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2021 Focused update of the 2017 consensus guidelines of the Asia Pacific Heart Rhythm Society (APHRS) on stroke prevention in atrial fibrillation

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Abstract

The consensus of the Asia Pacific Heart Rhythm Society (APHRS) on stroke prevention in atrial fibrillation (AF) has been published in 2017 which provided useful clinical guidance for cardiologists, neurologists, geriatricians, and general practitioners in Asia-Pacific region. In these years, many important new data regarding stroke prevention in AF were reported. The Practice Guidelines subcommittee members comprehensively reviewed updated information on stroke prevention in AF, and summarized them in this 2021 focused update of the 2017 consensus guidelines of the APHRS on stroke prevention in AF. We highlighted and focused on several issues, including the importance of AF Better Care (ABC) pathway, the advantages of non-vitamin K antagonist oral anticoagulants (NOACs) for Asians, the considerations of use of NOACs for Asian patients with AF with single 1 stroke risk factor beyond gender, the role of lifestyle factors on stroke risk, the use of oral anticoagulants during the “coronavirus

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disease 2019" (COVID-19) pandemic, etc. We fully realize that there are gaps, unaddressed questions, and many areas of uncertainty and debate in the current knowledge of AF, and the physician's decision remains the most important factor in the management of AF.

KEYWORDS

APHRS, atrial fibrillation, consensus guidelines, stroke prevention

1 | EPIDEMIOLOGY OF ATRIAL FIBRILLATION AND RISK OF ATRIAL FIBRILLATION-RELATED STROKE

Atrial fibrillation (AF) is a global problem, with an increasing incidence and prevalence with an ageing population.¹ Although the prevalence of AF appears to be greater in Western countries compared with Asian countries, numerically the population with AF in Asia is substantially greater than in Europe or North America.

In a recent meta-analysis of 58 articles from eight countries in Asia, the community- and hospital-based AF prevalence ranged from 0.37% to 3.56% and 2.8% to 15.8%, respectively.² In the year 2020, the prevalence rates of AF are around 1.5% in Taiwan and 2.1% in South Korea.^{3,4} Similar to western countries, the prevalence rates of AF will continuously increase in the following decades, which are projected to be 4.0% in Taiwan and 5.4% in South Korea in the year 2050 (Figure 1).^{3,4} Notably, the stroke risk of newly diagnosed patients with AF represented by CHA₂DS₂-VASc score of each year gradually increased from 3.53 in year 2000 to 4.44 in year 2011.³ Similarly, the proportions of patients having a CHA₂DS₂-VASc score ≥ 2 increased from 68.8% to 81.2% from 2006 to 2015 in South Korea.⁴

For Asian patients with AF, the annual risk of ischemic stroke is around 3.0% (1.60%–4.95%) based on the pooled analysis of eight studies.² In the Taiwan nonanticoagulated AF cohort, the annual risk

of ischemic stroke was 3.4% which was 3.34-fold higher compared with patients without AF.³ Importantly, the 1-year risk of ischemic stroke after newly diagnosed AF was similar from the year 2000 (4.45%) to 2010 (3.95%),³ and gradually decreased in the era of non-vitamin K antagonist oral anticoagulants (NOACs).⁵ The observed reduction in stroke risk may be contributed to the increasing initiation rates of oral anticoagulants (OACs) in newly diagnosed patients with AF which significantly increased from 13.6% to 35.6%, contemporaneous with the introduction of NOACs (Figure 2).⁵ A similar trend was also reported in Korean AF cohort.^{4,6,7} In the study by Lee et al., the increasing use of OACs (especially with the introduction of NOACs) had led to a reduction in ischaemic stroke-related emergency department visits with no appreciable rise in serious bleeds (Figure 3).⁷

The impact of AF on healthcare costs reflects the increased risk of mortality and morbidity of AF from stroke, heart failure and hospitalisations, which is projected to increase over the next decades in Asia.⁸ Data from UK suggest that AF confers a major impact on healthcare costs, accounting for approx 0.9%–1.6% of NHS expenditure, mostly from primary admissions.⁹ The total cost of AF care was equivalent to 0.78% of the Korean NHIS total expenditure in 2015.¹⁰ The stroke and mortality risks of AF are often in association with multiple cardiovascular and noncardiovascular comorbidities, that often occur in multimorbidity clusters, that would impact on prognosis.¹¹ The increasing use of OACs (particularly the NOACs) would result in a major reduction in stroke and cardiovascular events, but a more integrated approach to AF management is needed to address the healthcare burden and risks associated with AF.

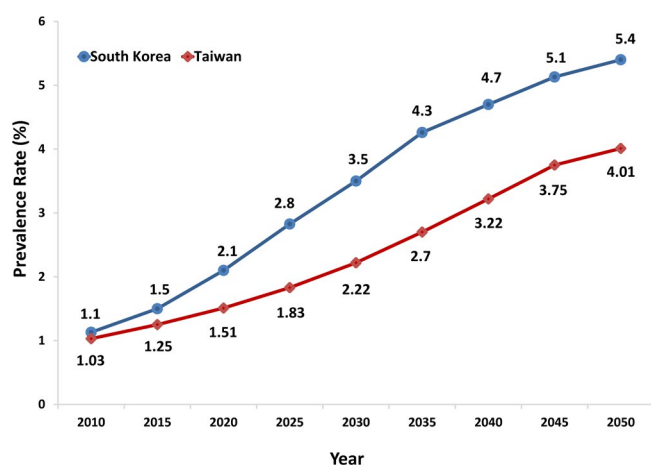
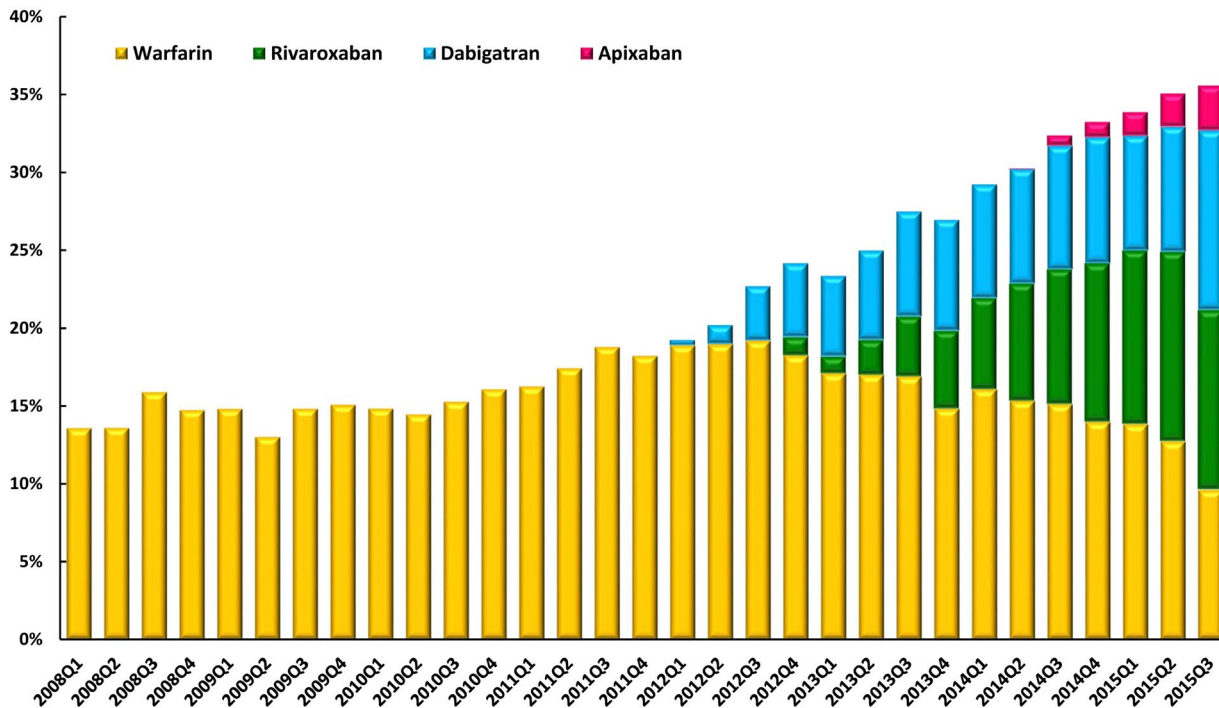


FIGURE 1 Projected prevalence of AF in Taiwan and South Korea. AF, atrial fibrillation. Data used in the figure were adapted from the papers by Chao et al. and Kim et al.^{3,4}

2 | THE IMPORTANCE OF INTEGRATED OR HOLISTIC CARE IN MANAGING PATIENTS WITH ATRIAL FIBRILLATION: IMPACT ON STROKE RISK REDUCTION AND ADVERSE OUTCOMES IN ATRIAL FIBRILLATION

Because patients with AF usually had multiple comorbidities, a more holistic and integrated approach to AF management has been proposed to improve the clinical outcomes in patients with AF.¹²

This integrated approach is directed at stroke prevention, better symptom management, and to tackle other cardiovascular risk factors/comorbidities (e.g., hypertension) aimed to reduce AF-related mortality, morbidity, and hospitalizations. This can streamline



	Incidence rate (%/year)		Adjusted HR (95% CI)	P value
Mortality				
2008	6.27			
2009	6.24		0.984 (0.912 – 1.061)	0.676
2010	6.32		0.987 (0.916 – 1.064)	0.733
2011	6.13		0.943 (0.875 – 1.016)	0.124
2012	6.00		0.921 (0.855 – 0.992)	0.030
2013	5.95		0.922 (0.856 – 0.994)	0.033
2014	5.93		0.908 (0.843 – 0.977)	0.010
2015	4.05		0.850 (0.762 – 0.948)	0.003
Ischemic stroke				
2008	4.58			
2009	4.69		1.005 (0.926 – 1.091)	0.903
2010	4.46		0.949 (0.874 – 1.031)	0.211
2011	4.67		0.946 (0.870 – 1.029)	0.180
2012	4.13		0.814 (0.745 – 0.888)	< 0.001
2013	4.11		0.805 (0.734 – 0.882)	< 0.001
2014	4.47		0.836 (0.762 – 0.915)	< 0.001
2015	3.97		0.693 (0.611 – 0.748)	< 0.001
ICH				
2008	0.56			
2009	0.67		1.126 (0.892 – 1.466)	0.204
2010	0.53		0.989 (0.799 – 1.255)	0.927
2011	0.63		1.099 (0.872 – 1.385)	0.423
2012	0.61		1.014 (0.804 – 1.288)	0.904
2013	0.61		1.045 (0.827 – 1.321)	0.711
2014	0.67		1.094 (0.868 – 1.386)	0.447
2015	0.51		0.953 (0.703 – 1.292)	0.755

FIGURE 2 Temporal trend of prescriptions of OACs and risks of clinical events in newly-diagnosed patients with AF. AF, atrial fibrillation; OACs, oral anticoagulants. The figure was redraw, and data were adapted from the paper by Chao et al⁵

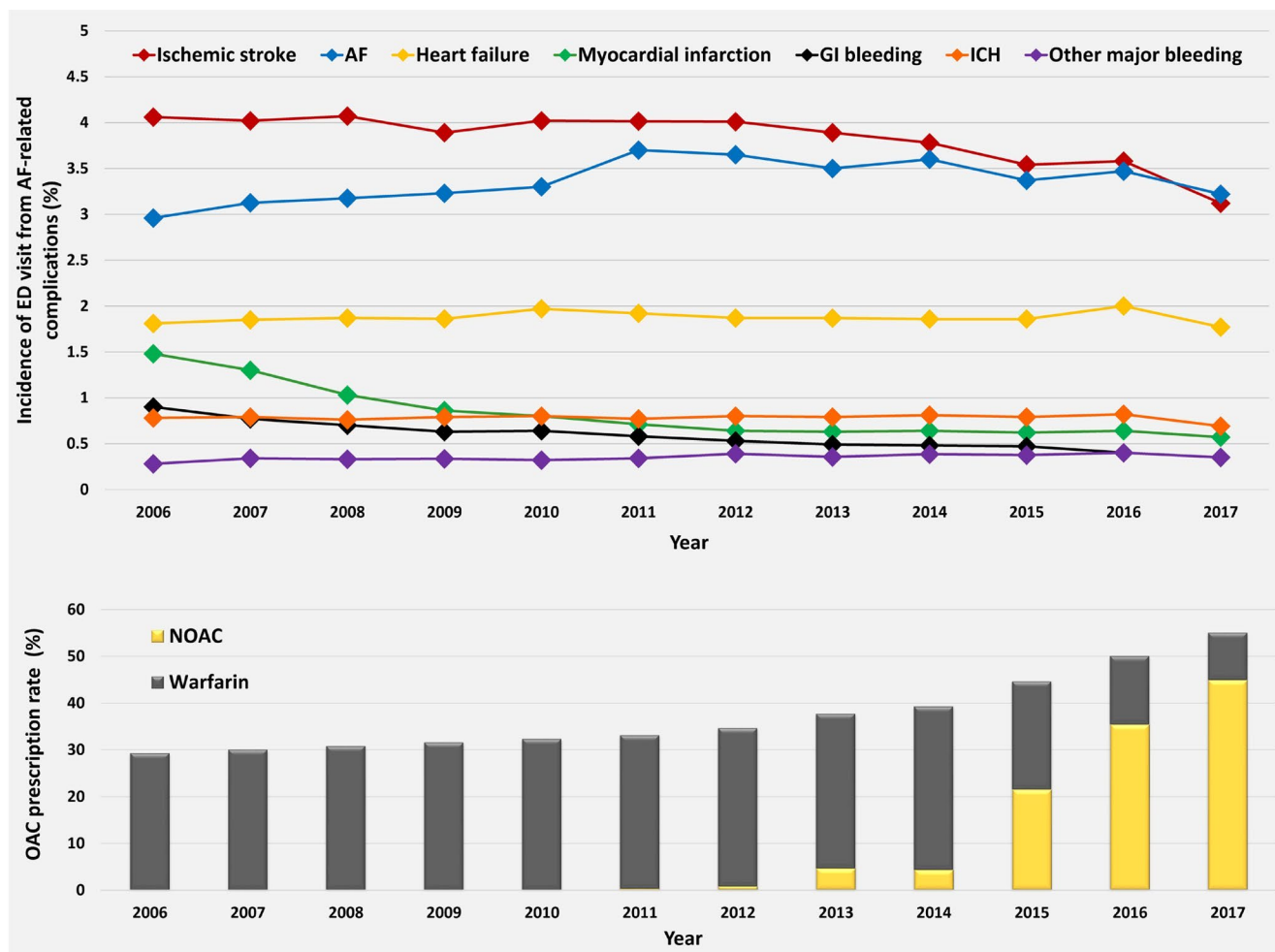


FIGURE 3 Temporal trends of incidence of ED visits from AF-related complications and OAC prescription rate. The figure was redraw and modified from the paper by Lee et al⁷

AF, atrial fibrillation; ED, emergency department; GI, gastrointestinal; ICH, intracranial hemorrhage; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

decision-making for a holistic approach to AF management in an integrated manner, proposed as the ABC (AF Better Care) Pathway (Figure 4)¹²:

- **“A” Avoid stroke** with anticoagulation, that is, well-managed warfarin (time in therapeutical range [TTR] > 65%–70%) or NOAC;
- **“B” Better symptom management** with patient-centred, symptom-directed decisions for rate or rhythm control; and
- **“C” Cardiovascular risk and comorbidity management** (BP control, heart failure, cardiac ischemia, sleep apnea, etc.) as well as lifestyle changes (obesity reduction, regular exercise, reducing alcohol/stimulants, psychological morbidity, etc.).

With the focus on patient-centered management, explanation using the simple ABC concept can also lead to improved understanding and disease awareness amongst patients, better knowledge about their condition and the priorities of management. Different healthcare professionals managing the patient with AF can also discuss the management based on the A, B, and C pillars of the ABC pathway.

