOAC was more effective (OR of stroke/systemic embolism, 0.65 vs. 0.85; p interaction=0.045) and safer (OR for major bleeding, 0.57 vs. 0.89; p interaction=0.046) in Asians than non-Asians. Among high-risk Asian AF population, dabigatran, rivaroxaban, and apixaban demonstrated similar risk of ischemic stroke and lower risk of intracerebral hemorrhage compared with warfarin. All-cause death was significantly lower only with dabigatran and apixaban, whereas not with rivaroxaban in a Korean study. However, rivaroxaban also decreased all-cause death in a different Korean study.

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

For Korean patients with AF, a reduced dosing regimen for dabigatran (110 mg b.i.d.) in patients aged ≥75 years or who have an estimated glomerular filtration rate (eGFR) of 30–50 mL/min; rivaroxaban (15 mg once daily [q.d.]) in patients aged ≥80 years or with an eGFR of 15–49 mL/min; apixaban (2.5 mg b.i.d.) if 2 of the 3 following criteria are present: age ≥80 years or an eGFR 15–29 mL/min or body weight ≤60 kg; or edoxaban (30 mg q.d.) if eGFR is 15–50 mL/min are recommended (Table 6).

Low anticoagulation rate
The OAC rate of total AF in the Korean nationwide cohort remains very low at about 18%, while the usage rate of aspirin exceeds 35%. However, the OAC rate of Korean AF was similar to the recent OAC rates of Taiwan nationwide cohort. Li et al. reported that the overall guideline adherence rate was only 13% and even lower among patients with a high

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose reduction criteria</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Creatinine clearance 30–50 mL/min or P-glycoprotein inhibitors* or Clopidogrel, aspirin, NSAIDs</td>
<td>Dabigatran 110 mg b.i.d.</td>
</tr>
<tr>
<td></td>
<td>Increased bleeding risk† or Age 75 years or more</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Age 80 years or more or Creatinine clearance 15–50 mL/min†</td>
<td>Rivaroxaban 15 mg q.d.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>At least 2: 1) age ≥80 years or more, 2) body weight ≥60 kg or less, 3) creatinine ≥1.5 mg/dL</td>
<td>Apixaban 2.5 mg b.i.d.</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>P-glycoprotein inhibitors* or Body weight ≤60 kg or creatinine clearance 15–29 mL/min‡</td>
<td>Edoxaban 30 mg q.d.</td>
</tr>
</tbody>
</table>

b.i.d., bis in die (twice a day or twice daily); NOAC, non-vitamin K antagonist oral anticoagulant; NSAID = nonsteroidal anti-inflammatory drug; q.d., quaque die (once a day or once daily).

*P-glycoprotein inhibitors: amiodarone, verapamil, dronedarone, etc.; †Increased bleeding risk: coagulopathy, thrombocytopenia, platelet dysfunction, recent major trauma or biopsy, infective endocarditis; §Should be used with caution in patients with significant renal impairment (creatinine clearance 15–29 mL/min).
CHA₂DS₂-VASc score in this non-selected nationwide AF registry. Moreover, guideline-adherent antithrombotic management was associated with a 38% lower risk of mortality.

The analysis of a prospective multicenter study performed in tertiary hospitals in Korea (COMparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation [CODE-AF] registry) showed the optimistic future of stroke prevention in patients with AF. The current OAC rate of AF patients with high stroke risk (CHA₂DS₂-VASc score ≥2) was about 83%. Consistently, in patients with at least 3-year regular hospital visit, OAC prescription rate was higher than nationwide AF registry and tertiary hospital-based registry. It was increased from 34.7% to 50.6%, whereas antiplatelet prescription decreased gradually from 48.2% to 31.5% between 2008 and 2015. However, the recent improvement of OAC rate in tertiary hospitals in Korea is related with increased NOAC use because it was >50%, whereas that of warfarin was still low at 20%. Among AF patients with a high stroke risk and at least 3-year regular hospital visits, OAC utilization was lower in the suburban/rural regions than that observed in the urban regions (48.2% vs. 51.8%, respectively; p<0.001).