The beneficial effect on clinical outcomes of ABC pathway adherent management, against non-ABC adherent care, have been consistently shown in different settings: post hoc analyses of adjudicated outcomes from clinical trial cohorts,^{13,14} prospective population cohorts globally,^{15–17} and a prospective cluster randomized trial published in 2020.¹⁸ These studies (including some from Asia [Figure 5])¹⁷ have been recently reviewed.¹⁹

A systematic review and meta-analysis showed a lower risk of all-cause death (OR: 0.42, 95% CI 0.31–0.56), cardiovascular death (OR: 0.37, 95% CI 0.23–0.58), stroke (OR: 0.55, 95% CI 0.37–0.82), and major bleeding (OR: 0.69, 95% CI 0.51–0.94), with management adherent to the ABC pathway compared with noncompliance (Figure 6).²⁰

A prospective cluster randomized trial conducted in China (mobile Health for improving screening and integrated care in AF, mAFA-II trial)¹⁸ showed that patients allocated to ABC pathway intervention (using mHealth technology) were associated with lower rates of the composite outcome of “ischemic stroke/systemic thromboembolism, death, and rehospitalization” compared with usual care (1.9% vs. 6.0%;

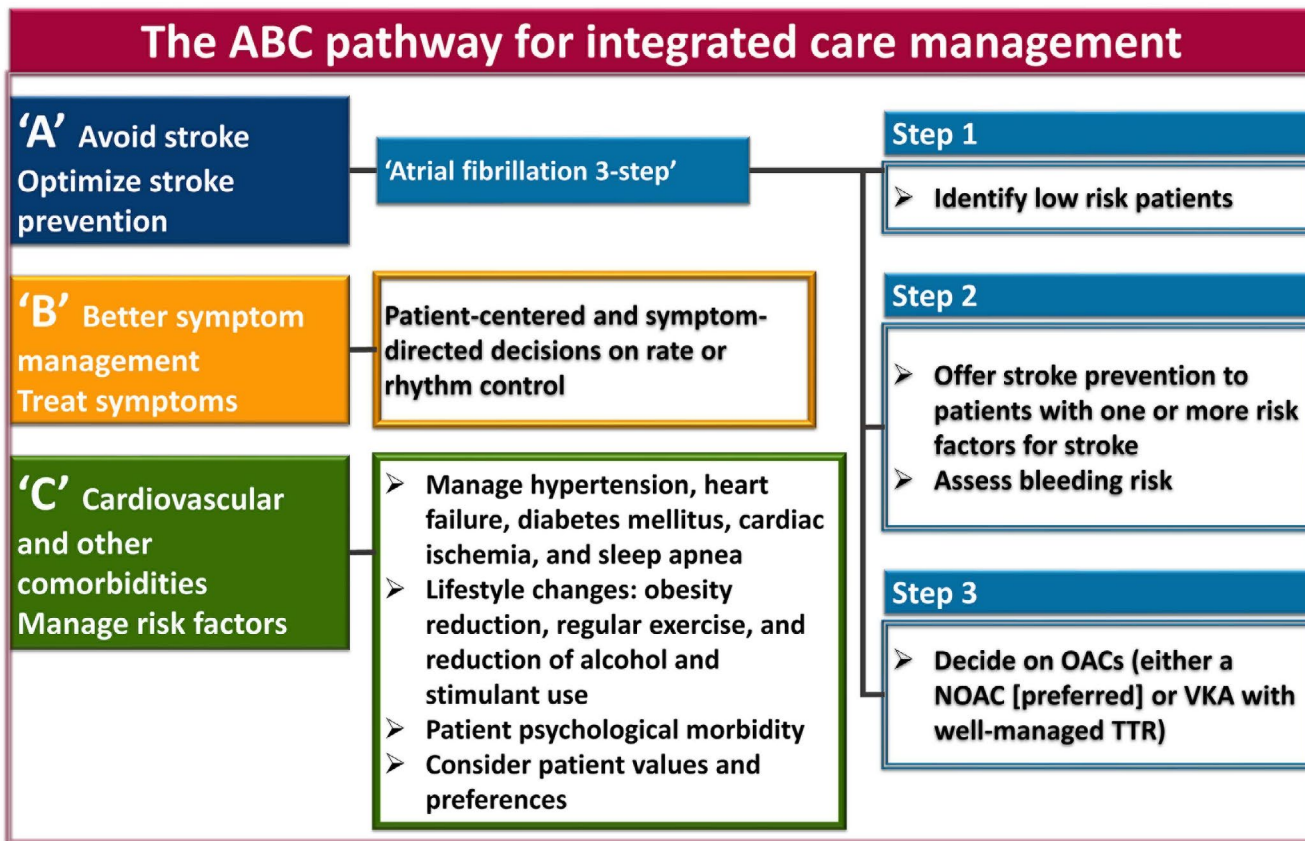
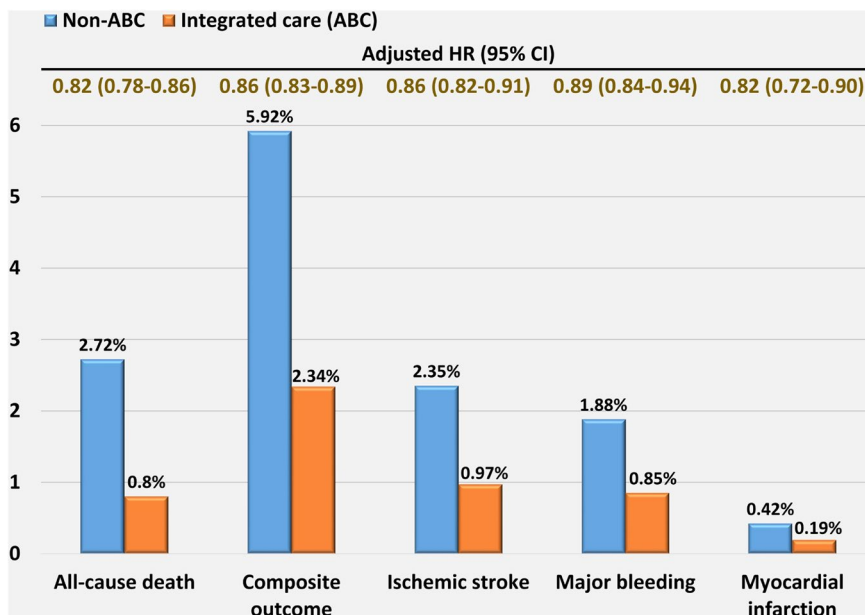


FIGURE 4 The ABC pathway of integrated care management. ABC, Atrial fibrillation Better Care; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; TTR, time in therapeutic range; VKA, vitamin K antagonist. The figure was redraw and modified from the paper by Lip et al¹²

FIGURE 5 Risks of adverse outcomes according to use of integrated ABC pathway in Asians. ABC, Atrial fibrillation Better Care; CI, confidence interval; HR, hazard ratio. The figure was based on the data adapted from the paper by Yoon et al¹⁷



hazard ratio [HR]: 0.39; 95% CI 0.22 to 0.67; $p < 0.001$). Rates of re-hospitalization were lower with intervention (1.2% vs. 4.5%; HR: 0.32; 95% CI: 0.17 to 0.60; $p < 0.001$). Subgroup analyses by gender, age, AF type, risk score, and comorbidities demonstrated consistently lower

HRs for the composite outcome for patients receiving the mFAA intervention compared with usual care (all $p < 0.05$). The ABC pathway intervention also leads to reduced major bleeds and increased oral anticoagulation uptake, versus usual care.²¹

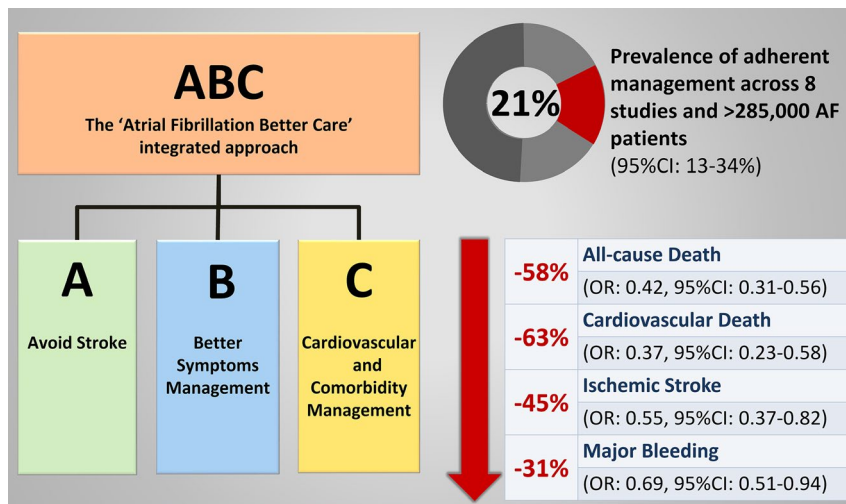


FIGURE 6 Impacts of adherence to the ABC pathway on clinical outcomes in patients with AF. ABC, Atrial fibrillation Better Care; CI, confidence interval; OR, odds ratio. The figure was redraw and modified from the paper by Romiti et al²⁰

The long-term extension cohort of mAFA-II showed that the beneficial impact of ABC pathway on clinical outcomes were maintained >1 year with high adherence (>70%) and persistence (>90%) of the intervention.²² A healthcare costs analysis has shown major cost savings by ABC pathway adherent treatment compared with non-ABC adherence.²³ Other population-based studies show that ABC pathway adherence was associated with a reduction in dementia risk,²⁴ and improved outcomes in patients with AF with high frailty risk.²⁵

The integrated care AF pathway approach ("simple as ABC...") has been adopted and promoted in the Primary Care Clinical Pathway for AF Detection & Management; <https://bit.ly/2FhrwXQ>). The key feedback from multidisciplinary colleagues is the reassurance felt that a holistic approach to management can be streamlined across primary-secondary care, not being regarded as complex but is "simple as ABC..." The ABC pathway is now included within guidelines from American College of Chest Physicians,²⁶ the Korean national AF guidelines,²⁷ and the 2020 European AF guidelines,²⁸ and is, therefore, recommended in this guideline as part of the holistic approach to AF management.

2.1 | Recommendation

1. An integrated care or holistic management approach, based on the ABC (AF Better Care) pathway is recommended to improve outcome in the Asian AF population:
 - **"A" Avoid stroke** with Anticoagulation, that is, well-managed warfarin (TTR > 65%–70%) or NOAC;
 - **"B" Better symptom management** with patient-centred, symptom-directed decisions for rate or rhythm control; and
 - **"C" Cardiovascular risk and comorbidity management** (BP control, heart failure, cardiac ischemia, sleep apnea, etc.) as well as lifestyle changes (obesity reduction, regular exercise, reducing alcohol/stimulants, psychological morbidity, etc.).

We highly emphasize the importance and recommend the use of ABC pathway for AF patient care. In this APHRS consensus document focused update, we will particularly focus on the "A" domain and update data for stroke prevention in AF, but would highlight the importance of full compliance with the ABC pathway to improve outcomes in patients with AF.

3 | STROKE RISK ASSESSMENT (AND RE-ASSESSMENT)

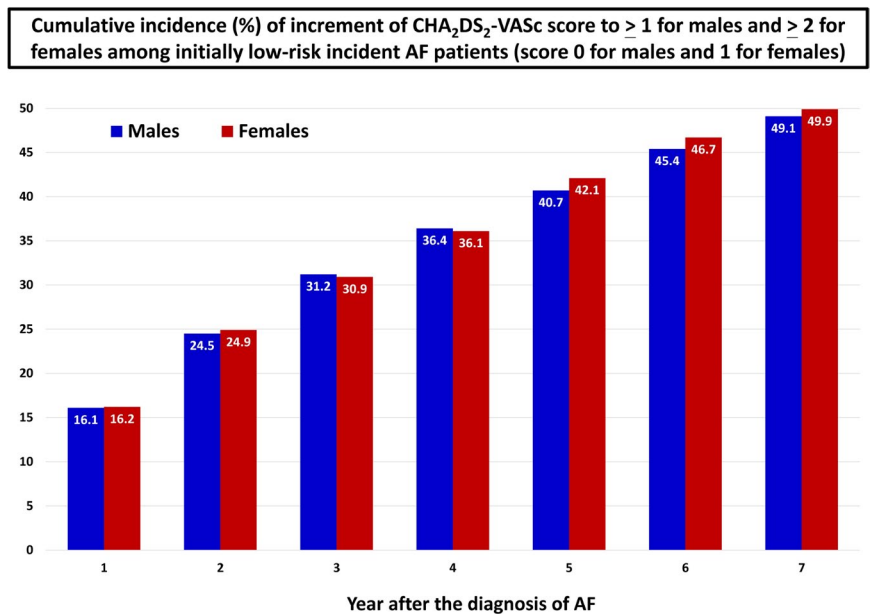
In our 2017 consensus document, we recommended the use of the CHA₂DS₂-VASc score for stroke risk assessment for Asian patients with AF.²⁹

In this focused update, we still recommend the use of the CHA₂DS₂-VASc score as the stroke risk prediction scheme since it has been well validated in Asian AF population.^{30–35} We recognise that there are more complicated clinical risk scores incorporating more clinical variables (e.g., Qstroke, GARFIELD score),³⁶ complex methodology (e.g., machine-learning approaches),³⁷ or the addition of biomarkers such as proteinuria (e.g., ATRIA-stroke) or other blood-based biomarkers (e.g., ABC-stroke), but these are not recommended in this focused update, given the importance to balance simplicity and practicality for daily clinical use against marginal improvements (at least statistically) in risk prediction.^{38,39} Many biomarkers are also nonspecific, indicative of a sick patient or a sick heart, being predictive of adverse outcomes other than what they were proposed.^{40,41}

We should acknowledge that all clinical risk stratification scores are simplifications to aid decision-making and to recognise the limitations of such scores. For example, there are many stroke risk factors,⁴² and only the more common and validated ones have been included into risk scores, such as the CHA₂DS₂-VASc score.

The impact of individual stroke risk factors is not uniform, and for a single CHA₂DS₂-VASc risk factor in those aged <65, and assuming an ischaemic stroke risk treatment threshold of ≥1%/year with NOACs, the tipping point with heart failure as a single risk was

FIGURE 7 Cumulative incidences of increment of CHA₂DS₂-VASc score to ≥ 1 (males) or ≥ 2 (females). AF, atrial fibrillation. The figure was redraw, and data were adapted from the papers by Chang et al. and Chao et al.^{47,49}



age 35 years, whereas for patients with hypertension, diabetes mellitus, and vascular diseases the age thresholds for treatment were 50 years, 50 years, and 55 years, respectively.^{43,44} Not all CHA₂DS₂-VASc risk factors carry equal weight, as event rates would be dependent on population studied (e.g., hospitalised vs. community), study type (trial vs. real world), ethnicity, and study methodology.⁴⁵ In addition, female gender is a stroke risk modifier rather than a risk factor, with an age dependency to risk; however, ignoring the female gender criterion may underestimate the stroke risks in female patients with ≥ 1 non gender stroke risks and lead to undertreatment of female patients.⁴⁶

In addition, stroke risk is not static, given that ageing and incident comorbidities would increase risk and the dynamic nature of stroke risk in AF would result in increments of their CHA₂DS₂-VASc scores.⁴⁷ For example, in a study from Taiwan which enrolled 31,039 patients with AF without comorbidities of the CHA₂DS₂-VASc score except for age and gender at baseline, the mean CHA₂DS₂-VASc scores increased from 1.29 to 2.31 during a follow-up of 171,956 person-years.⁴⁸ About 16.1% of men and 16.2% of women who were initially at low risk (score 0 for males or 1 for females) would have a CHA₂DS₂-VASc score of at least 1 (men) or 2 (women) at 1 year after incident AF (Figure 7).⁴⁹ Similar observations were reported in the study by Yoon et al. using the Korean nationwide AF registry.⁵⁰

Both the follow-up CHA₂DS₂-VASc score and change in stroke risk ("delta-CHA₂DS₂-VASc" score, i.e., the difference between the baseline and follow-up scores) had better predictive value for ischaemic stroke compared with the baseline CHA₂DS₂-VASc score.^{48,51} Almost 90% of initially low-risk patients with AF had a delta CHA₂DS₂-VASc score ≥ 1 before the occurrence of ischemic stroke.⁴⁸ For initially low-risk (CHA₂DS₂-VASc score 0 for males or 1 for females) nonanticoagulated patients with AF, the use of OACs once their CHA₂DS₂-VASc scores increased was associated with a lower risk of clinical events.⁵²

In summary, regular re-assessment of stroke risk of patients with AF and the timely prescriptions of OACs once the stroke risk of patients increased is important, given the increase in stroke risks with age and new comorbidities.

4 | FREQUENCY OF STROKE RISK REASSESSMENT

Data regarding the reasonable timing interval at which the stroke risk of patients with AF should be reassessed are limited. In the study by Chao et al. which studied 14,606 patients with AF with a baseline CHA₂DS₂-VASc score of 0 (males) or 1 (females), 6188 patients acquired new risk factors with the acquisition of 1 or more new comorbidities approx 4–5 months after their initial AF diagnosis. The most common incident comorbidity was hypertension, followed by heart failure, diabetes mellitus, and vascular disease; indeed, the onset of new comorbidities would depend on the type of comorbidity. Importantly, 596 of these original experienced ischemic stroke, and the duration from the acquirement of incident comorbidities to the occurrence of ischemic stroke was an average of 4.4 months for 90% of the patients.⁵² Based on these data, 4 months may be a reasonable timing interval at which the stroke risk of patients with AF should be reassessed. However, the optimal timing interval may be different in different healthcare systems.

4.1 | Recommendations

1. The CHA₂DS₂-VASc score is recommended for stroke risk assessment for Asian patients with AF.
2. The stroke risk of patients with AF is not static and should be reassessed regularly (at least annually and every 4 months if possible).

3. In patients with AF initially at low risk of stroke ($\text{CHA}_2\text{DS}_2\text{-VASc} = 0$ in men or 1 in women), a reassessment of stroke risk should ideally be made at 4 months after the index evaluation and OACs should be prescribed timely once their $\text{CHA}_2\text{DS}_2\text{-VASc}$ scores increase.

5 | BLEEDING RISK ASSESSMENT AND REASSESSMENT

As with the 2017 consensus document, the HAS-BLED score is recommended for bleeding risk assessment for Asian patients with AF in this focused update. In a PCORI systematic review and evidence appraisal, the HAS-BLED score was found to be the best score for bleeding risk prediction.⁵³ The HAS-BLED score is also validated for the prediction of intracranial bleeding, unlike other scores. In a recent analysis of ESC-EHRA EORP-AF General Long-Term Registry, the HAS-BLED score still performed better than ORBIT score in the contemporary cohort of patients with AF treated with NOACs.⁵⁴

Like the $\text{CHA}_2\text{DS}_2\text{-VASc}$ score, bleeding risks scores are simplifications, based on the more common and validated bleeding risk factors.⁵⁵ Indeed, individual components of the risk scores such as HAS-BLED do not carry equal weight, for example, uncontrolled BP is associated with a higher risk of intracranial bleeding (and other cardiovascular complications, including ischaemic stroke, mortality, and heart failure) compared with controlled BP (120–129/<80 mmHg).⁵⁶

The HAS-BLED score has been well validated in Asian cohorts, outperforming other bleeding risk scores (e.g., ATRIA, ORBIT, HEMORRH2AGES) and an approach simply focused only on modifiable bleeding risks.⁵⁷ Bleeding risk is also not static and may change among patients with AF initially having a low HAS-BLED score (≤ 2).⁵⁸ In a previous study from Taiwan, the accuracy of the follow-up or delta HAS-BLED score in the prediction of major bleeding was significantly higher than that of the baseline HAS-BLED score; importantly, the bleeding risk is higher within several months after the increment of the HAS-BLED score.⁵⁸ The HAS-BLED score has also been validated in patients with AF who are taking no antithrombotic therapy (e.g., when first diagnosed), antiplatelet therapy (e.g., when AF develops in patients on aspirin for vascular disease) and on

anticoagulation (whether warfarin or NOACs). Thus, the HAS-BLED score would be applicable at all steps of the patient pathway.