**BLEEDING RISK**

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

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

- **BP control**: Good control of BP is vital to reduce the risk of stroke and is essential to decrease the risk of bleeding (particularly intracranial haemorrhage) on antithrombotic therapy.
- **Anticoagulation control**: Among patients receiving vitamin K antagonist, maintenance of an INR in the therapeutic range (2.0–3.0) is essential. The proportion of TTR should be at least 65% but the ultimate aim/target should be 100%.
- **Concomitant medication predisposing to bleeding**: Nonessential use of concomitant antiplatelet drugs and NSAIDs should be avoided since these medications increase the risk of bleeding in patients receiving OACs.
- **Alcohol intake**: Excessive alcohol intake (chronic or binge drinking) increases the risk of bleeding predominantly due to the risk of trauma, but in chronic alcohol abuse through poor medication adherence, hepatic and variceal disease.
- **Lifestyle factors**: Avoidance of work and/or leisure activities that have the potential to cause serious trauma should be advised.
- **Bridging periods off anticoagulation**: Interruption of OAC should be avoided to reduce stroke risk since the majority of cardiovascular procedures (e.g., pacemaker implantation or percutaneous coronary intervention [PCI]) can be safely performed on OAC. Bridging (i.e., stopping OAC and providing anticoagulation cover with heparin) should be used in patients with mechanical heart valves but does not appear to be otherwise advantageous.
- **Appropriate choice of OAC**: Choice of OAC should be made on an individual basis after stroke and bleeding risk assessment, discussion with the patient and adherence to the
prescribing label.

- Falls risk and cognitive impairment: The benefits of ischemic stroke reduction generally outweigh the risk of harm from serious bleeding with OAC use. One estimate was that the patient would need to fall 295 times per year for the risk from falls to outweigh the benefits of stroke reduction.\(^{(155)}\)

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

**Bleeding risk assessment**

Attention to modifiable bleeding risks is important. However, only relying on this to assess bleeding risk is an inferior strategy to a formal bleeding assessment score, as shown in independent cohorts even from Asia.\(^{(156-158)}\)

There are multiple bleeding risk scores that have been proposed for bleeding risk stratification, with the HEMORR\(_2\)HAGES (hepatic or renal disease, ethanol abuse, malignancy, older, reduced platelet count/function, hypertension, anemia, genetic factors, excessive fall risk, and stroke), HAS-BLED (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile INR, elderly [0.65], drugs/alcohol concomitantly [1 point each]), ATRIA, ORBIT, and ABC-bleeding scores that have been derived and validated in AF populations.\(^{(159)}\)

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

**Recommendations for stroke prevention in patients with AF**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>The CHA(_2)DS(_2)-VASc score is recommended for stroke risk prediction in patients with AF.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>OAC is recommended for all male AF patients with a CHA(_2)DS(_2)-VASc score ≥2, and all female AF patients with a CHA(_2)DS(_2)-VASc score ≥3.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>OAC should be considered in male AF patients with a CHA(_2)DS(_2)-VASc score of 1, and female AF patients with a CHA(_2)DS(_2)-VASc score of 2 considering individual characteristics and patient preferences.</td>
<td>Ita</td>
<td>B</td>
</tr>
<tr>
<td>In male or female AF patients without additional stroke risk factors (i.e., CHA(_2)DS(_2)-VASc score of 0 in males or 1 in females), anticoagulant or antiplatelet therapy is not recommended for stroke prevention.</td>
<td>III (harm)</td>
<td>B</td>
</tr>
<tr>
<td>In patients with one episode of AF, then stroke prevention with same principles should be recommended.</td>
<td>Ita</td>
<td>B</td>
</tr>
<tr>
<td>Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>When OAC is initiated in a patient with AF who is eligible for a NOAC, a NOAC is recommended in preference to a vitamin K antagonist.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>When patients are treated with a vitamin K antagonist, TTR should be kept as high as possible (ideally aiming for TTR &gt;65–70%) and be closely monitored.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Bleeding risk assessment should be performed for all patients with AF at every patient contact and should initially focus on potentially modifiable bleeding risk factors.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>The HAS-BLED score is recommended to address modifiable bleeding risk factors in all AF patients. Those potentially at high risk (HAS-BLED score ≥3) warrant more frequent and regular reviews or follow-up.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients on vitamin K antagonists with consistently low time in INR therapeutic range (e.g., TTR &lt;65%), we recommend considering interventions to improve TTR or switching to NOACs.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
LEFT ATRIAL APPENDAGE OCCLUSION AND EXCLUSION

Left atrial appendage occlusion devices
Transcatheter left atrial appendage (LAA) occlusion or percutaneous LAA ligation has been performed since LAA was proven to be the major source of thrombus formation in patients with non-valvular AF. Two RCTs (PROTECT AF and PREVAIL) have directly compared the LAA occlusion using a Watchman device® with vitamin K antagonist, and these data suggested that LAA occlusion was non-inferior to vitamin K antagonist for the prevention of stroke in AF patients with a moderate stroke risk.\textsuperscript{[160-163]} Recently published longer-term follow-ups of RCTs have demonstrated that the LAA occlusion might reduce the risk of thromboembolic stroke compared with vitamin K antagonist.\textsuperscript{[164]} A high implantation success rate (98%) with an acceptable procedure-related complication rate of 4% at 30 days was reported in a large recent European registry.\textsuperscript{[165,166]} However, these data were in contrast with the analyses from insurance databases and systematic reviews that claimed higher serious complications related with the implantation procedure, possibly identifying a certain degree of reporting bias. There is also uncertainty how a LAA occlusion would compare against a NOAC. Therefore, the Korean AF guideline recommends that AF patients with contraindications for long-term OAC therapy, a recurrent thromboembolic event, or a high risk of stroke despite OAC therapy may be considered to have LAA occlusion for stroke prevention purposes (class IIb).

Left atrial appendage occlusion or exclusion
Surgical LAA occlusion or exclusion in conjunction with cardiac surgery has been performed with multiple techniques for many decades. The feasibility and safety of surgical LAA occlusion/exclusion were proven in various observational studies.\textsuperscript{[167]} However, limited controlled trial data have been published. The role of concomitant AF surgery and LAA occlusion has been evaluated and reported in an RCT in 2015 without showing a clear benefit of LAA exclusion for stroke prevention in the subgroup undergoing AF surgery. A large RCT is currently underway.\textsuperscript{[168]} Therefore, the Korean AF guideline recommends that patients with AF undergoing cardiac surgery may benefit from surgical occlusion or the exclusion of LAA for stroke prevention (class IIb). Patients undergoing thoracoscopic AF surgery may benefit from surgical occlusion or the exclusion of LAA for stroke prevention (class IIb).

RATE CONTROL
Heart rate control is a substantial part of the treatment of patients with AF despite the remarkable advancement of pharmacologic and non-pharmacologic rhythm control management. An adequately and appropriately controlled ventricular rate can reduce or eliminate symptoms, improve hemodynamics, and prevent tachycardia-induced cardiomyopathy.

Rate control can be achieved with beta-blockers, non-dihydropyridine calcium channel blockers, digoxin, or combination therapy. Certain antiarrhythmic agents including amiodarone and sotalol also have rate-controlling effects, but they should be reserved for patients requiring rhythm control therapy. When considering which drug to use, clinicians should consider the patient’s symptoms, hemodynamic status, presence of HF, and precipitating factors for AF. Medications for acute and long-term rate control are presented in Table 7.
Acute rate control
In patients with new-onset AF, heart rate control is often needed to control symptoms. Clinicians should identify causes of increased heart rate, such as infection, anemia, and thyrotoxicosis. Beta-blockers and non-dihydropyridine calcium channel blockers (diltiazem/verapamil) are preferred for acute rate control because of their rapid action and effectiveness at high sympathetic tone. Beta-blockers and non-dihydropyridine calcium channel blockers (diltiazem/verapamil) are preferred for acute rate control because of their rapid action and effectiveness at high sympathetic tone. Bradycardia, AV block, and hypotension. Lethargy, headache, peripheral edema, upper respiratory tract symptoms, gastrointestinal upset, and dizziness. Use with caution in combination with beta-blockers. Reduce dose with hepatic impairment and start with smaller dose in renal impairment. Contra-indicated in left ventricular failure with pulmonary congestion or LVEF <40%.