Appropriate use of the HAS-BLED score has been tested in the mAFA-II trial,¹⁸ which was a prospective cluster randomised trial, which compared a mHealth integrated care approach against usual care. The intervention arm used the HAS-BLED to identify and mitigate modifiable bleeding risks, and schedule high bleeding risk patients for regular review and follow-up; this led to lower major bleeding rates at one year and an increase in OAC use.²¹ In contrast, the usual care arm has higher major bleeding and a decline in OAC use (Figure 8). A recent study from Taiwan further demonstrated that for anticoagulated patients with AF with a baseline HAS-BLED score of 0–2 which increased to ≥ 3 , the continuation of OACs was associated with better clinical outcomes.⁵⁹ A high HAS-BLED score is not a reason to withhold OACs even among patients with AF with one nongender risk factor ($\text{CHA}_2\text{DS}_2\text{-VASc}$ score 1 for males and 2 for females) but a high bleeding risk (HAS-BLED score ≥ 3) as the use of OACs was still associated with a lower risk of composite adverse events of ischemic stroke, intracranial hemorrhage (ICH) or mortality (adjust hazard ratio [aHR] 0.781) in this population.⁶⁰

In summary, bleeding risk reassessment is important for anticoagulated patients with AF, and the appropriate and responsible use of bleeding risk scores such as the HAS-BLED score is to identify and mitigate modifiable bleeding risk factors and to identify high bleeding risk patients for early review and follow-up.

5.1 | Recommendations

1. For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment with the HAS-BLED score is recommended to help identify nonmodifiable and address modifiable bleeding risk factors and to identify patients potentially at high bleeding risk for early and more frequent clinical review and follow-up.
2. The bleeding risk of patients with AF is not static which should be re-assessed regularly, and the identified modifiable bleeding risk factors should be corrected.

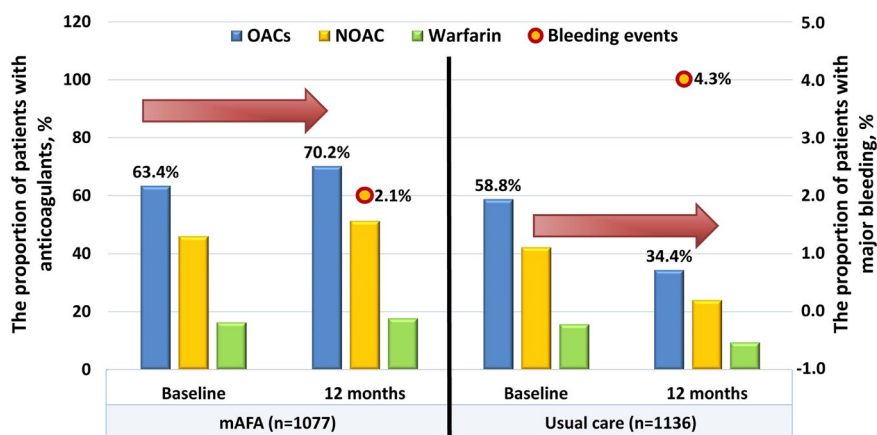


FIGURE 8 Use of OACs and risk of bleeding among patients received integrated care approach and usual care. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OACs, oral anticoagulants. The figure was redraw and modified from the paper by Guo et al²¹

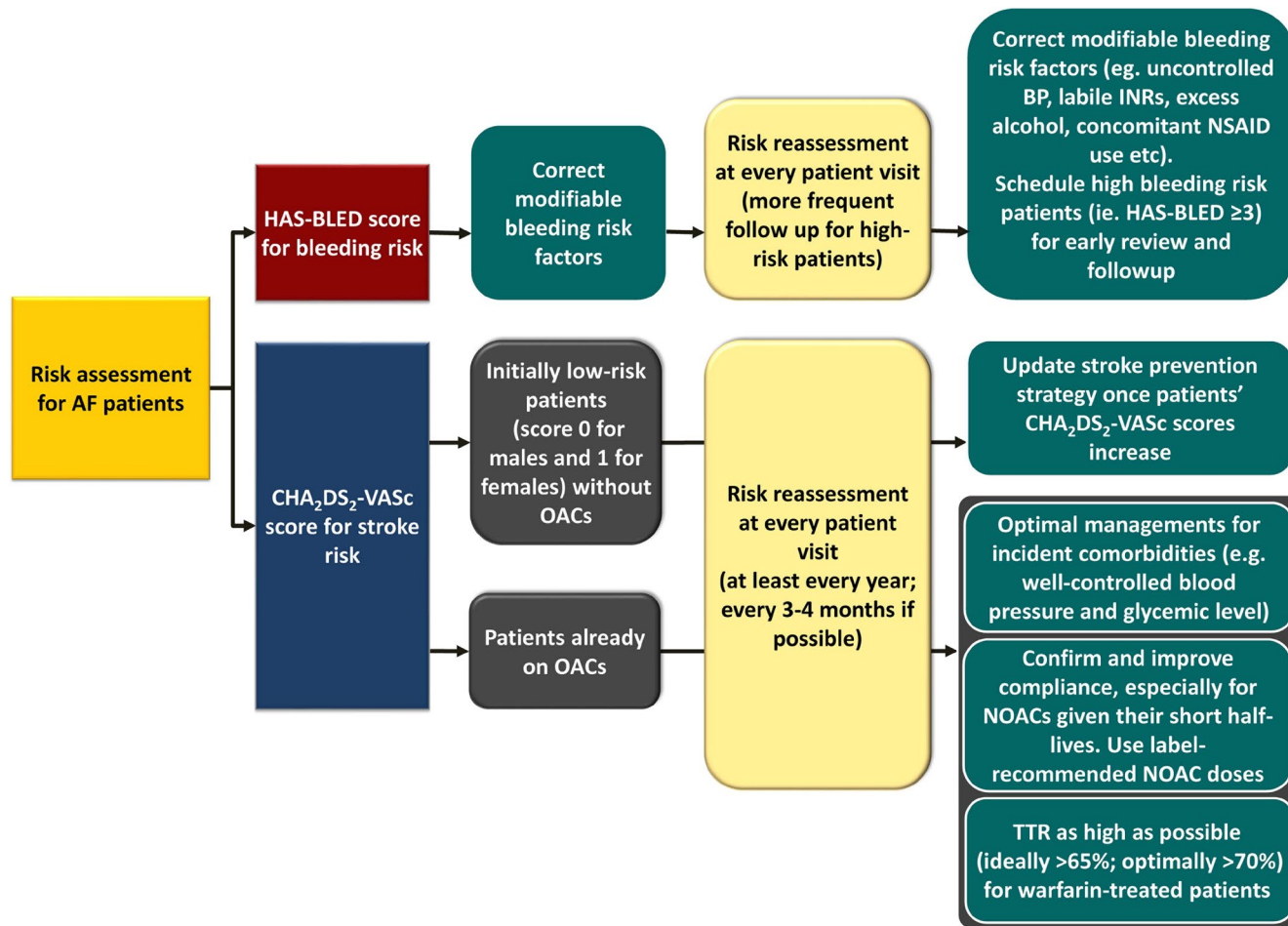


FIGURE 9 Stroke and bleeding risk assessment in AF. AF, atrial fibrillation; BP, blood pressure; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, nonsteroidal anti-inflammatory drugs; OACs, oral anticoagulants; TTR, time in therapeutic range. The figure was redraw and modified from the paper by Chang et al⁴⁷

- An increased HAS-BLED score in anticoagulated patients with AF should not be the only reason to withhold OACs but reminds physicians to correct modifiable bleeding risk factors and follow-up patients more closely.

In this focused update, we emphasise the dynamic natures of CHA₂DS₂-VASc and HAS-BLED scores and highly emphasize the clinical importance of risk reassessment. The recommended clinical practice about stroke and bleeding risk assessment is summarized in Figure 9.

6 | APPROACH TO STROKE PREVENTION IN ASIAN PATIENTS WITH ATRIAL FIBRILLATION

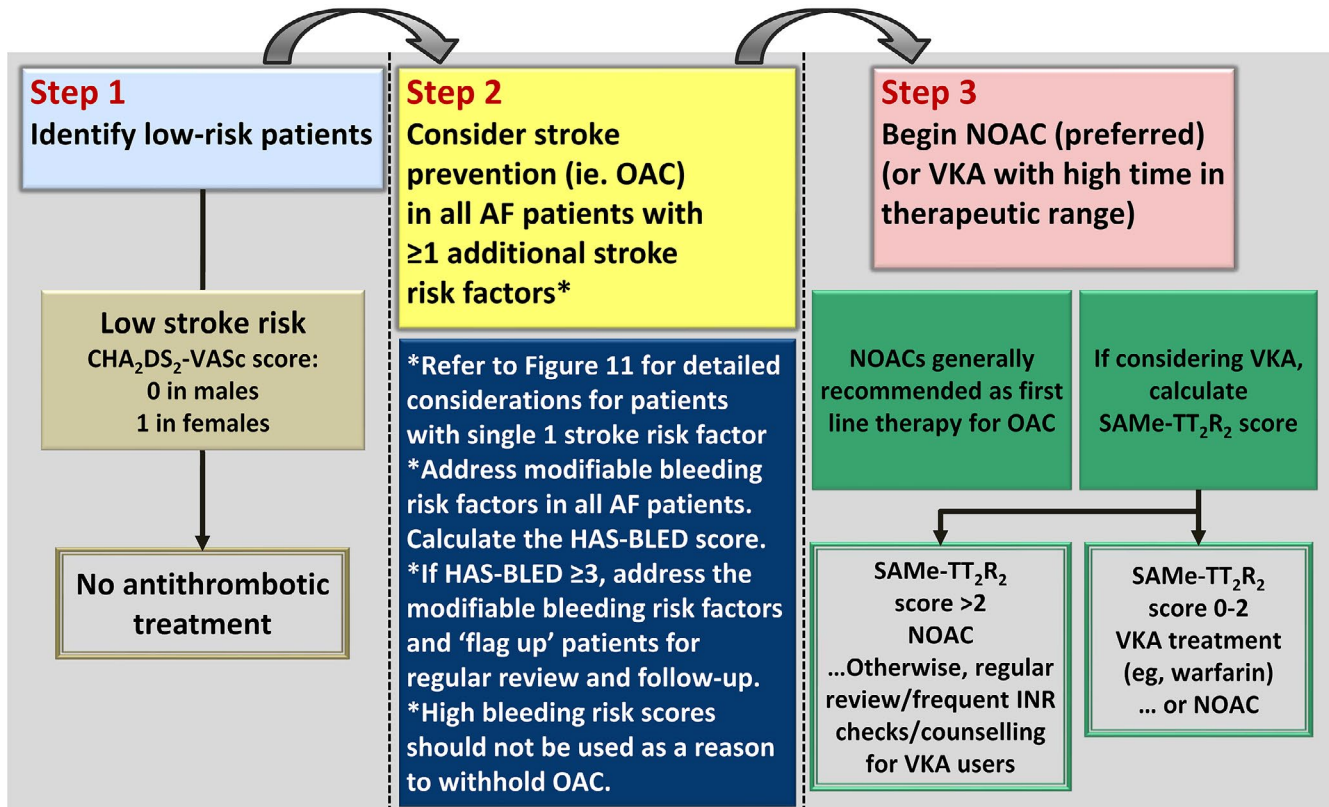
Given the limitations of all stroke risk scores in predicting high stroke risk in patients with AF and the dynamic nature of stroke risk, the artificial categorisation into low-, moderate-, and high-risk strata is discouraged. Thus, stroke prevention (which is oral anticoagulation)

should be the default strategy, unless patients are at low risk (defined as CHA₂DS₂-VASc score 0 in males or 1 in females). Figure 10 shows our recommendations, which were consistent to other guidelines.²⁶

Patients with AF and significant valvular heart disease (VHD) (previously referred to as “valvular AF”) defined as prosthetic mechanical heart valves or moderate–severe mitral stenosis, should be offered warfarin, when oral anticoagulation is recommended.⁶¹ Indeed, NOACs are contraindicated in such patients.

In other patients without significant VHD (so-called “nonvalvular AF”), the first step (**Step 1**) is to identify low-risk patients (CHA₂DS₂-VASc score 0 in males or 1 in females) where no antithrombotic therapy is recommended. The next step (**Step 2**) is to offer stroke prevention (i.e., oral anticoagulation) to patients with ≥1 nongender stroke risk factors (i.e., CHA₂DS₂-VASc score ≥1 in males or ≥2 in females). Most of the randomised trials included patients with ≥2 nongender stroke risk factors, but some clinical trials with warfarin (ACTIVE-W), dabigatran and apixaban [RE-LY, ARISTOTLE, AVERROES] included patients with a single nongender stroke risk factor.^{62–64}

The simple classification of the recommendation as “class IIa” or “class IIb” may be too simplistic regarding this issue, and a more

**Rationale:**

Step 1: CHA₂DS₂-VASc score can identify low risk patients more reliably than other stroke prediction schemes

Step 2: Not all risk factors were equal regarding the risk of stroke. Bleeding risk is dynamic, and high bleeding scores should be used simply to identify potential modifiable factors and patients who may need more frequent follow-up.

Step 3: We recommended NOACs as first line therapy for OAC. If VKA therapy is being considered, the SAME-TT₂R₂ score can be used to identify patients who are good candidates for this approach.

FIGURE 10 Three-step approach for the use of OACs for stroke prevention in AF. AF, atrial fibrillation; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; OACs, oral anticoagulants; VKA, vitamin K antagonist. The flowchart was redraw and modified from the paper by Lip et al²⁶

delicate approach for these patients is required.⁶⁵ Because the risk of stroke of each CHA₂DS₂-VASc risk component was not the same and age is an important driver, patients' ages and the comorbidities, which contribute to the score 1 for males or 2 for females could be considered when making management decisions about the use of OACs or not.^{43,66-69} as summarized in Figure 11. As OAC is being started, bleeding risk assessment is recommended, using the HAS-BLED score to identify and mitigate modifiable bleeding risks, and to identify high bleeding risk patients for early review and follow-up.

Step 3 is to make the choice of OAC. We recommend the use of NOACs in preference to warfarin for stroke prevention. If NOACs are used, the recommended label dosing is important, given that the best outcomes are with label-adherent prescribing.⁷⁰⁻⁷⁵ Apart from guideline-directed anticoagulation prescribing, adherence, and persistence with therapy are important.⁷⁶⁻⁷⁸

If warfarin is considered, we recommend a target INR 2.0-3.0 with an average TTR ≥65% (ideally ≥70%). We do not recommend low intensity anticoagulation or lower target INRs, given the higher risk of thromboembolism although bleeding risk is lower.⁷⁹ Of note, a "one-off" INR reading gives no indication of the quality of

anticoagulation control, and many serious bleeds occur when the INR is between 2.0 and 3.0.⁸⁰ A high TTR is associated with low rates of stroke and bleeding,⁸¹ but many factors influence the quality of anticoagulation control. The more common and validated factors associated with poor labile INRs have been used to formulate clinical risk scores such as the SAME-TT₂R₂ scores. A high SAME-TT₂R₂ score (>2) is associated with a likelihood of poor TTR, and such patients should be flagged up for more attention to ensure good quality anticoagulation (e.g., education and counselling, more frequent INR checks) or to reconsider the decision to prescribe NOACs (if suitable).⁸²⁻⁸⁶

6.1 | Recommendations

1. In patients with AF with mechanical heart valves or moderate-to-severe mitral stenosis, warfarin is recommended.
2. For stroke prevention in patients with AF without significant VHD (i.e., mechanical heart valves or moderate-to-severe mitral stenosis; so-called "valvular AF") who are eligible for OAC,

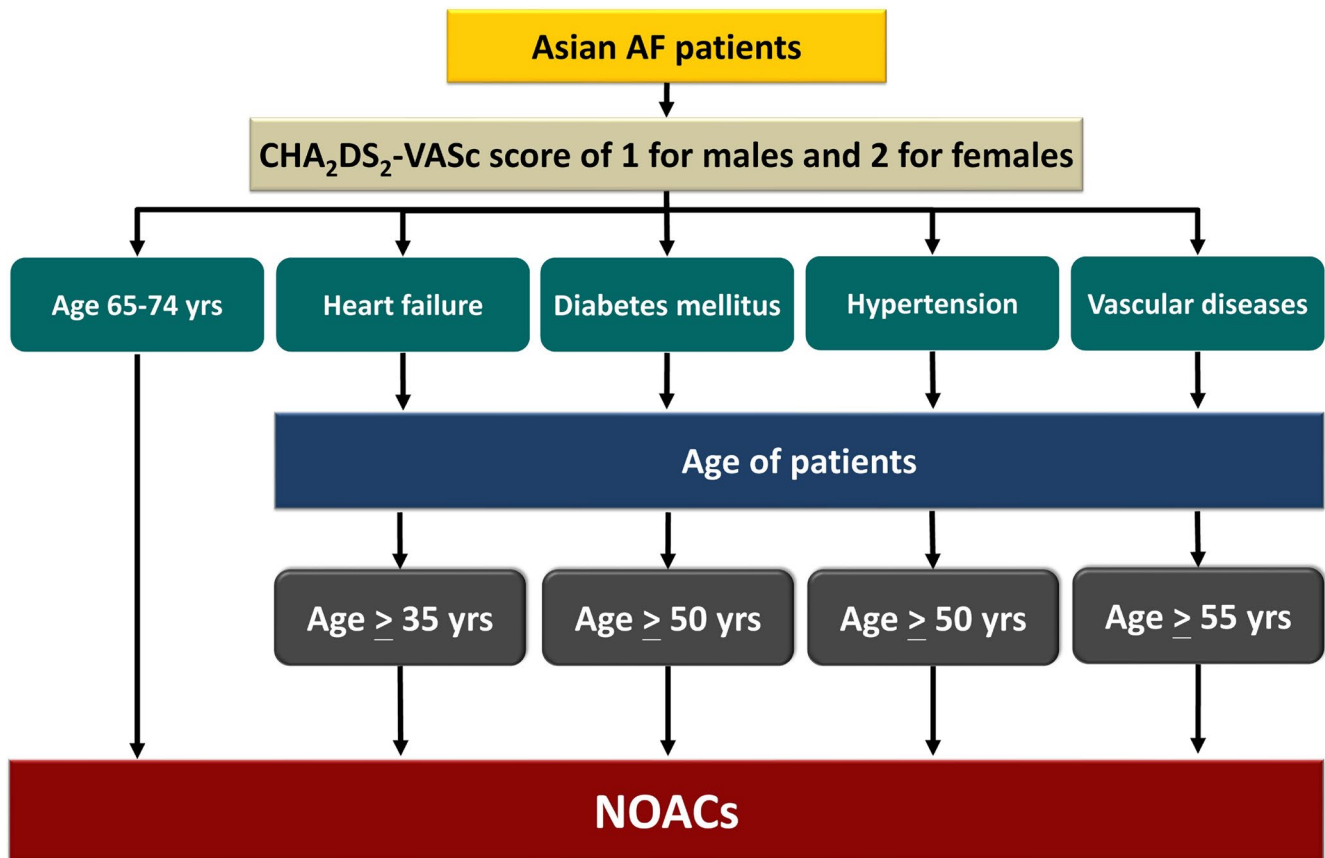


FIGURE 11 Considerations about the use of NOACs for Asian patients with AF with a $\text{CHA}_2\text{DS}_2\text{-VASc}$ score of 1 (males) or 2 (females). AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant

NOACs are recommended in preference to vitamin K antagonists (VKAs).