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

Table 7. Rate control therapy in patients with AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute rate control (IV)</th>
<th>Long-term rate control (PO)</th>
<th>Adverse effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Not available</td>
<td>1.25–10 mg q.d. or split</td>
<td>Bradycardia, AV block, and hypotension.</td>
<td>Bronchospasm is rare. In cases of asthma, recommend beta-1 selective agents. Contra-indicated in acute HF and a history of severe bronchospasm.</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Not available</td>
<td>12.5–100 mg b.i.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nebivolol</td>
<td>Not available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>500 mcg/kg IV bolus over 1 minutes, then 50–250 mcg/kg/min</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg IV bolus over 2 minutes, then 5–15 mg/h</td>
<td>60–120 mg t.i.d.</td>
<td>Bradycardia, AV block, and hypotension.</td>
<td>Use with caution in combination with beta-blockers. Reduce dose with hepatic impairment and start with smaller dose in renal impairment. Contra-indicated in left ventricular failure with pulmonary congestion or LVEF &lt;40%.</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Verapamil</td>
<td>0.075–0.15 mg/kg IV bolus over 2 minutes, then 5 mcg/kg/min</td>
<td>40–120 mg t.i.d.</td>
<td>Dizziness, malaise, lethargy, headache, hot flushes, gastrointestinal upset, and edema.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td>Gastrointestinal upset, dizziness, blurred vision, headache, and rash. In toxic states (serum levels &gt;2 ng/mL), digoxin is proarrhythmic and can aggravate HF, particularly with coexistent hypokalemia.</td>
<td>High plasma levels associated with increased risk of death. Check renal function before starting and adapt dose in patients with CKD. Contra-indicated in patients with accessory pathways, ventricular tachycardia and hypertrophic cardiomyopathy with outflow tract obstruction.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg IV with repeated dosing to a maximum of 0.75–1.5 mg over 24 hours</td>
<td>0.0625–0.25 mg q.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>300 mg IV over 1 hour, then 10–50 mg/hr over 24 hours (preferably via central venous catheter)</td>
<td>100–200 mg q.d.</td>
<td>Hypotension, bradycardia, nausea, QT prolongation, pulmonary toxicity, skin discoloration, thyroid dysfunction, corneal deposits and cutaneous reaction with extravasation.</td>
<td>Suggested as adjunctive therapy in patients where heart rate control cannot be achieved using combination therapy.</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; AV = atrioventricular; b.i.d. = twice a day or twice daily; CKD = chronic kidney disease; ER = extended release; HF = heart failure; IV = intravenous; LVEF = left ventricular ejection fraction; PO = per os; q.d. = once a day or once daily; t.i.d. = 3 times a day.
In patients with left ventricular dysfunction (EF <40%), beta-blockers, digoxin, or their combination are preferred. However, beta-blockers should be avoided in patients with asthma or COPD. Beta-blockers help rate control but may not have prognostic benefit in HF. Lenient rate control (heart rate <110/min) is usually acceptable regardless of HF status, but stricter rate control is required if symptoms remain uncontrolled (Figure 11).

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

**Recommendations for rate control in patients with AF**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥40%.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF &lt;40%.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Combination therapy comprising different rate controlling agents should be considered if a single agent does not achieve the necessary heart rate target.</td>
<td>Ia</td>
<td>C</td>
</tr>
<tr>
<td>In patients with hemodynamic instability or severely depressed LVEF, amiodarone may be considered for acute control of heart rate.</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td>In patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), antiarrhythmic drugs (AADs) should not routinely be used for rate control.</td>
<td>III</td>
<td>(harm)</td>
</tr>
<tr>
<td>A resting heart rate of &lt;110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy.</td>
<td>Ia</td>
<td>B</td>
</tr>
<tr>
<td>Rhythm rather than rate control strategies should be considered as the preferred management in preexcited AF and AF during pregnancy.</td>
<td>Ia</td>
<td>C</td>
</tr>
<tr>
<td>AV node ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, accepting that these patients will become pacemaker dependent.</td>
<td>Ia</td>
<td>B</td>
</tr>
</tbody>
</table>

**RHYTHM CONTROL**

The purpose of rhythm control management is to improve hemodynamic instability and AF-related symptoms for restoring and maintaining sinus rhythm. The restoration and maintenance of sinus rhythm after AAD treatment are more effective than those after
placebo treatment. However, it remains inconclusive whether superior rhythm control management improves prognosis in anticoagulated patients with AF. Additional invasive ablation therapy has been developed for and applied in medically refractory AF patients and prospective large-scale trials (CODE-AF, EAST-AFNET, and CABANA) attributed quality of life and prognosis improvements to the beneficial effect of rhythm control strategies in patients with AF.

**Acute rhythm control strategy**

Electrical direct current cardioversion is the only rapid and effective procedure to restore sinus rhythm in hemodynamically unstable AF patients. Electrical cardioversion was safely conducted in sedated or anesthetized AF patients with intravenous midazolam or propofol; when used, vital signs, especially O$_2$ saturation, should be monitored. During the post-cardioversion period, the skin to which the patch is attached and serial ECG should be monitored for burns or severe bradycardia.

Pretreatment with flecainide, propafenone, amiodarone, and sotalol (not beta-blocker, verapamil, or digoxin) could improve the efficacy of restoration and maintenance of sinus rhythm during the post-cardioversion period. AADS for pharmacological cardioversion are presented in Table 8. Proper anticoagulation is needed in AF patients prior to electrical cardioversion because anticoagulation dramatically reduced the risk of embolic stroke. AF patients planned to undergo electrical cardioversion should be anticoagulated from 3 weeks before to 4 weeks after unless permanent anticoagulation is indicated. A recent NOAC trial demonstrated the efficacy of preventing the occurrence of embolic stroke in AF patients subjected to electrical cardioversion.