3. Clinical pattern of AF (i.e., whether first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis, if stroke risk factors are present.
4. For stroke risk assessment, a risk-factor-based approach is recommended, using the $\text{CHA}_2\text{DS}_2\text{-VASc}$ stroke risk score to initially identify patients at "low stroke risk" ($\text{CHA}_2\text{DS}_2\text{-VASc} = 0$ in men or 1 in women) who should not be offered antithrombotic therapy.
5. In patients with AF with $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 2 in men or ≥ 3 in women, OAC is recommended for stroke prevention.
6. In patients with AF with a $\text{CHA}_2\text{DS}_2\text{-VASc}$ score of 1 in men or 2 in women, OAC should be considered for stroke prevention. Different age thresholds for different comorbidities may help guide NOACs use (e.g., age 35 years for heart failure, 50 years for hypertension or diabetes mellitus and 55 for vascular diseases).
7. If a VKA is used, a target INR of 2.0–3.0 is recommended, with individual TTR $\geq 65\%$ (ideally $\geq 70\%$)
 - A high $\text{SAME-TT}_2\text{R}_2$ score (>2) is associated with a likelihood of poor TTR, and such patients have more attention to ensure good quality anticoagulation (e.g., education and counselling, more frequent INR checks) or to reconsider the decision to prescribe NOACs (if suitable).

8. In patients on VKAs with low time in INR therapeutic range (e.g., TTR $< 70\%$), recommended options are as follows:
 - a. Switching to an NOAC but ensuring good adherence and persistence with therapy
 - b. Efforts to improve TTR (e.g., education/counselling and more frequent INR checks).
9. Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in patients with AF.
10. Estimated bleeding risk, in the absence of absolute contraindications to OAC, or patients at high risk of falls, should not in itself guide treatment decisions to use OAC for stroke prevention.

7 | REVIEW UPDATE DATA REGARDING WARFARIN (INCLUDING INR RANGE) IN ASIA

When OAC is being considered, NOACs are the preferred option for stroke prevention in AF because the benefits of NOAC on efficacy and safety compared with the VKAs are more profound in Asian than non-Asian population.⁸⁷ In some settings, the use of VKA is still needed because of the high cost of NOACs or in patients with specific indications including moderate to severe mitral stenosis and mechanical heart valves. Maintenance of a high TTR has been shown to reduce the risk

of ischemic and bleeding events and should be the primary goal in the treatment of these patients independent of the type management approach. Conversely, a change in the approach to these patients needs to be considered if a low TTR is consistently observed.

For the optimal management of VKA therapy, INR of 2.0–3.0 is recommended. However, there is some debate about optimal INR in Asian patients with nonvalvular AF. Japanese guidelines have stated that INR of 1.6 to 2.6 is recommended in elderly Japanese patients with AF. The recommendations on INR range for stroke prevention in different Asian guidelines is summarized in Table 1.^{27,88–91}

Several observational studies suggested that low-intensity warfarin therapy can reduce hemorrhage without increasing thromboembolism for East Asian patients with NVAF receiving warfarin therapy, but the evidence is weak and no focus on quality of anticoagulation control, as reflected by TTR.^{92,93} In a systematic review and evidence appraisal, low-intensity anticoagulation, or lower target INRs is associated with a higher risk of thromboembolism although bleeding risk may be lower.⁷⁹ Of note, a “one-off” INR reading does not reflect the quality of anticoagulation control, especially since many serious bleeds actually occur when the INR is between 2.0 and 3.0.⁸⁰ Hence, we strongly recommend evidence-based management, with the strongest data currently for INR 2.0 to 3.0 and TTR ideally $\geq 65\%$ (or even 70%) in Asian patients.⁹¹ We should ensure TTR is $\geq 65\%$ (optimal $\geq 70\%$), with appropriate education and counselling, or more frequent INR checks. Efforts to improve OAC uptake, adherence, and persistence with therapy are also crucial, as are efforts to improve service provisions.^{94–96}

7.1 | Recommendations

1. The use of VKA is recommended in patients with moderate to severe mitral stenosis and mechanical heart valve.
2. For the optimal management of VKA therapy, INR of 2.0–3.0 is recommended in Asian patients with AF, with attention to ensure TTR is $\geq 65\%$.

8 | UPDATES OF THE SUBANALYSES OF TRIALS IN ASIA

The results of the four pivotal Phase III NOAC trials showed that all NOACs were at least noninferior to warfarin in prevention of stroke/thromboembolism, and NOACs were associated with lower rates of intracranial bleeding than was warfarin. In the meta-analysis of four NOACs,⁹⁷ NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; $p < 0.0001$), mainly driven by a reduction in hemorrhagic stroke (RR 0.49, 95% CI 0.38–0.64; $p < 0.0001$). NOACs also significantly reduced all-cause mortality (RR 0.90, 95% CI 0.85–0.95; $p = 0.0003$) and ICH (RR 0.48, 95% CI 0.39–0.59; $p < 0.0001$), but increased gastrointestinal bleeding (GIB) (RR 1.25, 95% CI 1.01–1.55; $p = 0.04$). There was a greater relative risk (RR) reduction in major bleeding with NOACs when the TTR was less than 66% than when it was 66% or more (RR 0.69, 95% CI 0.59–0.81 vs. RR 0.93, 95% CI 0.76–1.13; p for interaction 0.022).

The efficacy and safety of NOACs was more profound in Asian population than non-Asian population.⁸⁷ Comparing with VKAs, standard-dose NOACs reduced stroke or systemic embolism (OR = 0.65 vs. 0.85, p interaction = 0.045) more in Asians than in non-Asians and were safer in Asians than in non-Asians for major bleeding (OR = 0.57 vs. 0.89, p interaction = 0.004), hemorrhagic stroke (OR = 0.32 vs. 0.56, p interaction = 0.046). There was no excess of GI bleeds in Asians, whereas GIB was significantly increased in non-Asians (OR = 0.79 vs. 1.44, p interaction = 0.041). Generally, reduced-dose NOACs were safer than VKAs without heterogeneity in efficacy and safety between Asians and non-Asians, except for ischemic stroke, major, and GIB.⁸⁷ In the recent subanalysis of ENGAGE AF-TIMI 48 trial comparing patients of Asian and non-Asian races, Asians treated with warfarin had a higher-adjusted risk of ICH (aHR 1.71, $p = 0.03$) compared with non-Asians.⁹⁸ Compared with warfarin, higher-dose edoxaban significantly reduced ICH while preserving the efficacy of stroke prevention in both Asians and non-Asians. Two of

TABLE 1 Summary of the recommendations on INR range for stroke prevention in nonvalvular atrial fibrillation in different Asian guidelines

Guidelines	Recommended INR range	Statements within the guidelines
2013 Japanese Circulation Society ⁸⁸	INR 2.0–3.0 INR 1.6–2.6 (in patients aged ≥ 70 years)	To obtain maximum benefit from warfarin therapy, the TTR should be kept above 60%
2015 The Indian consensus guidance on stroke prevention in atrial fibrillation ⁸⁹	INR 2.5 (2.0–3.0) <75 years INR 2.0 (1.6–2.5) >75 years	
2016 Taiwan Heart Rhythm Society ⁹⁰	INR 2.0–3.0	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 $>65\%$
2018 Korean Heart Rhythm Society ²⁷	Among patients receiving vitamin K antagonist, maintenance of an INR in the therapeutic range (2.0–3.0) is essential	When patients are treated with a vitamin K antagonist, TTR should be kept as high as possible (ideally aiming for TTR $>65\%$ –70%) and be closely monitored

Note: The table was adapted from the paper by Chao et al.⁹¹

Abbreviations: INR, international normalized ratio; TTR, time in therapeutic range.

three net clinical outcomes appeared to be more favorably reduced with edoxaban in Asians compared with non-Asians ($p_{\text{int}} = 0.063$ for primary, 0.037 for secondary, and 0.032 for third net clinical outcomes, respectively).

9 | REAL-WORLD DATA ABOUT NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN ASIA

In a systematic review and metaanalysis of real-world comparisons of NOACs for stroke prevention in Asian patients with AF,⁹⁹ the NOACs were associated with lower risks of thromboembolism (HR 0.70; [95% CI 0.63–0.78]), acute myocardial infarction (0.67; [0.57–0.79]), all-cause mortality (0.62; [0.56–0.69]), major bleeding (0.59; [0.50–0.69]), ICH (0.50; [0.40–0.62]), GIB (0.66; [0.46–0.95]), and any bleeding (0.82; [0.73–0.92]) than warfarin. The effectiveness and safety of four NOACs versus warfarin persisted in the subgroups of either standard-dose or low-dose NOACs. Although real-world data are no substitute for randomised trials, this meta-analysis shows that the NOACs had greater effectiveness and safety compared with warfarin in real-world practice for stroke prevention, among Asian patients with NVAF.⁹⁹

NOACs also showed better effectiveness and safety than warfarin in “high-risk” real-world Asian AF populations including the very elderly, those with low body weight or liver disease.^{68,100–105}

10 | THE IMPORTANCE OF ON-LABEL DOSING OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN ASIANS

Varying degrees of renal function require recommendations for reduced dosing regimens of NOACs; however, different cutoff values for age, body weight, or interacting drugs also require consideration for appropriate dose selection. In routine clinical practice in Asia, prescribed NOAC doses are often inconsistent with drug labeling.^{70–73,75} These prescribing patterns may be associated with worse safety profiles with no benefit in effectiveness in patients with severe kidney disease and worse effectiveness with no benefit in safety in apixaban-treated patients with normal or mildly impaired renal function.^{106,107}

In meta-analysis of four NOAC trials, low-dose NOAC regimens showed similar overall reductions in stroke or systemic embolic events to warfarin (RR 1.03, 95% CI 0.84–1.27; $p = 0.74$), and a more favorable bleeding profile (RR 0.65, 95% CI 0.43–1.00; $p = 0.05$), but significantly more ischemic strokes (RR 1.28, 95% CI 1.02–1.60; $p = 0.045$).⁹⁷

In patients eligible for reduced-dose NOACs, effects of reduced-dose NOACs compared with warfarin on stroke or systemic embolism (RR 0.84, 95% CI 0.69–1.03) and on major bleeding (RR 0.70, 95% CI 0.50–0.97) were consistent with those of full-dose NOACs relative to warfarin (RR 0.86, 95% CI 0.77–0.96 for stroke or systemic embolism and RR 0.87, 95% CI 0.70–1.08

for major bleeding; interaction p values of 0.89 and 0.26, respectively). In addition, NOACs were associated with reduced risks of hemorrhagic stroke, ICH, fatal bleeding, and death regardless of patients' eligibilities for NOAC dose reduction (interaction $p > 0.05$ for each).¹⁰⁸

When checking the eligibility and determining the dosages of NOACs, it should be emphasized that the creatinine clearance (CCr) of patients with AF should be calculated using CG equation which was adopted in four pivotal randomized clinical trials.¹⁰⁹ Compared with CG formula, MDRD or CKD-EPI equations would overestimate the renal functions of patients with AF, especially for the elderly (≥ 75 years) and those with a low body weight (< 50 kg).¹¹⁰ The overestimations of the estimated glomerular filtration rates (eGFRs) would potentially result in inappropriate dosing of NOACs (mainly overdoing), and may therefore, attenuate the advantages of NOACs compared with warfarin.¹¹⁰

A dose reduction of rivaroxaban in Asian patients might be necessary but lacks the confirmation in large adequately powered prospective randomized clinical trials. Pharmacokinetic modeling data indicated that, at steady state, the distribution of both the maximum concentration and area under the curve of rivaroxaban in Japanese patients with AF who received a 15 mg o.d. dose of rivaroxaban would be comparable with the C_{max} and AUC 0–24, in Caucasian patients with AF who received a 20 mg o.d. dose. Accordingly, instead of the 20 mg and 15 mg o.d. dose, the 15 and 10 mg o.d. doses of rivaroxaban was selected in Japan. The Korean AF guidelines recommend the use of 15 mg o.d. dose of rivaroxaban in very elderly (≥ 80 years) patients with AF.²⁷ Another recent study from Taiwan, which compared the clinical outcomes of patients with AF receiving rivaroxaban following ROCKET-AF and J-ROCKET AF dosing regimen demonstrated that the risks of stroke/systemic and major bleeding did not differ significantly between two groups.¹¹¹ However, a lower risk of major bleeding was observed for J-ROCKET AF dosing among patients with an eGFR < 50 ml/min with a borderline p value of 0.0445.¹¹¹ Of note, off-label underdoing rivaroxaban (10 mg/day for patients with an eGFR > 50 ml/min) should be avoided since it was associated with a 2.75-fold higher risk of ischemic stroke.⁷² Further prospective studies are necessary to investigate the dosing issue of NOACs, and on-label or guideline-adherent dosing of NOACs is recommended in Asian patients with AF until more data are available.

10.1 | Recommendations

1. Because NOAC are more effective and safer than warfarin in Asian patients with AF, NOACs are the recommended choice of oral anticoagulation in Asian patients with AF.
2. The Cockcroft–Gault (CG) equation should be adopted to calculate CCr to determine the dosing of NOACs.
3. On-label or guideline-adherent dosing of NOACs is recommended in Asian patients.

11 | ATRIAL FIBRILLATION COMPLICATING ACUTE CORONARY SYNDROME/PERCUTANEOUS CORONARY INTERVENTION

AF often occurs in patients with coronary artery disease (CAD). It has been reported that 5%–8% of patients who undergo percutaneous coronary intervention (PCI) have AF.^{112,113} Importantly, patients with CAD and AF are at high risk of stroke.

In the warfarin era, a major concern in Asian patients with AF was the risk of serious bleeding by combining OAC with antiplatelets;

however, temporal trends of patients with AF undergoing PCI after introduction of NOAC show increasing use of OAC and combination therapy with antiplatelets, especially in the NOAC era (Figure 12).¹¹⁴

Patients with CAD and AF are not only at risk of stroke but also at risk of bleeding due to associated comorbidities, and decision-making should balance ischemic and bleeding risks when considering the duration, type, and treatment regime especially given the potential sensitivity of Asians to bleeding risks on OAC (Figure 13).^{115,116}

In the warfarin era, the WOEST study demonstrated a higher bleeding risk of triple therapy compared with double therapy of OACs and clopidogrel.¹¹⁷ More recently, the safety and efficacy of

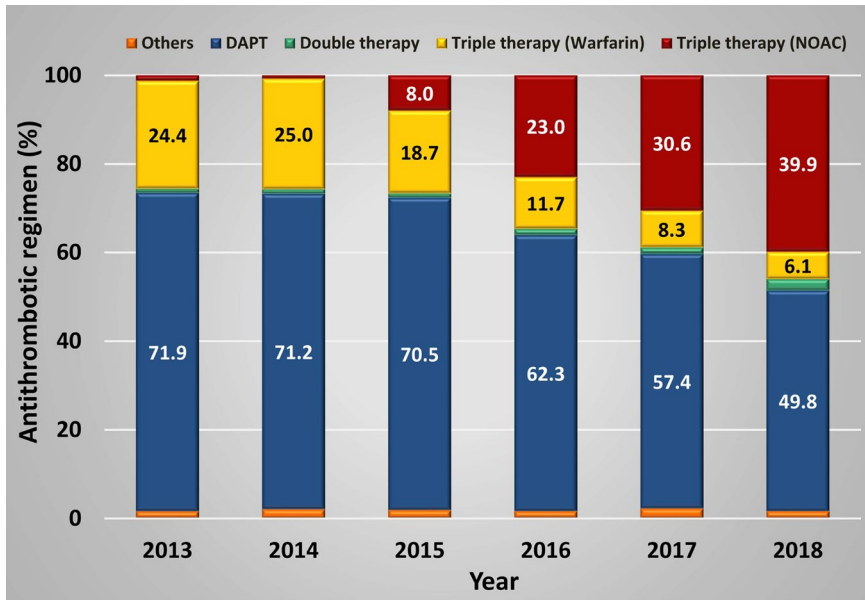


FIGURE 12 Increasing use of OACs (especially NOACs) and combination therapy with antiplatelet agents among patients with AF undergoing percutaneous coronary intervention. AF, atrial fibrillation; DAPT, dual antiplatelet therapy; NOAC, non-vitamin K antagonist oral anticoagulant. The figure was redraw, and data were adapted from the paper by Kwon et al¹¹⁴

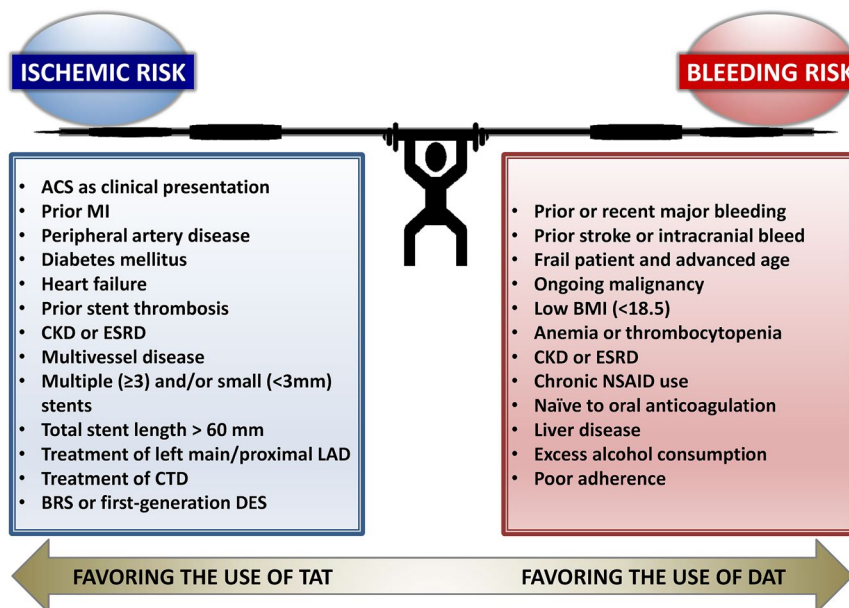


FIGURE 13 Factors tipping the balance between ischemic and bleeding risk in patients with AF presenting with ACS and/or undergoing PCI. ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; BRS, bioresorbable scaffold; CKD, chronic kidney disease; CTO, chronic total occlusion; DAT, dual antithrombotic therapy; DES, drug-eluting stent; ESRD, end-stage renal disease; LAD, left anterior descending artery; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; TAT, triple antithrombotic therapy. The figure was redraw and modified from the paper by Vitolo et al¹¹⁵

NOACs in combination with antiplatelet drugs in patients with CAD and AF have been reported in the PIONEER AF-PCI,¹¹⁸ RE-DUAL PCI,¹¹⁹ AUGUSTUS,¹²⁰ and ENTRUST-AF PCI trials.¹²¹ The summary of those trials is presented in Table 2.

In the PIONEER AF-PCI, RE-DUAL PCI, and ENTRUST-AF PCI trials, dual therapy with an NOAC and a P2Y12 inhibitor was compared with a triple therapy with warfarin plus a dual antiplatelet therapy (DAPT). In the RE-DUAL PCI trial, elderly patients (≥ 80 years; age ≥ 70 years in Japan) were given 110-mg of dabigatran when assigned to the dual therapy group. The PIONEER AF-PCI and RE-DUAL PCI trials demonstrated that dual therapy decreased bleeding and did not increase thrombotic events, compared with triple therapy. In the ENTRUST-AF PCI trial, dual therapy was noninferior to triple therapy for bleeding. The RE-DUAL PCI trial was also adequately powered to investigate a comparison of the combined dabigatran arms against warfarin for the composite thrombotic outcomes, and no significant difference was seen. The highest ticagrelor use was in RE-DUAL PCI, where 12% of the trial cohort used ticagrelor instead of clopidogrel; no significant interaction was evident.¹²² Based on these trials, an NOAC-based anticoagulation strategy was safer than a warfarin-based strategy in terms of bleeding.

The role of aspirin was tested in the AUGUSTUS trial using a two-by-two factorial design.¹²⁰ In the AUGUSTUS trial, the use of apixaban reduced bleeding by 31% as compared with VKAs, and the use of aspirin resulted in an increase in bleeding by 47%, that is, dual therapy with apixaban and a P2Y12 inhibitor was associated with a lower rate of bleeding than triple therapy or dual therapy with warfarin. Furthermore, patients taking apixaban had a lower incidence of death or hospitalization than those taking VKAs, mainly driven by a reduction in the incidence of hospitalizations. The rate of the incidence of death or ischemic events did not differ significantly between aspirin and a placebo or between apixaban and VKAs,

although was numerically greater in the placebo treated patients compared with aspirin. The incidence of stroke decreased by 50% in patients with apixaban as compared with VKAs.

In all four trials, randomization was performed after the PCI, and all patients were treated by triple therapy during the periprocedural period, in which stent thromboses were most likely to occur. Thus, this consensus recommends an initial period of triple therapy with OAC plus a DAPT during the PCI and following 7–28 days, depending on the balance between thrombotic and bleeding risks (Figure 14), as recommended by 2021 European Heart Rhythm Association (EHRA) Practical Guide on the use of NOACs in patients with AF.¹²³ Indeed, in patients at very high bleeding risks and acceptable thrombotic risk, aspirin may be dropped much earlier. In contrast, where patients have a high thrombotic risk (e.g., post-ACS) but acceptable bleeding risks, the period of triple therapy should be continued for at least 4 weeks.

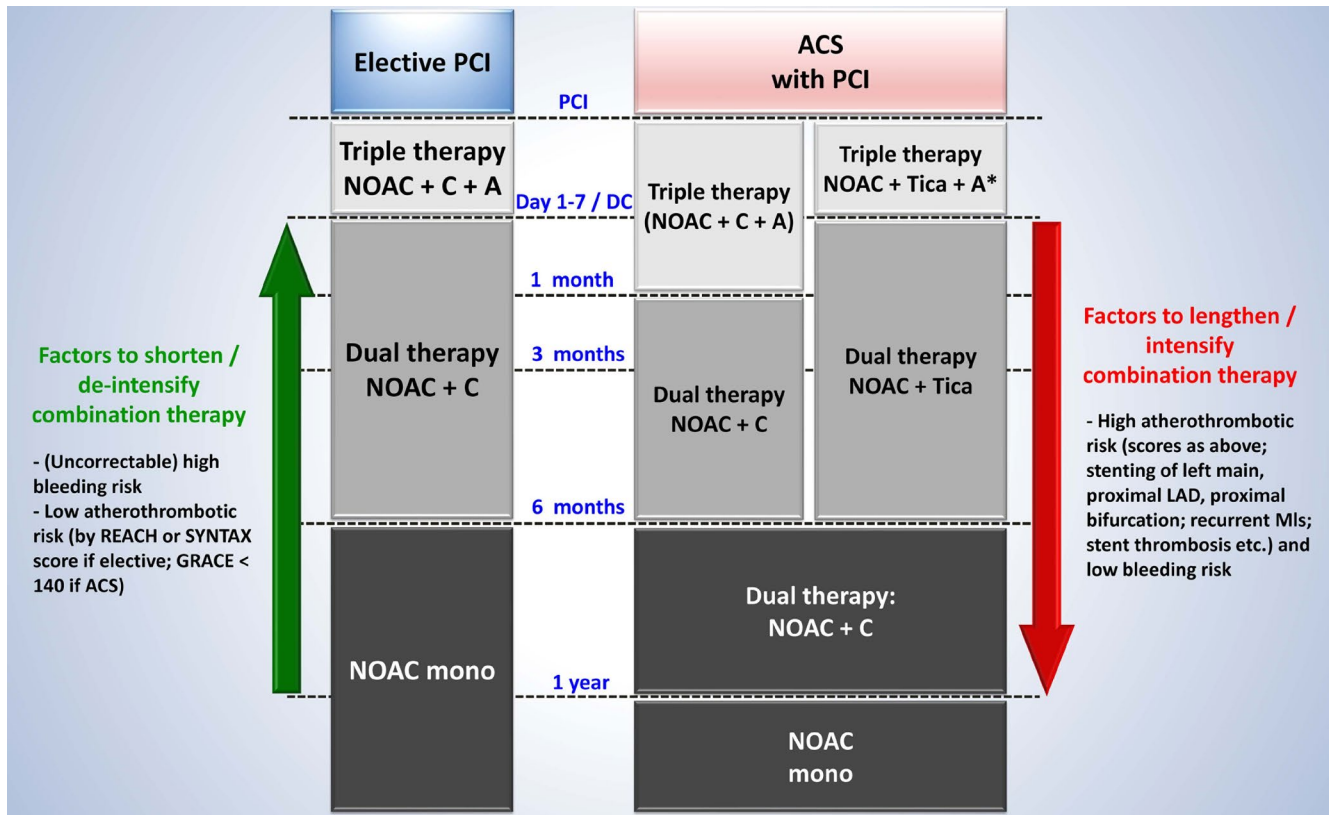
Following the period of triple therapy, patients should be managed with an OAC plus a P2Y12 inhibitor, usually clopidogrel. After 1 year, the patient should be managed with OAC alone. The OAC strategy should be an NOAC (ideally with the potential for less bleeding) or if on warfarin, with good quality anticoagulation control (TTR $\geq 70\%$).

Beyond 1 year, the evidence suggests that OAC monotherapy is the preferred option, given similar or worse MACE and more bleeding with combining NOAC and antiplatelets.¹²⁴ The AFIRE trial included patients with AF who underwent PCI or coronary artery bypass grafting (CABG) more than 1 year earlier or did not require revascularization.¹²⁵ The patients were assigned to receive monotherapy with rivaroxaban (10 mg once daily for patients with an eGFR of 15 to 49 ml/min or 15 mg once daily for patients with an eGFR ≥ 50 ml/min) or a combination of rivaroxaban plus a single antiplatelet drug. This trial was stopped early because of mortality in the combination therapy. The incidence of both cardiovascular and noncardiovascular death was lower in the rivaroxaban monotherapy group. For the primary efficacy

TABLE 2 Summary of four randomized clinical trials in patients with coronary artery disease and atrial fibrillation^{118–121}

	PIONEER-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST-AF PCI
No. of participating patients (Asian patients, %)	2124 (4.0%)	2725 (NA)	4614 (3.1%)	1506 (11.2%)
Randomization	<ul style="list-style-type: none"> Rivaroxaban 15 mg + a P2Y12 inhibitor (group 1) Rivaroxaban 2.5 mg + DAPT (group 2) VKA + DAPT (group 3) 	<ul style="list-style-type: none"> Dabigatran 110 mg + a P2Y12 inhibitor Dabigatran 150 mg + a P2Y12 inhibitor VKA + DAPT (except US, dabigatran 110 mg + a P2Y12 inhibitor or VKA + DAPT for elderly patients) 	A 2X2 factorial design <ul style="list-style-type: none"> Apixaban 5 mg versus VKA Aspirin versus placebo 	<ul style="list-style-type: none"> Edoxaban 60 mg + a P2Y12 inhibitor versus VKA + DAPT
Duration from the PCI to randomization	Within 72 h	Within 120 h	Within 14 days	4 h to 5 days
Primary endpoint	Major or minor bleeding	Major or minor bleeding	Major or minor bleeding	Major or minor bleeding
Hazard ratio for the primary endpoint	Group 1 versus group 3: 0.59 (0.47–0.76) group 2 versus group 3: 0.63 (0.50–0.80)	Dabigatran 110 mg versus VKA + DAPT: 0.52 (0.42–0.63) Dabigatran 150 mg versus VKA + DAPT: 0.72 (0.58–0.88)	Apixaban 5 mg versus VKA: 0.69 (0.58–0.81) Aspirin versus placebo: 1.89 (1.59–2.24)	edoxaban + a P2Y12 inhibitor versus VKA + DAPT: 0.83 (0.65–1.05)

Abbreviations: DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.

**In all patients:**

- Avoid use of BMS / first generation DES
- Use PPI if on triple / dual therapy
- Minimize bleeding risk by assessing and treating modifiable bleeding risk factors (e.g., hypertension, etc.)
- Close follow-up; check for signs of (occult) bleeding

*If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data)

FIGURE 14 Anticoagulation therapy after elective PCI or ACS in patients with AF. A = aspirin 75–100 mg QD; C = clopidogrel 75 mg QD; Tica = Ticagrelor 90 mg BID. AF, atrial fibrillation; ACS, acute coronary syndrome; BID, twice daily; BMS, bare metal stent; DES, drug-eluting stent; LAD, left anterior descending artery; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; QD, once daily. The figure was redraw and modified from the 2021 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF by Steffel et al¹²³

endpoint (a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause), monotherapy was noninferior to dual therapy (HR 0.72, 95% CI: 0.55–0.95). Additionally, monotherapy decreased major bleeding by 41%. Therefore, monotherapy with rivaroxaban is recommended rather than a combination of rivaroxaban with an antiplatelet drug in patients with AF with stable CAD such as more than 1 year after a PCI or CABG. Although the AFIRE trial only investigated rivaroxaban at the J-ROCKET AF dosing, it may approve the concept that monotherapy with an NOAC at the stroke prevention dosing without a combination of an antiplatelet drug is favored for patients with AF with stable CAD.

11.1 | Recommendations

1. In patients with AF eligible for NOACs, it is recommended to use an NOAC in preference to a VKA in combination with antiplatelet therapy.

2. In patients with high bleeding risk (HAS-BLED ≥ 3), rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk.
3. In patients with high bleeding risk (HAS-BLED ≥ 3), dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk.
4. In patients with AF with an indication for a VKA in combination with antiplatelet therapy, the VKA dosing should be carefully regulated with a target INR of 2.0–2.5 and TTR > 70%.

11.1.1 | Patients with acute coronary syndrome

1. In patients with AF with ACS undergoing an uncomplicated PCI, early cessation (≤ 1 week) of aspirin and continuation of dual therapy with an OAC and a P2Y₁₂ inhibitor (preferably

TABLE 3 Outlines and major outcomes of four randomized trials on NOACs versus VKA for AF ablations^{130–133}

	VENTURE-AF	RE-CIRCUIT	AXAFA-AFNET	ELIMINATE-AF				
NOAC	Rivaroxaban 20 mg QD (evening)	Dabigatran 150 mg BID	Apixaban 5 mg BID ^a	Edoxaban 60 mg QD ^a (evening)				
Comparator	VKA (INR, 2.0–3.0)	VKA (INR, 2.0–3.0)	VKA (INR, 2.0–3.0)	VKA (INR, 2.0–3.0)				
Study design	Open-label, randomized	Open-label, randomized	Open-label, randomized	Open-label, randomized				
No. of patients (NOAC vs. VKA)	124 versus 124	317 versus 318	318 versus 315	375 versus 178				
Enrollment from Asian countries	No	Yes	Yes	Yes				
Duration of administration before ablation	>3 weeks	4–8 weeks	>30 days	3–4 weeks				
Follow-up period after ablation	>30 days	8 weeks	>30 days	90 days				
Patient characteristics								
Mean or median age (years)	59.6 ± 10.2	59.1 ± 10.4	64 (58, 70)	60.5 (53–67)				
Percentage of male patients	71.0%	74.8%	67.0%	71.5%				
Percentage of paroxysmal AF	73.4%	67.6%	58.0%	67.6%				
Mean CHA ₂ DS ₂ -VASc score	1.6	2.1	2.4	0/1 in 49.8%				
Primary endpoints	ISTH/GUSTO/TIMI major bleeding	ISTH major bleeding	All-cause death, stroke, or major bleeding	All-cause death, stroke (ischaemic, haemorrhagic, or undetermined), or ISTH major bleeding				
Major complication rates								
	Rivaroxaban	VKA	Dabigatran	VKA	Apixaban	VKA	Edoxaban	VKA
ISTH major bleeding	0%	0.8%	1.6%	6.9%	3.1%	4.4%	2.4%	1.7%
Ischemic stroke	0%	0.8%	0%	0.3%	0.6%	0%	0.3%	0%
Death	0%	0.8%	0%	0%	0.3%	0.3%	0%	0%
Composite	0%	2.4%	1.6%	7.2%	4.0%	4.7%	2.7%	1.7%

Abbreviations: AF, atrial fibrillation; INR, international normalized ratio; NOACs, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonist.

^aDose reduced when dose reduction criteria were met.

clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis.

- Triple therapy with aspirin, clopidogrel, and an OAC for longer than 1 week after an ACS should be considered when risk of stent thrombosis outweighs the bleeding risk, with the total duration (≤ 1 month) decided according to assessment of these risks.

11.1.2 | Elective percutaneous coronary intervention

- After uncomplicated PCI for stable CAD, early cessation (≤ 1 week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.
- After uncomplicated PCI for stable CAD, triple therapy with aspirin, clopidogrel, and an OAC for longer than 1 week should be considered when risk of stent thrombosis outweighs the bleeding risk, with the total duration (≤ 1 month) decided according to assessment of these risks.

Stable CAD

In patients with stable CAD, such as more than 1 year after the PCI or CABG, a standard dose of NOAC monotherapy is recommended.

Footnotes

Risk of stent thrombosis encompasses the following: (i) risk of thrombosis occurring, and (ii) risk of death should stent thrombosis occur, both of which relate to anatomical, procedural, and clinical characteristics. Risk factors for stable CAD (chronic coronary syndrome, CCS) patients includes the following: stenting of left main stem or last remaining patent artery; suboptimal stent deployment; stent length >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

12 | MANAGEMENT OF ORAL ANTICOAGULANTS BEFORE, DURING, AND AFTER ATRIAL FIBRILLATION ABLATION

Catheter ablation procedures for AF are associated with both pro-thromboembolic and bleeding risks, and appropriate anticoagulation

managements before, during, and after the procedure are quite important. Because the COMPARE randomized study demonstrated lower risks of both thromboembolism and bleeding complications under uninterrupted VKA compared with interrupted VKA with heparin bridging,¹²⁶ it is generally accepted that the procedure should be performed without interrupting VKA, when anticoagulation control is appropriate.¹²⁷

NOACs are currently used in many patients even in those undergoing AF ablation. The Japanese catheter ablation registry of AF (J-CARAF) during 2011–2016 showed that of the 9048 patients with periprocedural oral anticoagulation, 3231 (35.7%) were treated with VKA, whereas the other 5817 (64.3%) were managed with NOACs.¹²⁸ A meta-analysis of nonrandomized studies showed that interrupted dabigatran for a minimum period (12–24 h) before the procedure was associated with similar thromboembolism and bleeding complication rates to uninterrupted VKA.¹²⁹

Several randomized, prospective clinical trials on uninterrupted NOACs versus uninterrupted VKA have been conducted (Table 3). These trials include VENTURE-AF study for rivaroxaban versus VKA¹³⁰; RE-CIRCUIT study for dabigatran versus VKA¹³¹; AXAFA-AFNET 5 study for apixaban versus VKA¹³²; and ELIMINATE-AF study for edoxaban versus VKA.¹³³ In these studies, therapeutic doses of NOACs and VKA with target prothrombin time-international normalized ratio (PT-INR) between 2.0 and 3.0 were generally administered for >3 weeks before ablation, with exception of short-period administration in some cases in which transesophageal or intracardiac echocardiography confirmed the absence of intra-atrial thrombus. After the ablation procedure, the drugs were continued for >30 days. During the procedure, heparin was given to maintain activated clotting time >300 s in all studies. The RE-CIRCUIT,¹³¹ AXAFA-AFNET 5,¹³² and ELIMINATE-AF¹³³ studies included patients enrolled from the Asian countries. The incidences of major complications in uninterrupted NOACs versus uninterrupted VKA groups in each study are shown in Table 3.