A meta-analysis demonstrated that AADS could also efficiently restore and maintain sinus rhythm as rhythm control management. In AF patients with stable hemodynamic status, prescription AADS could be the main option (easily available) in general practice without sedation or starvation during pretreatment compared with electrical cardioversion. Flecainide and propafenone are the most common AADS for acute rhythm management, but they are relatively contraindicated in AF patients without structural heart disease. Amiodarone could be prescribed to AF patients with structural heart disease and reduce the heart by >10–12 beats per minute within intravenous infusion after 8–12 hours. Both amiodarone and flecainide are more efficient at restoring sinus rhythm than sotalol. A single oral dose of flecainide 200–300 mg or propafenone 450–600 mg could be taken to control paroxysmal AF-related symptoms and restore sinus rhythm out of the hospital in experienced AF patients as confirmed in previous hospitalization (Figure 12A).

### Table 8. AADS for pharmacological cardioversion

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosage</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Oral</td>
<td>Oral 600–800 mg daily in divided doses to a total load of up to 10 g, then 200 mg q.d. as maintenance</td>
<td>Gastrointestinal upset, constipation, bradycardia/AV block, hypotension, QT prolongation, torsades de pointes (rare), phlebitis (IV), increased INR</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>150 mg over 10 minutes, then 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours or change to oral dosing</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>Oral</td>
<td>200–300 mg</td>
<td>Atrial flutter with 1:1 AV conduction, ventricular proarrhythmia, hypotension</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Oral</td>
<td>450–600 mg</td>
<td>Atrial flutter with 1:1 AV conduction, ventricular proarrhythmia, hypotension</td>
</tr>
</tbody>
</table>

AAD = antiarrhythmic drug; AV = atrioventricular; INR = international normalized ratio; IV = intravenous; q.d. = once a day or once daily.
Long-term rhythm control strategy

Physician preference and the improvement of AF-related symptoms, drug compliance, pro-arrhythmic side effects, and extra-cardiac toxicities should be considered in long-term rhythm control management. AADs for the maintenance of sinus rhythm are presented in Table 9. In addition, lifestyle modifications and well-controlled cardiovascular disease could be additionally beneficial for preventing AF recurrence and maintaining sinus rhythm in patients treated with AADs during long-term rhythm control management.232

Figure 12. AF rhythm control management. (A) acute onset AF and (B) long-term AF. AF = atrial fibrillation.
AAD safety must be considered in terms of pro-arrhythmic side effects and extra-cardiac toxicities. Flecainide, propafenone, and pilsicainide are indicated to control rhythm in AF patients without structural heart disease but are contraindicated in AF patients with ischemic heart disease or with left ventricular dysfunction due to poor prognosis. Extra-cardiac toxicity is rarely reported. Flecainide, propafenone, and pilsicainide should be prescribed with an AV nodal blocker for the prevention of use dependency (increased ventricular rate in atrial flutter). Propafenone has a beta-blocker effect and is a substrate (7% of the general population has no CYP2D2). In a recent meta-analysis, class IC AAD use was not significantly correlated with all-cause mortality compared with class IA AAD and class III sotalol uses. Class IC AADs also significantly reduced the recurrence of AF and had efficacy similar to dronedarone but inferior to amiodarone.

Amiodarone can be prescribed in patients with left ventricular dysfunction. QT interval and U wave should be monitored to prevent torsade de pointes. In particular, long-term amiodarone therapy may have extra-cardiac toxicity in the liver, thyroid, lung, skin, and cornea. Therefore, amiodarone should be replaced by an alternative AAD if any side effects or toxicities appear during long-term therapy. Dronedarone reduces the heart rate, maintains sinus rhythm, and reduces cardiovascular mortality and hospitalization in paroxysmal or persistent AF patients. However, dronedarone increased the mortality rate in decompensated HF. Sotalol showed inferior efficacy to amiodarone and similar efficacy to propafenone for maintaining sinus rhythm. Sotalol could effectively suppress the re-entry mechanism. Sotalol may be the first choice for long-term rhythm control management in AF patients with ischemic heart disease. However, sotalol is prone...
to inducing QT prolongation, and caution is needed in females, renal impairment and if left ventricular hypertrophy is present.\textsuperscript{238)

**Recommendations for rhythm control strategies in patients with AF**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm control therapy is indicated for symptom improvement in patients with AF.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Management of cardiovascular risk factors and avoidance of AF triggers should be pursued in patients on rhythm control therapy to facilitate maintenance of sinus rhythm.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>With the exception of AF associated with hemodynamic instability, the choice between electrical and pharmacological cardioversion should be guided by patient and physician preferences.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>The choice of AAD needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Dronedarone, flecainide, propafenone, or sotalol are recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable CAD, and without HF.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with HF.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Amiodarone is more effective in preventing AF recurrences than other AAD, but extracardiac toxic effects are common and increase with time. For this reason, other AAD should be considered first.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Patients on AAD therapy should be periodically evaluated to confirm their eligibility for treatment.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ECG recording during the initiation of AAD therapy should be considered to monitor heart rate, detect QRS and QT interval prolongation, and the occurrence of AV block.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>AAD therapy is not recommended in patients with prolonged QT interval (&gt;0.5 seconds) or those with significant sinoatrial node disease or AV node dysfunction who do not have a functioning permanent pacemaker.</td>
<td>III</td>
<td>(harm)</td>
</tr>
<tr>
<td>Adding atrial-based bradycardia pacing to drug treatment that induces or exacerbates sinus node dysfunction should be considered to allow continuation of AAD therapy in patients in whom AF ablation is declined or not indicated.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Continuation of AAD therapy beyond the blanking period after AF ablation should be considered to maintain sinus rhythm when recurrences seem likely.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

**Anticoagulation in patients who undergo cardioversion**

The periprocedural risk of thromboembolic events during cardioversion can be substantially reduced by adequate anticoagulation.\textsuperscript{210} In patients with AF or an atrial flutter ≥48 hours or with an unknown duration, OAC with vitamin K antagonist (INR, 2.0–3.0) is recommended for at least 3 weeks before electrical or pharmacological cardioversion and 4 weeks afterward regardless of CHA\textsubscript{2}DS\textsubscript{2}-VASc score.\textsuperscript{3} If early cardioversion is attempted, TEE should be performed to exclude the presence of left atrial thrombus.\textsuperscript{240} After 4 weeks, long-term anticoagulation is decided based on each patient’s risk of stroke using CHA\textsubscript{2}DS\textsubscript{2}-VASc score. Subgroup analyses of phase 3 clinical trials\textsuperscript{249-251} and recent prospective RCTs of rivaroxaban,\textsuperscript{252} edoxaban,\textsuperscript{253} and apixaban\textsuperscript{254} have demonstrated that electrical cardioversion in patients treated with a NOAC for ≥3 weeks had similar periprocedural thromboembolic and bleeding risks to those treated with warfarin. Therefore, anticoagulation using NOAC can be an alternative to vitamin K antagonist in patients who undergo cardioversion. Because routine coagulation tests do not accurately measure the anticoagulation effects of NOACs, if patient adherence to the NOAC regimen is uncertain, TEE can be performed prior to cardioversion.\textsuperscript{255} No RCTs have compared anticoagulation strategies in patients with AF or an atrial flutter ≤48 hours. It is common practice to perform cardioversion after a single dose of unfractionated heparin (UFH) or low molecular weight
heparin (LMWH) without TEE. Although data are limited, it is reasonable to administer a single dose of NOAC ≥4 hours before cardioversion instead of UFH or LMWH. Importantly, TEE or anticoagulation ≥3 weeks before cardioversion can be considered in patients with a high stroke risk or an AF duration ≤48 hours.

Recommendations for stroke prevention in patients undergoing cardioversion

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>TEE is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients where thrombus is identified on TEE, effective anticoagulation is recommended for at least 3 weeks.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Early cardioversion can be performed without TEE in patients with a definite duration of AF &lt;48 hours.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In patients where thrombus is identified on TEE, effective anticoagulation is recommended for at least 3 weeks.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

ANTICOAGULATION IN SPECIFIC CONDITIONS

Atrial fibrillation patients undergoing percutaneous coronary intervention

Antithrombotic regimen

An estimated 5–15% of AF patients may undergo PCI in the future. However, it is very challenging to choose optimal antithrombotic regimens for AF patients treated with PCI. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (clopidogrel) is essential for patients treated with PCI to prevent stent thrombosis. On the other hand, OAC is imperative to preventing stroke in AF patients. Thus, theoretically, triple therapy, combining all drugs including DAPT and OAC, may be a reasonable choice as an initial antithrombotic regimen. However, prolonged triple therapy has been associated with an increased risk of bleeding and even mortality. In a large Korean observational study, triple therapy with aspirin, clopidogrel, and warfarin was associated with a 4.5-fold increased risk of major bleeding compared to DAPT.