In a meta-analysis of these four trials comparing NOACs versus VKA,¹³³ the rate of death were 0.1% versus 0.2%, respectively; ischemic stroke, 0.2% versus 0.2%, respectively; major bleeding, 2.1% versus 4.2%, respectively; and the composite outcome, 2.4% versus 4.6%, respectively. Another meta-analysis of six randomized studies¹³⁴ on uninterrupted NOACs (dabigatran, rivaroxaban, and apixaban) versus uninterrupted VKA revealed that the incidence of major bleeding was significantly lower in the NOAC group (1.68%) than the VKA group (3.80%) (OR = 0.45, 95% CI = 0.26–0.81, $p = 0.007$); whereas the incidence of ischemic stroke or TIA was low and similar between NOAC (0.21%) and VKA groups (0.21%). Furthermore, the incidence of silent cerebral thromboembolic events (in three studies) was similar between NOAC (14.0%) and VKA groups (13.3%). Similar results were reported by another meta-analysis, which included three randomized and nine nonrandomized studies on uninterrupted NOACs versus uninterrupted VKA.¹³⁵ These meta-analyses therefore indicate that in the

periprocedural period of catheter ablation for AF, uninterrupted NOACs shows a similar efficacy profile but a better safety profile than uninterrupted VKA.

Interrupted NOAC protocols versus uninterrupted regimes have been tested by prospective, randomized studies done in Asian countries. A single-center study from Japan¹³⁶ demonstrated that both of uninterrupted ($n = 421$) versus interrupted protocols ($n = 423$), in the latter of which NOACs were interrupted on the day of the procedure and reinitiated on the next morning, showed a low risk of symptomatic thromboembolism (0.2% vs. 0.2%) and major bleeding events (0.5% vs. 0.9%) and similar incidence of silent cerebral ischemic lesions (19.8% vs. 22.0%). Another study from Korea¹³⁷ demonstrated comparable efficacy and safety among uninterrupted ($n = 106$) versus single-dose skipped ($n = 110$) versus 24-h skipped NOAC protocols ($n = 110$), regardless of the type of NOAC used. The ABRIDGE-J study¹³⁸ compared minimally interrupted dabigatran (holding 1–2 doses and reinitiating after ablation, $n = 220$) with uninterrupted VKA ($n = 222$) and found no difference in the incidence of thromboembolic events but fewer major bleeding events in minimally interrupted dabigatran (1.4% vs. 5.0%, $p = 0.03$). The prospective KYU-RABLE study¹³⁹ ($n = 513$) in which uninterrupted edoxaban was administered once daily in the morning, with one dose delayed after the procedure on procedural day, supports this minimally interrupted protocol of NOAC therapy. Notwithstanding the small-sized study cohorts which may be underpowered for the thromboembolic outcomes, an ablation strategy with minimally interrupted periprocedural NOACs may be an option.

12.1 | Recommendations

- We recommend a preferential use of NOACs over VKA because of their safety profile relative to VKA in addition to their ease of management before and after ablation.
- NOAC dosing protocols, uninterrupted or minimally interrupted, should be determined in each institution, depending on the volume of AF ablation done, experience of the operator, backup system in case of life-threatening complications, baseline renal function and thromboembolism and bleeding risks of each patient, time of administration of once-daily NOACs (morning or evening), preparation of specific antidotes to NOACs, etc. (Figure 15).
 - a. For most patients, an uninterrupted NOAC strategy may be the preferred option.
- When VKA is used, it should be controlled within a therapeutic range and uninterrupted throughout the periprocedural period unless bleeding events preclude its continuous use.
- In general, OAC therapy is continued for 2 months following ablation in all patients. Beyond this time, a decision to continue OAC long term is determined primarily by the presence of CHA₂DS₂-VASc stroke risk factors rather than the rhythm status.

FIGURE 15 A flowchart about the general recommendation for NOACs in the periprocedural period of catheter ablation. NOACs, non-vitamin K antagonist oral anticoagulants; TEE, transesophageal echocardiography

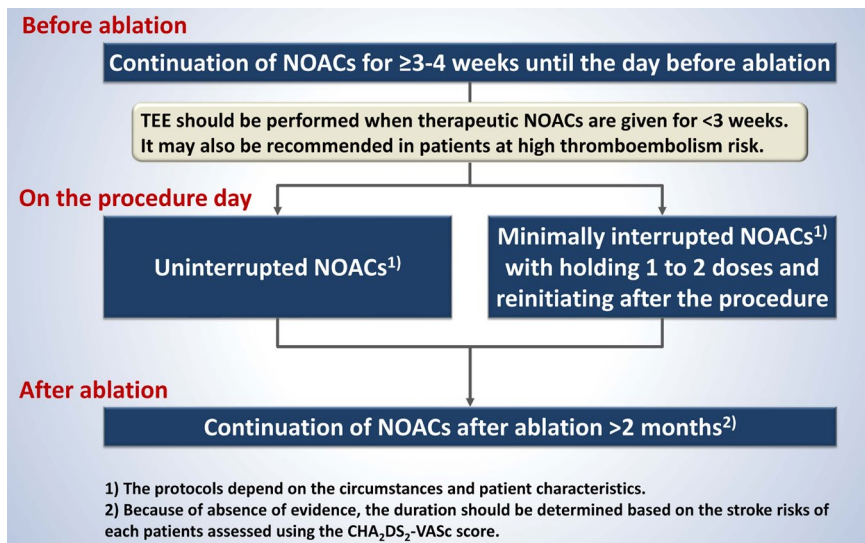
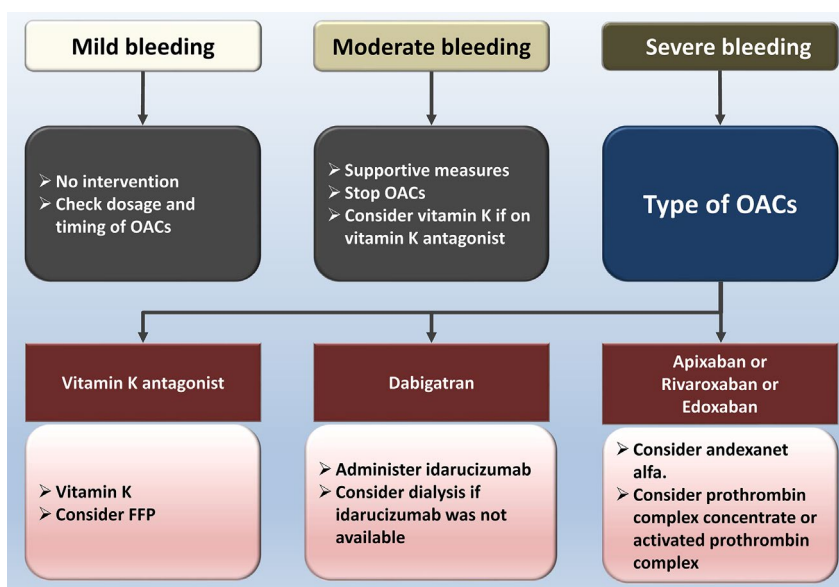


FIGURE 16 General principles of managements of bleeding for anticoagulated patients with AF. AF, atrial fibrillation; FFP, fresh frozen plasma; NOACs, non-vitamin K antagonist oral anticoagulants; OACs, oral anticoagulants



13 | REVERSAL AGENTS

The general principles of managements of bleeding are summarized in Figure 16. For severe bleeding or life-threatening bleeding, reversal agents could be considered to reverse the anticoagulant effects of NOACs.

Idarucizumab is a monoclonal antibody fragment and binds dabigatran with an affinity that is 350 times as high as that observed with thrombin.¹⁴⁰ In the RE-VERSE AD study, the efficacy and safety of idarucizumab was tested in patients who had serious bleeding or required urgent procedures. In an interim analysis of the first 90 patients, idarucizumab reversed the anticoagulant effect of dabigatran within minutes in 88%–98% of patients.¹⁴¹ In the whole cohort of 503 patients, median time to cessation of bleeding 2.5 h in those with uncontrolled bleeding who could be assessed.¹⁴² For the periprocedural group, the median time to the initiation of the intended procedure was 1.6 h. Periprocedural

hemostasis was assessed as normal in 93.4% of the patients, mildly abnormal in 5.1%, and moderately abnormal in 1.5%. At 90 days, thrombotic events had occurred in 6.3% of the patients in the uncontrolled bleeding group and in 7.4% in the periprocedural group, while the mortality rate was 18.8% and 18.9%, respectively. No serious adverse safety signals were noted. More recently, it was found that although both dabigatran and idarucizumab were renally cleared, impaired renal function did not affect the reversal of anticoagulation.¹⁴³ The REVERSE-AD study results were consistent and supported by observations from a post-approval global registry (RE-VECTO), which also showed that off-label use was minimal.¹⁴⁴ Idarucizumab is approved in many countries for patients treated with dabigatran when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.

Andexanet alfa is a recombinant modified human factor Xa decoy protein that is catalytically inactive but which retains the

ability to bind factor Xa inhibitors in the active site with high affinity.¹⁴⁵ In a clinical study of older healthy volunteers, andexanet reversed the anticoagulant activity of apixaban and rivaroxaban within minutes after administration and for the duration of infusion, without clinical evidence of toxic effects.¹⁴⁶ In the multicenter, open-label, single-arm ANNEXA-4 trial, 352 patients with acute major bleeding associated with factor Xa inhibitors (mostly on rivaroxaban and apixaban) were given an initial bolus and subsequent 2-h infusion of andexanet alfa. This substantially reduced anti-factor Xa activity after the bolus (75%–92%), and this effect persisted till the end of the infusion. Good or excellent hemostatic efficacy was achieved in 82% 12 h after the infusion.¹⁴⁷ During 30 days follow-up, 49 patients (14%) died, and 34 (10%) experienced a thrombotic event. Similar data are based on an earlier interim analysis of this study,¹⁴⁶ and andexanet alfa was granted accelerated approval by the FDA for the reversal of anticoagulation if needed due to life-threatening or uncontrolled bleeding in patients treated with apixaban or rivaroxaban.

When managing OAC-related bleeding, it is important to survey for occult malignancies that are the cause/origin of the bleeding, for example, gastrointestinal (GI) tract cancer in patients with GIB.¹⁰⁹ In a nationwide study from Taiwan, incident GI cancers were diagnosed in 1 of 37 patients with AF at 1 year after OAC-related GI bleeding and were more common among patients treated with NOACs (1/26) compared with warfarin (1/41).¹⁴⁸ Interestingly, the risk of mortality after GI tract cancers were diagnosed was lower in patients treated with NOACs than in those treated with warfarin (23.5% vs. 51.8%; adjusted HR 0.441; $p < 0.001$), and more patients treated with NOACs (33.8%) underwent surgery than those

treated with warfarin (18.9%) suggesting that NOACs may serve as a stronger “screening test” than warfarin and may be able to disclose GI cancers at an earlier stage when operation is possible, therefore leading to a better prognosis.¹⁴⁸ Similar findings have been reported for anticoagulated patients presenting with hematuria among whom the possibility of underlying bladder cancers should be kept in mind.¹⁴⁹

13.1 | Recommendations

- Idarucizumab is indicated for the reversal of dabigatran in patients with serious bleeding or requiring urgent procedures.
- Andexanet alfa can be useful for reversing anticoagulation in patients treated with Factor Xa inhibitors with life-threatening or uncontrolled bleeding.
- The possibility of occult malignancies that are the cause/origin of the bleeding should be kept in mind when managing OAC-related bleeding.

14 | STROKE PREVENTION IN SPECIAL PATIENT GROUPS

14.1 | Elderly

The prevalence of AF is increasing in recent decades, and the prevalence in elderly population has increased more rapidly, in worldwide and also in Asians.^{3,150,151} Stroke prevention in older patients with

TABLE 4 Interaction between different age groups and the efficacy and safety outcomes of NOAC compared with warfarin in NOAC pivotal trials^{156–159}

	Dabigatran 110 mg	Dabigatran 150 mg	Rivaroxaban	Apixaban	Edoxaban
Stroke/SEE (HR and 95% CI, each NOAC compared with warfarin)					
<65 years	0.93* (0.70–1.22)	0.63* (0.46–0.86)	0.95 (0.76–1.19)	1.16 (0.77–1.73)	0.94 (0.65–1.37)
65–74 years				0.72 (0.54–0.96)	0.89 (0.68–1.16)
≥75 years	0.88 (0.66–1.17)	0.67 (0.49–0.90)	0.80 (0.63–1.02)	0.71 (0.53–0.95)	0.83 (0.66–1.04)
<i>p</i> for interaction	0.81	0.81	0.31	0.11	0.84
Major bleeding (HR and 95% CI, each NOAC compared to warfarin)					
<65 years	0.62* (0.50–0.77)	0.70* (0.57–0.86)	0.96 (0.78–1.19)	0.78 (0.55–1.11)	0.81 (0.58–1.12)
65–74 years				0.71 (0.56–0.89)	0.75 (0.60–0.94)
≥75 years	1.01* (0.83–1.23)	1.18* (0.8–1.42)	1.11 (0.92–1.34)	0.64 (0.52–0.79)	0.83 (0.71–0.99)
<i>p</i> for interaction	<0.001	<0.001	0.33	0.63	0.78
Intracranial bleeding (HR and 95% CI, each NOAC compared to warfarin)					
<65 years	0.22 (0.11–0.45)	0.43 (0.25–0.74)	0.54 (0.33–0.89)	0.87 (0.43–1.74)	1.03 (0.46–2.29)
65–74 years				0.35 (0.20–0.60)	0.42 (0.25–0.70)
≥75 years	0.37 (0.21–0.64)	0.42 (0.25–0.70)	0.80 (0.50–1.28)	0.34 (0.20–0.57)	0.40 (0.26–0.62)
<i>p</i> for interaction	0.28	0.91	0.26	0.20	0.11

Note: Significant *p*-values are denoted in bold. *Relative risk

Abbreviations: CI, confidence interval; HR, hazard ratio; NOACs, non-vitamin K antagonist oral anticoagulants; SEE, systemic embolic event.

AF is important as stroke risk increased dramatically with age.^{67,68} However, oral anticoagulant (OAC) treatment has been underutilized in elderly.¹⁵²

In pivotal trials of NOAs, the proportions of elderly patients (age ≥ 75 years) included ranged from 31% to 43%.^{63,153–155} Meta-analyses of pivotal NOAC trials showed no interaction between different age groups and efficacy/safety of NOAC compared with warfarin.⁹⁷ Generally, the higher events rate in elderly population resulted in a larger absolute risk reduction from NOAC compared with warfarin; but the presence of interaction by different age groups varied by different clinical outcomes in each NOAC trial (Table 4).^{156–159}

For extreme elderly defined as ≥ 90 years, a previous observational study reported that OAC treatment may be considered as stroke prevention, with NOACs being the more favorable choice.¹⁰⁰ In a further analysis of 64,169 patients with AF ≥ 65 years of age, the clear safety signal in favor of NOACs over warfarin was evident irrespective of age strata (65–74, 75–89, ≥ 90 years), being most marked in very older adults.⁶⁸ Actually, the introduction of NOACs has changed the landscape for stroke prevention in elderly (≥ 85 years) Asian patients with AF. The Initiation rates of OACs after AF was newly diagnosed in the elderly significantly increased from 9.5% to 34.3%, mainly due to the introduction of NOACs (from 0% to 26.2%), and the 1-year risk of ischemic stroke after AF diagnosis decreased in the era of NOACs.¹⁵² Importantly, certain conditions and comorbidities such as renal impairment and history of GIB are more common in elderly population, and stroke prevention is even more challenging in this high-risk population. In the recent report from Taiwan, which focused on very elderly (≥ 90 years) patients with AF with a history of ICH, GIB, or chronic kidney disease (CKD), NOACs were still associated with a lower risk of composite adverse events compared with warfarin or non-OACs.¹⁶⁰ Therefore, “old age” itself should not be the solely reason to withhold OACs for stroke prevention.

What is the “optimal” dose of NOAC in the elderly AF patient with a high bleeding risk is an important and difficult issue. The phase 3 Edoxaban Low-Dose for Elder CARE patients with AF (ELDERCARE-AF) study was performed to compare edoxaban 15 mg per day versus placebo among elderly (≥ 80 years) Japanese patients with AF who are deemed ineligible for standard OAC treatment (CCr 15 to 30 ml/min; history of bleeding from critical organs; body weight ≤ 45 kg; continuous use of nonsteroidal anti-inflammatory drugs [NSAIDs] or antiplatelet drugs).¹⁶¹ The results showed that edoxaban 15 mg was superior to placebo in preventing stroke or systemic embolism (HR 0.34; $p < 0.001$) and did not result in a significantly higher incidence of major bleeding than placebo (HR 1.87, $p = 0.09$).¹⁶² However, it should be emphasized that the results of ELDERCARE-AF just proved the concept that even the off-labelling low-dose edoxaban was better than non-use of OACs (rather than being against the use of standard-dose NOACs). NOACs at the on-labelling dose should still be considered

first for stroke prevention in elderly patients with AF until high-quality data of direct comparisons of different dosing NOACs are available.