Recent well-designed RCTs suggested dual therapy with a single antiplatelet agent and an OAC might be safer and show similar efficacy to triple therapy for preventing ischemic/thromboembolic events. Dual therapy with clopidogrel and NOAC was suggested to be a safe initial alternative regimen to triple therapy. However, in patients with high ischemic event risk, short-term triple therapy still seems warranted. Thus, we recommend the following (Figure 13). First, as initial antithrombotic treatment, triple therapy should be used for as short a duration as possible unless patients are at high risk of ischemic events. Second, dual therapy should be continued after the cessation of the triple therapy until 12 months after PCI. Third, dual therapy with clopidogrel and NOAC could be considered as an alternative initial antithrombotic regimen in patients with a high risk of bleeding (e.g. HAS-BLED ≥3). Fourth, monotherapy with OAC should be considered 12 months after PCI.
Meanwhile, the safety of potent P2Y12 inhibitors (prasugrel, ticagrelor) has not been well evaluated in this population. Clopidogrel is the first recommended P2Y12 inhibitor. We discuss the evidence of dual therapy and monotherapy below.

**Dual therapy with clopidogrel and warfarin**

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

**Dual therapy with clopidogrel and non-vitamin K oral anticoagulants**

The efficacy and safety of dual therapy with clopidogrel and NOAC have been demonstrated in RCTs. In the PIONEER AF-PCI trial, dual therapy with a fixed dose of rivaroxaban 15 mg and a P2Y12 inhibitor (mostly clopidogrel) was compared with triple therapies with very-low-dose rivaroxaban (2.5 mg b.i.d.) or warfarin. In that study, the two rivaroxaban arms

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Figure 13. Suggested algorithm for antithrombotic therapy in patients undergoing PCI. NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; TTR = time in therapeutic range.
reduced the risk of clinically significant bleeding compared with triple therapy with warfarin, while the ischemic/thrombotic events were comparable. The results should be interpreted carefully. The trial design is complex (DAPT duration varied) and underpowered for the comparison of the ischemic events. Rivaroxaban 2.5 mg has not been evaluated for stroke prevention in AF patients.

The RE-DUAL PCI trial compared dual therapy with two doses of dabigatran (110 or 150 mg b.i.d.) combined with a P2Y12 inhibitor (clopidogrel in 88%, ticagrelor in 12%) and triple therapy consisting of aspirin, a P2Y12 inhibitor (clopidogrel in 92%, ticagrelor in 8%), and warfarin. The dabigatran arms were associated with a reduced risk of major or clinically relevant nonmajor bleeding (dabigatran 110 mg: HR, 0.52; dabigatran 150 mg: HR, 0.72) compared to triple therapy with warfarin, while the risk of ischemic/thromboembolic events was comparable. This trial was also underpowered to compare the individual ischemic/thromboembolic events, although as an adequately powered secondary efficacy composite outcome, the combined dabigatran arms were no significantly different to the warfarin-based arm. Both used dosages of dabigatran that have been proven to prevent stroke in AF patients.

The AUGUSTUS and ENTRUST-AF trials are the ongoing RCTs of apixaban and edoxaban, respectively. The AUGUSTUS trial in particular will present the efficacy and safety of many different regimens of antithrombotic therapy including triple therapy with on-label dosages of NOAC.

**Monotherapy with oral anticoagulation**

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

**Anticoagulation in patients who undergo catheter ablation of atrial fibrillation**

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

**Anticoagulation therapy and renal function**

Patients with AF and moderate to severe renal dysfunction are at an increased risk of simultaneous ischemic stroke and major bleeding. Therefore, the use of OACs in AF patients with renal dysfunction is troublesome. In AF patients with moderate to severe renal dysfunction and a CHA\(_2\)DS\(_2\)-VASc score ≥2, the use of OACs was approved as beneficial for lowering the event rate of ischemic stroke despite the mildly increased risk of bleeding.

In a meta-analysis, NOACs were better than warfarin for reducing the risk of stroke/systemic embolism as well as major bleeding in AF patients with mild to moderate renal dysfunction. During NOAC use, renal function should be monitored carefully.

In patients with moderate renal dysfunction, NOAC dose should be reduced. Dabigatran should be reduced to 110 mg b.i.d. in patients with creatinine clearance of 30–50 mL/min. Rivaroxaban should be reduced to 15 mg q.d. in patients with creatinine clearance of 15–50 mL/min. Apixaban should be reduced to 2.5 mg b.i.d. in patients with serum creatinine ≥1.5 mg/dL and age ≥80 years or body weight ≤60 kg. Edoxaban should be reduced to 30 mg q.d. in patients with creatinine clearance of 15–50 mL/min. Table 3 shows the recommended dose reduction of NOAC in Korea.

In patients with severe renal dysfunction (creatinine clearance <15 mL/min), NOAC use is not recommended. OAC use may be inappropriate in patients with renal dysfunction who are on dialysis, although the data are weak and often do not consider TTR. However, if TTR is >70%, warfarin may have some benefits even in dialysis patients. However, apixaban has United States Federal Drug Administration (FDA)-approved indication for use in hemodialysis patients. Based on data from the apixaban package insert, patients with AF may receive full-dose therapy (5 mg b.i.d.) while on hemodialysis as long as they are <80 years of age and weigh > 60 kg in the United States. If a patient is on dialysis and is >80 years of age or weighs <60 kg, then the dose is reduced to 2.5 mg b.i.d. A recent study in end stage renal failure showed no significant differences between anticoagulants in the risks of stroke or systemic embolism; however, Apixaban was associated with a 28% lower risk of major bleeding than warfarin. The results of the current analysis are in contradiction to bleeding-related morbidity and mortality attributed to dabigatran and rivaroxaban in a previous analysis of hemodialysis patients, suggesting that the increased bleeding risk in end-stage kidney disease is not a drug class effect for all DOACs. No prospective study has examined OAC therapy in patients with renal transplantation. Nonetheless, OAC doses should be adjusted according to the creatinine clearance of the donor’s kidney.

In patients with a creatinine clearance ≥ 95 mL/min, dabigatran 150 mg b.i.d., rivaroxaban 20 mg q.d., and apixaban 5 mg b.i.d. are recommended. Edoxaban 60 mg q.d. is not recommended according to FDA approval. Recent studies showed that edoxaban was effective overall, but low-dose edoxaban had lower relative effectiveness for preventing stroke or systemic embolism than with warfarin at higher creatinine clearance levels (>95 mL/min) in Korean AF patients. Similar data was observed for CrCl >95 mL/min with apixaban and rivaroxaban, but not dabigatran.
Anticoagulation therapy in elderly patients

Increasing age is a risk factor for simultaneous stroke and major bleeding in patients with AF.\textsuperscript{295-299} The elderly population is fragile and prone to falls. Nonetheless, OAC use is recommended in elderly AF patients because of the high benefit/risk ratio.\textsuperscript{300} Recent Asian data showed that Among patients with AF ≥90 years of age, warfarin was associated with a lower risk of ischemic stroke and positive net clinical benefit. Compared with warfarin, NOACs were associated with a lower risk of intracranial haemorrhage. Thus, OACs may still be considered as thromboprophylaxis for elderly patients, with NOACs being the more favorable choice.\textsuperscript{300,301-303}

All 4 NOACs in the elderly population are approved as beneficial for the risk reduction of intracranial bleeding compared with warfarin.\textsuperscript{265-286} In the ARISTOTLE trial, apixaban 5 mg b.i.d. reduced major bleeding in patients 65–74 years of age and ≥75 years of age.\textsuperscript{303} In the ENGAGE-TIMI trial, edoxaban 60 mg q.d. decreased the risk of major bleeding in patients <75 years of age but had similar risks in patients >75 years of age compared with warfarin.\textsuperscript{288} However, dabigatran showed a significant age–treatment interaction in the RELY trial. Dabigatran 150 mg b.i.d. reduced major bleeding in patients <75 years of age but an increased risk of major bleeding in patients >75 years of age compared with warfarin.\textsuperscript{265} In the ROCKET-AF trial, rivaroxaban demonstrated a similar risk of major bleeding as warfarin and no age-treatment interaction.\textsuperscript{260} However, the J-ROCKET study and many real-world data suggested that low-dose rivaroxaban might be safe and effective in elderly Asian AF patients with relatively low body weight.\textsuperscript{145,104,105} Therefore, the Korean AF guideline recommends low-dose rivaroxaban (15 mg q.d.) in patients aged ≥80 years.\textsuperscript{208}

CONCLUSIONS

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

The Korean versions of separate guidelines for OAC, rate and rhythm control, risk factor management, and integrated treatment of AF patients are available in the Korean Journal of Medicine (http://ekjm.org/) or the home page of the Korean Heart Rhythm Society (http://k-hrs.org/intro.asp).

ACKNOWLEDGEMENTS

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REFERENCES


189. Kotecha D, Kirchhof P. Rate and rhythm control have comparable effects on mortality and stroke in atrial fibrillation but better data are needed. *Evid Based Med* 2014;19:222-3.


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PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

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266. Lopes RD, Vora AN, Liaw D, et al. An open-Label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: rationale and design of the AUGUSTUS trial. *Am Heart J* 2018;200:17-23.