14.2 | Low body weight

Although there is no absolute cutoff for defining low body weight, Asians tend to be smaller and leaner than non-Asians (e.g., 20 kg less on average in ENGAGE AF-TIMI 48)⁹⁸; thus, patients with low body weight are more common among Asians than among non-Asians. The effects of NOACs are closely related to plasma concentrations, which are affected by body distribution volume.¹⁶³ Extremely low body weight may influence the efficacy and safety of NOACs. Although NOACs have shown better net clinical benefits than warfarin, being underweight has been associated with an increased risk of major bleeding in patients taking NOACs.¹⁶⁴ Body weight ≤ 60 kg was a dose reduction criterion for apixaban and edoxaban.^{154,155} For apixaban, there was no interaction between different body weight groups (≤ 60 kg, 61–120 kg, and >120 kg) and the efficacy of apixaban compared with warfarin.¹⁶⁵ In terms of safety outcome such as major bleeding, a large RR reduction was observed in patients with ≤ 60 kg than those with 61–120 kg and >120 kg.¹⁶⁵ For edoxaban versus warfarin, there was no significant interaction between different body mass index (BMI) category groups and the outcomes; however, the underweight patients defined as BMI <18.5 kg/m² occupied small proportion of total population (0.8%, $n = 177$), so data were limited especially in the comparison between edoxaban and warfarin.¹⁶⁶ A recent subanalysis of ENGAGE AF-TIMI 48 trial, which focused on patients at extremes of body weight has demonstrated that the pharmacokinetic/pharmacodynamic profile of edoxaban was consistent across extremes of BW, resulting in similar efficacy compared with warfarin, while major or clinically relevant nonmajor bleeding and net outcomes were most favorable with edoxaban compared with warfarin in patients with LBW.¹⁶⁷ For rivaroxaban, limited data are available for patients with <60 or <50 kg. In recent observational data including a large population of patients with AF with ≤ 60 kg taking OACs ($n = 21,589$), NOAC was associated with lower risks of ischemic stroke and major bleeding than warfarin, and these results were largely consistent in patients with <50 kg.¹⁰¹ In addition, on-label NOAC dosing should still be applied in patients with low body weight to achieve the best net clinical benefit.¹⁰¹

14.3 | Chronic kidney disease

CKD is an independent predictor of risk of thromboembolic and bleeding events.¹⁶⁸ All NOACs have some degree of renal elimination, with the greatest renal dependency for excretion with dabigatran (80%) and the least with renal dependency for apixaban (27%). However, there are no head-to-head NOAC comparison trials and, therefore, insufficient evidence to recommend one agent

CCr	≥50 mL/min	30-49 mL/min	15-29 mL/min	<15 mL/min or ESRD on RRT
Dabigatran	150 mg bid or 110 mg bid	150 mg bid or 110 mg bid	⊘	⊘
Edoxaban	60 mg qd [#]	30 mg qd	30 mg qd	⊘
Rivaroxaban	20 mg qd	15 mg qd	15 mg qd	⊘
Apixaban	5 mg bid*	5 mg bid*	2.5 mg bid or 5 mg bid* according to the labelling in different countries	⊘

Closely monitor renal function
The CCr should be calculated using CG equation

*Use 2.5 mg BID if 2 of 3 of the following criteria are present: age ≥80 years old, body weight ≤60 kg, serum creatinine ≥1.5mg/dL.
[#] 30mg qd if body weight ≤60kg or concomitant potent P-Gp inhibitor therapy

FIGURE 17 Recommendations about the dosing of NOACs according to renal function. bid, twice daily; CCr, creatinine clearance; qd, once daily; ESRD, end-stage renal disease; NOACs, non-vitamin K antagonist oral anticoagulants; RRT, renal replacement therapy

over another. The dose adapted on the basis of CCr according to approved indications (Figure 17).

There have been several meta-analyses addressing the efficacy and safety of NOACs compared with warfarin in patients with mild to moderate CKD.¹⁶⁹⁻¹⁷¹ The data are consistent across studies that all NOACs are associated with lower risks of thromboembolic events compared with warfarin in patients with mild to moderate CKD (CCr 30 to 79 ml/min).^{169,170} For major bleeding, NOAC showed significantly lower risk of major bleeding compared with warfarin in patients with mild CKD (defined as CCr 50 to 79 ml/min); however, there was no significant difference between NOAC and warfarin in patients with moderate CKD (defined as CCr 30 to 49 ml/min).^{169,170} Indirect comparisons suggested that apixaban and edoxaban high-dose regimen might be more likely associated with a better net clinical profile in patients with AF with moderate CKD (defined as CCr from 25-30 to 50 ml/min).¹⁷¹

14.3.1 | End-stage renal disease undergoing hemodialysis

The CHA₂DS₂-VASc score could also be used to predict ischemic stroke risk in patients with AF with ESRD undergoing dialysis.¹⁷² However, the benefit of OAC treatment in patients with AF and ESRD has been controversial. In a Korean nationwide cohort study, warfarin use was significantly associated with an increased risk of hemorrhagic stroke (HR 1.44, 95% CI 1.09-1.91) without any benefit for preventing thromboembolic events.¹⁷³ Warfarin-based OAC treatment did not show definite benefit for patients with ESRD and AF compared with no antithrombotic therapy. Recently, there has been a few studies suggesting that apixaban or rivaroxaban can be a safer alternative to warfarin in those population.¹⁷⁴⁻¹⁷⁷ There was no difference in the risks of stroke/systemic embolism between apixaban (*n* = 2351) and warfarin (*n* = 23,172) (HR 0.88, 95% CI 0.69-1.12), but apixaban was associated with a significantly lower risk

of major bleeding (HR 0.72, 95% CI 0.59-0.87).¹⁷⁴ Among patients with nonvalvular AF and stage 4 or 5 CKD or undergoing hemodialysis, rivaroxaban (*n* = 1896) did not significantly reduce stroke or systemic embolism (HR 0.55, 95% CI 0.27-1.10) or ischemic stroke (HR 0.67, 95% CI 0.30-1.50) alone, but it was associated with a significant reduction of major bleeding by 32% compared with warfarin (*n* = 4848).¹⁷⁶ Despite some favorable data of NOACs, a recent meta-analysis, which included 16 observational studies (2 or 16 ones investigated NOACs) showed that OACs were not associated with a reduced risk of thromboembolism in patients with AF on long-term dialysis.¹⁷⁸ In addition, a recent cohort study and meta-analysis from Taiwan demonstrated that the use of OAC was not associated with a lower risk of IS/SE in ESRD patients with AF when compared with those without OAC use. Besides, NOACs did not provide benefit over warfarin regarding effectiveness and safety in patients with AF undergoing dialysis.¹⁷⁹ These diverse results may point out the necessities of high-quality trials of "OACs (especially NOACs) versus non-OACs" in this population.

14.4 | Abnormal liver function

Liver disease is often accompanied by a combination of complex abnormalities of the coagulation pathways^{180,181}; thus, patients with advanced liver disease have higher risks of thromboembolism and bleeding.^{182,183} In addition, significant impairment of liver function can affect hepatic clearance and drug metabolism.¹⁸⁴ However, even in patients with liver cirrhosis, warfarin-based oral anticoagulation was associated with a lower risk of ischemic stroke and a positive net benefit compared with no antithrombotic therapy.¹⁰³

The use of warfarin in patients with advanced liver disease is challenging due to intrinsically prolonged prothrombin time.¹⁸⁵ Although NOAC could be considered as an alternative to warfarin, patients with liver function abnormalities (i.e., active or significant liver disease including viral hepatitis and cirrhosis, alanine

transaminase/aspartate transaminase/alkaline phosphatase ≥ 2 –3 times the upper limit of normal [ULN] or bilirubin ≥ 1.5 times the ULN) were largely excluded from the pivotal NOAC clinical trials.^{63,153,154} Although NOACs were not associated with an increased risk of serious liver injury irrespective of baseline liver status,¹⁸⁶ data about optimal OAC treatment in patients with liver function impairment were limited. In a small retrospective cohort study including patients with impaired liver function ($n = 633$), NOAC showed similar risks of stroke or systemic embolism, major bleeding, and GIB compared with warfarin.¹⁸⁷ In a post-hoc analysis of ENGAGE AF-TIMI 48 trial, bleeding, but not thromboembolic events, was increased in patients with liver disease, and a history of liver disease did not alter the relative efficacy and safety of higher-dose edoxaban compared with warfarin.¹⁸⁸ Also, in a large Asian population with AF and liver disease, NOACs showed better effectiveness and safety than warfarin, which was consistent in those with significant active liver disease, defined as in the pivotal clinical trials.¹⁰²

All four NOACs may be used in patients with mild and transient liver function abnormalities including Child–Turcotte–Pugh A cirrhosis, and dabigatran, apixaban, and edoxaban may be used with caution in patients with Child B cirrhosis.^{189–191} Rivaroxaban use should be avoided in patients with Child B cirrhosis and all four NOACs are contraindicated in patients with Child C cirrhosis and any liver disease combined with significant coagulopathy and an increased risk of clinically relevant bleeding.¹⁹²

14.5 | Valvular heart disease

AF often co-exists with various types of VHDs. Valvular AF is defined as patients with AF and VHD including moderate to severe rheumatic mitral stenosis or having mechanical prosthetic valve (EHRA type 1 VHDs).¹⁹³ Patients with valvular AF have significantly higher risks of thromboembolic events than those with nonvalvular AF.¹⁹⁴ Other VHDs are defined as EHRA type 2 VHDs¹⁹³ and these patients also showed higher thromboembolic and bleeding risk.¹⁹⁵

The efficacy of warfarin in stroke prevention in patients with valvular AF has long been established. Although the pivotal clinical trials of NOACs did not include patients with valvular AF (EHRA type 1 VHDs), patients with EHRA type 2 VHDs were allowed to participate.^{196–199} The efficacy and safety of NOACs do not appear to be different with respect to the valvular status of patients, including those with bioprosthetic valves²⁰⁰ and pooled high-dose NOAC group shows a significantly lower risk of thromboembolic events and a similar risk of major bleeding compared with the warfarin group²⁰¹ and consistent results were observed in a large Asian nationwide cohort with VHDs.²⁰²

There has been only one published randomized controlled study comparing warfarin and NOAC in patients with mechanical prosthetic valve.²⁰³ This study was prematurely terminated because of excessive thromboembolic and bleeding events with dabigatran.²⁰³ Although there was a signal for the positive net benefit of NOACs

compared with warfarin in patients with mitral stenosis,²⁰⁴ further randomized clinical trials are needed to consider NOAC as an alternative to warfarin in patients with rheumatic mitral stenosis. A randomized, open-label study is planned to compare dabigatran and warfarin among Asian patients with AF with moderate or severe mitral stenosis (DABigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis [DAVID-MS]) and hope the results of the trial could be able to provide important data and information.²⁰⁵

14.6 | Hypertrophic cardiomyopathy

AF is the most common cardiac arrhythmia in patients with hypertrophic cardiomyopathy.²⁰⁶ Observational data highlight a high stroke risk in patients with hypertrophic cardiomyopathy and AF, confirming the need for OAC.^{207,208} In a large nationwide observational cohort including Asian population, the annual risk of AF-associated stroke in hypertrophic cardiomyopathy was more than 1% even in younger patients and those with CHA₂DS₂-VASc score of 0 or 1 point.²⁰⁹ Consistent with these results, the risk of stroke in patients with hypertrophic cardiomyopathy and AF without any CHA₂DS₂-VASc stroke risk factors was similar to that of those patients without hypertrophic cardiomyopathy with CHA₂DS₂-VASc score of 3.^{210,211} Despite the higher stroke risk, the use of OACs among patients with hypertrophic cardiomyopathy and AF was suboptimal in the daily practice.²¹⁰ Although most experience was from warfarin, recent observational studies demonstrated that NOACs were associated with lower risks of thromboembolic events and major bleeding compared with warfarin.^{212,213}

14.7 | Prior stroke and intracranial hemorrhage

14.7.1 | Prior stroke

Prior stroke or transient ischemic attack (TIA) is a powerful predictor of subsequent stroke, with an increased risk by 2.2 to 2.5.²¹⁴ When prescribing OACs to patients with prior stroke/TIA, physicians should consider that these patients are also at higher risk for ICH during OAC than those without prior stroke/TIA.^{215–220}

Previous pivotal randomized clinical trials of NOACs that included a varied number of patients with AF and a history of stroke/TIA reported following subgroup analyses for these population.^{217–220} The efficacy and safety of NOACs between patients with and without prior stroke/TIA were similar, indicating that NOACs can be used safely even in patients with prior stroke/TIA.^{217–220} An updated meta-analysis including 20,500 patients with AF with previous stroke/TIA showed that NOACs were associated with a significant reduction of stroke, stroke or systemic embolism, hemorrhagic stroke, and ICH compared with warfarin.²²¹ In a recent report from South Korea, NOACs were

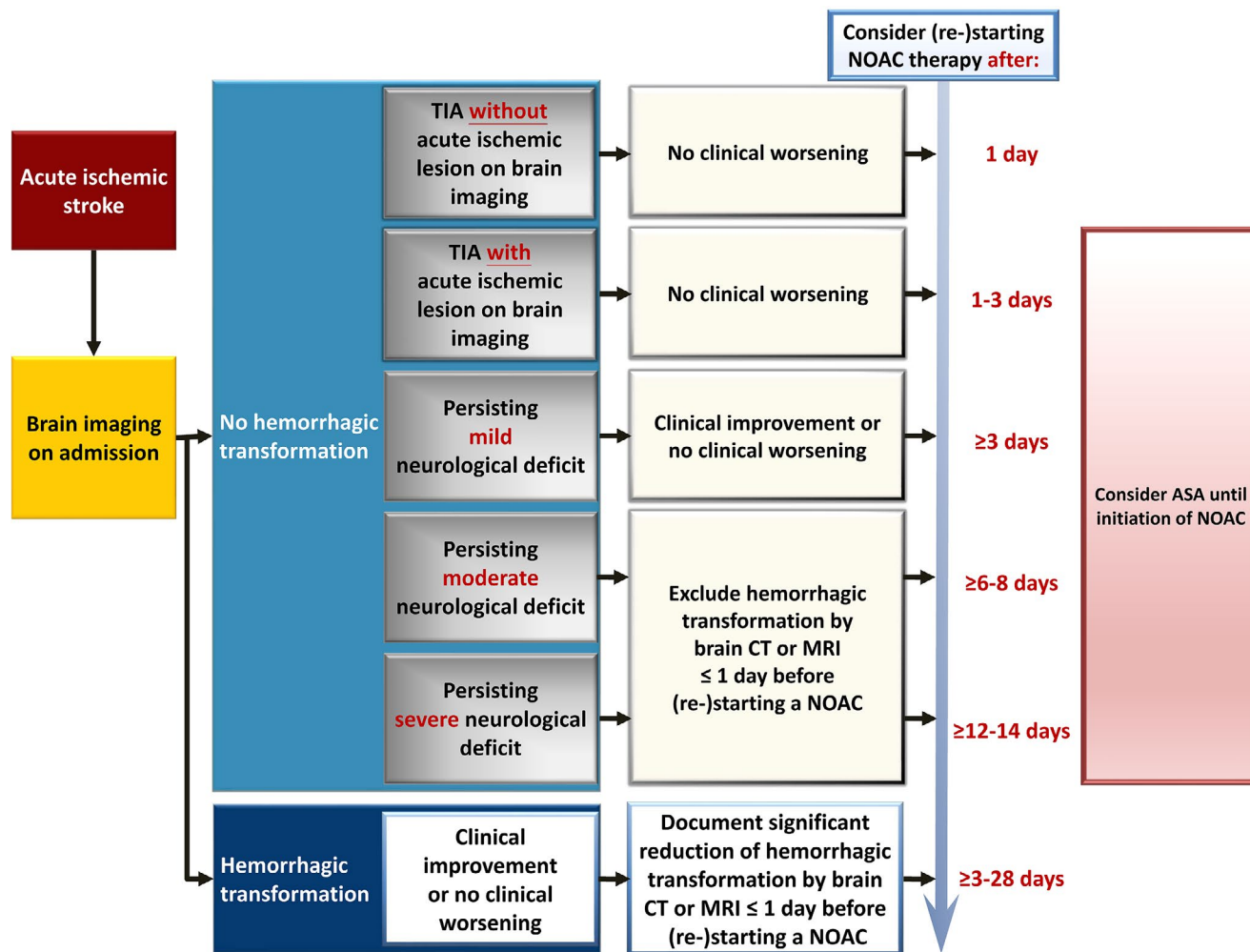


FIGURE 18 Use of OACs after acute ischemic stroke or transient ischemic attack. CT, computed tomography; MRI, magnetic resonance imaging; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischaemic attack. The figure was redraw and modified from the 2021 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF by Steffel et al¹²³

associated with lower risks of recurrent stroke, major bleeding, composite clinical outcomes, and mortality in Asian patients with AF with the history of stroke.²²²

The 2021 EHRA practical guide on the use of NOACs suggests that the initiations of OACs between 1 and 28 days after an ischemic stroke, depending on whether the presence of hemorrhagic transformation at brain imaging on admission and stroke severity.¹²³ For patients without hemorrhagic transformation, OACs could be considered between 1 and 12–14 days depending on the severity of stroke. For patients with hemorrhagic transformation, OACs would be considered once clinical status improved and significant reduction of hemorrhagic transformation was documented at follow-up brain CT or MRI performed ≤ 1 day before re-starting/initiations of NOACs. A multidisciplinary team approach including stroke neurologists and cardiologists should help decision-making, taking patient values and preferences into consideration. The suggestions about the use of OACs after acute ischemic stroke are summarized in Figure 18, based on the recommendations of 2021 EHRA Practical Guide on the use of NOACs in patients with AF.¹²³

14.7.2 | Prior intracranial hemorrhage

Patients with AF with a history of prior ICH have a higher risk of both ischemic stroke and recurrent ICH.²²³ Although randomized trials are lacking, the positive net clinical benefits of OAC therapy in patients with prior ICH were consistently observed in previous observational studies.^{224–227} In a previous report from the Taiwan nationwide claims database, use of warfarin was found to be possibly beneficial for patients with AF with prior ICH having a CHA₂DS₂-VASc score ≥ 6 compared with no antithrombotic therapy.²²³ Because all pivotal clinical trials of NOACs excluded patients with a history of spontaneous ICH,^{63,153–155} data about comparisons between warfarin and NOACs among these patients were only available from retrospective observation studies. It seems that NOACs were associated with a lower risk of all-cause mortality (HR 0.517), ICH (HR 0.556), and major bleeding (HR 0.645) compared with warfarin, whereas the rate of ischemic stroke was similar.²²⁸ Similar findings have been reported from South Korea.²²⁹ Therefore, among patients with AF with prior ICH, OACs should generally still

be considered with NOACs being as the preferred choice for stroke prevention.

For patients with AF who experienced acute ICH, OAC treatment can be resumed/initiated after 4–8 weeks, especially when the cause of bleeding or the relevant risk factor has been treated.²³⁰ A multidisciplinary team approach including stroke neurologists and cardiologists should help decision-making, taking patient values and preferences into consideration. However, further studies are needed to find optimal timing point of OAC resumption and patient subgroup who are more beneficial for early OAC resumption, especially in the NOAC era.

14.8 | Adherence issue

It is critical to educate patients about the importance of strict adherence. Strict adherence to NOAC intakes is more crucial as its anticoagulation effect diminishes within 12–24 h after the last intake.²³¹ Although actual adherence of NOAC intake varied depending on the data sources and definition,^{77,232–236} adherent NOAC users (proportion of days covered [PDC] $\geq 80\%$) accounted for 64% of all NOAC users in recent Asian real-world observational cohort study.⁷⁶ Adherent use of NOAC showed better outcomes without increasing bleeding risk and maintaining $\geq 90\%$ of adherence achieved optimal effectiveness of NOAC.⁷⁶ Cost-effective and feasible tools should be developed for high-risk patients with low adherence.²³⁷

15 | LEFT ATRIAL APPENDAGE OCCLUSION

The efficacy, safety, and procedural aspects, as well as the limitations of current data on LAA occlusion has recently been the subject of a detailed expert consensus statement EHRA/EAPCI on catheter-based LAA occlusion.²³⁸ More recently, the role of surgical occlusion of the LAA in patients with AF undergoing cardiac surgery has gained prominence with publication of the LAAOS III trial.²³⁹ The latter showed that stroke/SE occurred in 4.8% in the LAA occlusion group and in 7.0% in the no-occlusion group (HR: 67; 95% CI 0.53 to 0.85; $p = 0.001$). The incidence of perioperative bleeding, heart failure, or death did not differ significantly between the trial groups. Thus, among participants with AF who had undergone cardiac surgery, the risk of ischemic stroke or systemic embolism was lower with concomitant LAA occlusion performed during the surgery than without it.

15.1 | Catheter-based left atrial appendage occlusion

15.1.1 | Efficacy

There are two RCTs comparing percutaneous LAA occlusion with the Watchman device to warfarin in patients with nonvalvular AF and high risk of stroke.^{240,241} Data from these and their associated

registries^{242,243} demonstrate noninferiority to warfarin for prevention of ischemic stroke or systemic embolism >7 days post procedure. There were more ischemic strokes in the device group (1.6 vs. 0.9 events/100 patient years, $p = 0.05$), largely driven by procedure related strokes, and a significant reduction in hemorrhagic stroke (0.15 vs. 0.96/100 patient years, $p = 0.004$).²⁴³ To date, there are limited data comparing LAA occlusion devices with NOACs. Noninferiority to NOACs has been examined in the PRAGUE-17 trial, ClinicalTrials.gov identifier NCT02426944,²⁴⁴ which showed that in patients with AF at high risk for stroke (CHA₂DS₂-VASc: 4.7 ± 1.5) and increased risk of bleeding, LAAO was noninferior to NOACs in preventing major AF-related cardiovascular, neurological, and bleeding events. There were no differences between groups for the components of the composite endpoint: all-stroke/TIA (subdistribution HR [sHR]: 1.00; 95% CI: 0.40 to 2.51), clinically significant bleeding (sHR: 0.81; 95% CI: 0.44 to 1.52), and cardiovascular death (sHR: 0.75; 95% CI: 0.34 to 1.62). Major LAAC-related complications occurred in nine (4.5%) patients.²⁴⁵

15.1.2 | Safety

Safety data are available from the RCTs^{240,241} and several registries,^{242,246–248} including two conducted in the Asia-Pacific region.^{249,250} In modern practice, there is high implantation success of 95%–98.5%.^{241,246,248,249}

Procedure and device-related complications in first 7 days were high in the earlier PROTECT AF trial²⁴⁰ at 8.7% but lower at 4.2% in the subsequent PREVAIL trial.²⁴¹ Similar reduction in complication rate has been seen over time in registries, with early data showing high complication rate of 8.6%²⁴¹ reducing to 2.2%–3% for more contemporaneous registries.^{246,249,251} However, trials and registries have selection bias and real-world data suggest that the complication rate may be significantly higher.²⁵²

The rate of early device thrombosis in meta-analysis and registry data is 3.7%–3.9%,^{248,253} and there are no RCTs to guide the duration of anticoagulation and number, type, and duration of antiplatelet agents, although registry data suggest safety of single antiplatelet agent. Other “real-world” reports of device-related thrombus (DRT) suggest incidence rates as high as 7.2% per year²⁵⁴ as well as high annual rates of mortality (7.4%), ischemic strokes (4.3%), and major hemorrhages (4.5%).²⁵⁵ The EURO-C-DRT Registry reported that substantial proportion of DRT (18%) was detected >6 months after LAA closure, highlighting the need for imaging follow-up, especially since such patients were at high risk for stroke and mortality (13.8% and 20.0%, respectively).²⁵⁶

Although there are registry data on safety of LAA occlusion in patients with a contra-indication to anticoagulation,²⁴⁸ there are no published RCT data on efficacy and safety of LAA occlusion devices in this cohort. This is being examined in the currently enrolling ASAP-TOO trial,²⁵⁷ ClinicalTrials.gov identifier NCT02928497.

15.2 | Issues specific to the Asia-pacific region

Asians are significantly underrepresented in clinical trials and registries of LAA occlusion devices with <1% of patients in the PROTECT-AF and PREVAIL trials and associated registries being of Asian ethnicity.²⁴³ However, evidence for safety and efficacy in Asian patients come from two small registries from the Asia Pacific region – the WASP registry²⁴⁹ performed in South-East Asia and Australia with 106/203 patients being of Asian ethnicity and the SALUTE registry of 54 patients in Japan.²⁵⁰ The WASP registry suggested important differences in anatomy and need for larger device sizes in Asian patients.²⁴⁹

The lack of comparative data to NOACs may be especially pertinent in the Asia-Pacific region given the more profound benefits of NOACs in Asian populations, especially with respect to reduced incidence of ICH.⁸⁷

Finally, cost-effectiveness analysis has been performed using healthcare costs from the United States^{258,259} and may not be applicable in the Asia-Pacific region, especially when one considers the diverse healthcare systems, costs, and funding models across the region.

15.3 | Recommendations

1. LAA occlusion may be considered for stroke prevention in patients with AF and clear contraindications for long-term anticoagulant treatment (e.g., intracranial bleeding without a reversible cause).
2. Surgical occlusion or exclusion of the LAA is recommended for stroke prevention in patients with AF undergoing cardiac surgery.

16 | ROLE OF ENVIRONMENTAL AND LIFESTYLE FACTORS IN ATRIAL FIBRILLATION

Cardiovascular risk factors, including lifestyle factors and comorbidities, affect the risk and prognosis of AF. Management of these risk factors, unhealthy lifestyle behaviors and practices, and comorbidities is important for stroke prevention and to control the burden of AF and symptoms associated with AF. This strategy constitutes the “C” component of the AF Better Care (ABC) pathway.²⁸ Lifestyle modifications, including weight loss, physical activity, alcohol abstinence, and risk factor modifications including BP control have been shown to reduce AF burden.^{56,260–266}

Unhealthy lifestyle factors tend to cluster together, and increased numbers of unhealthy lifestyle factors (current smoking, heavy drinking (>30 g/day), and lack of regular exercise) have been associated with a higher risk of incident AF.^{267,268} Overall, the promotion of a healthy lifestyle to lower the risk of new-onset AF and AF-related complications is recommended.

16.1 | Body weight: Role of obesity and low body weight

Obesity is an important and potentially modifiable risk factor for AF and can affect the incidence and persistence of AF.^{269,270} Obesity is also associated with other cardiovascular disease risks, including hypertension, sleep apnea, impaired glucose tolerance, and diabetes, which are all associated with incident AF and AF-related complications.

Aggressive weight reduction and risk factor modification has been shown to reduce AF recurrences and arrhythmia burden, as well as AF symptom burden; thus, there is improved maintenance of sinus rhythm and beneficial effects on cardiac remodeling compared with conventional therapy in patients with obesity.^{260,262,271,272} For example, in patients diagnosed with overweight or obesity concomitant with AF, >10% weight reduction was associated with reduction in the AF burden and reversal of AF type and natural progression.^{260,273} Underweight patients are not uncommon in the Asian population, and these patients show an increased risk of AF.²⁷⁴ Moreover, fluctuations in body weight were associated with an increased risk of AF, particularly among those with low body weight.²⁷⁵

With regard to clinical outcomes, the risk of the composite outcome of ischemic stroke, thromboembolism, or death is higher in those with overweight and obesity, even after adjustment for CHA₂DS₂-VASc scores.²⁷⁶ However, in a systematic review and meta-analysis, an obesity paradox was observed in patients with AF taking anticoagulation therapy, particularly with regard to all-cause and cardiovascular death in subgroup analyses of randomized trial cohorts.²⁷⁷ Another study showed that the risk of ischemic stroke, major bleeding, and mortality was lower in Asian patients with AF, who showed a high BMI and received OACs compared with those with normal weight, whereas underweight patients had an increased risk of mortality and composite outcome compared with normal weight.²⁷⁸ For stroke prevention, NOACs are generally associated with better outcomes than those with warfarin administration in Asians across patients of different body weights, particularly in underweight patients.¹⁰¹ Given the observed obesity paradox in patients with AF, keeping a normal body weight is recommended.

16.2 | Alcohol

Excessive alcohol consumption is a well-known risk factor and trigger for AF.²⁷⁹ Excessive alcohol consumption acts synergistically with other lifestyle risk factors for AF, including hypertension, obesity, obstructive sleep apnea, and cardiomyopathy to magnify their effects. Excessive alcohol consumption is a known clinical risk factor for bleeding during anticoagulation therapy and is included in the HAS-BLED score.²⁸⁰ High alcohol consumption is also associated with an increased risk of thromboembolism and death in patients with incident AF.²⁸¹ Asian data have

shown that high alcohol consumption was associated with a high ischemic stroke risk.²⁸²

One recent randomized trial has reported that alcohol abstinence reduced the risk of recurrent AF in those with heavy alcohol consumption patterns.²⁸³ Alcohol abstinence was also associated with a low risk of incident AF in patients with newly diagnosed type 2 diabetes,²⁸⁴ and alcohol abstinence after a diagnosis of AF was associated with a low risk of ischemic stroke.²⁸²

16.3 | Smoking

Smoking is associated with an increased risk of incident AF,^{285,286} and smoking cessation seems to lower the risk of AF compared with current smokers.^{285,286} In Asian patients with AF with a low CHA₂DS₂-VASc score, smoking was identified as a risk factor for ischemic stroke.²⁸⁷ Furthermore, quitting smoke after incident AF was associated with a low risk of ischemic stroke, lower stroke severity, and death from cerebrovascular events.²⁸⁸

16.4 | Air pollution

Epidemiological studies have suggested that elevated ambient particulate matter (PM) <2.5 μm (PM_{2.5}) or <10 μm (PM₁₀) in aerodynamic diameter are consistently associated with adverse cardiac events. In the Asian general population, long-term exposure of PM_{2.5} is associated with the increased incidence of new-onset AF.^{289,290}

16.5 | Physical activity

Moderate-intensity exercise (150 min/week) or vigorous-intensity exercise (75 min/week) recommended by the 2018 Physical Activity Guidelines Advisory Committee is known to improve cardiovascular health. Physical inactivity is associated with an increased risk of incident AF,²⁹¹ and regular exercise could reduce

AF burden and improve AF-related symptoms and patients' quality of life.²⁹²⁻²⁹⁵ However, the risk of AF increased in those who participate in extreme endurance exercise that far exceeds the levels recommended by the Physical Activity Guidelines Advisory Committee report.²⁹⁶ Cardiorespiratory fitness generally reduces the AF burden and symptom severity in patients with obesity and concomitant AF, which may be attributable to the beneficial effects of weight loss.²⁶¹

One recent observational study in Asian patient with incident AF reported that regular exercise was associated with low risks of heart failure, mortality, and dementia in addition to a marginal benefit on ischemic stroke.^{297,298} Regular moderate exercise (170–240 min/week) showed maximal cardiovascular benefits in patients who initiated exercise after diagnosis of AF. Patients who initiated or continued regular exercise after diagnosis of AF were associated with a lower risk of dementia than persistent non-exercisers, with no risk reduction associated with exercise cessation.²⁹⁸

16.6 | Recommendations

- The promotion of a healthy lifestyle (smoking cessation, reduced alcohol consumption, regular exercise) is recommended to lower the risk of new-onset AF and AF-related complications (Figure 19).
- Appropriate weight control is an important strategy to improve outcomes in patients with AF.
- Reduced consumption or alcohol abstinence is recommended in patients with AF with moderate-to-high levels of alcohol use to minimize AF burden and stroke risk.
- Smoking cessation is recommended in patients with AF to reduce the stroke risk, even in those categorized as low-risk patients based on the CHA₂DS₂-VASc score.
- Regular exercise based on the recommendations of the 2018 Physical Activity Guidelines Advisory Committee (150 min/week of moderate-intensity exercise or 75 min/week of vigorous-intensity exercise) can improve cardiovascular outcomes in patients with AF.

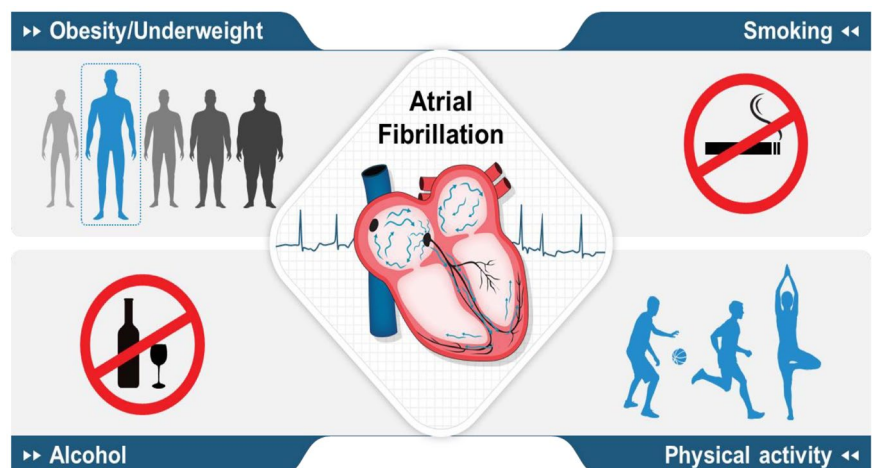


FIGURE 19 The integration of lifestyle management in patients with AF. AF, atrial fibrillation

17 | OAC USE IN PATIENTS WITH ATRIAL FIBRILLATION DURING THE “CORONAVIRUS DISEASE 2019” (COVID-19) PANDEMIC

AF is a common clinical manifestation in hospitalized patients with COVID-19 infection and is associated with a higher risk of mortality and/or requirement for intensive care.^{299–302} The latter is perhaps unsurprising given the higher risk of adverse outcomes in COVID-19 with associated cardiovascular comorbidities.³⁰²

During the COVID-19 pandemic, TTR values associated with VKA (e.g., warfarin) treatment may be suboptimal with the lack of INR monitoring, and in appropriate patients, a switch to NOACs may be appropriate.³⁰³ Furthermore, the anticoagulated patients with AF may not seek medical help even in case of bleeding.³⁰⁴ Thus, for the outpatients during the COVID-19 pandemic (during the lockdown phase or discharge after recovery from COVID-19 infection), NOAC therapy in replacement of VKA (except for the absolute contraindications of NOACs like prosthetic mechanical valve or moderate-to-severe mitral stenosis) is recommended to minimize the necessity for frequent clinic/office visits for INR monitoring and contact with healthcare workers.³⁰⁵ Remote anticoagulation management/monitoring for elderly patients with nonvalvular AF receiving NOACs during the COVID-19 pandemic was associated with a reduction in bleeding complications and delays in the first outpatient revisit after discharge.³⁰⁶

COVID-19 is associated with a prothrombotic state, perhaps due to cytokines and immunothrombosis.³⁰⁷ For patients already treated with NOACs or VKA are infected with COVID-19 and particularly in case of severe infection requiring hospitalization, patients should ideally continue their anticoagulation rather than discontinue, although outcome data are conflicting.^{308–311}

Conversion from NOAC or VKA into low molecular weight heparin (LMWH) during the hospitalization course (especially if severely affected, requiring intensive care unit admission) may be preferable due to less drug interaction with antiviral drugs (e.g., remdesivir) or immunomodulating drugs (e.g., dexamethasone, baricitinib, or tocilizumab), and a higher risk of clinical deterioration due to severe COVID-19 infection (particularly of coagulation and renal function).^{305,307} It would therefore be reasonable to shift NOACs into alternative LMWH for patients with severe COVID-19 infection as long as antiviral agents are deemed necessary and until discharge. LMWH regimes have been tested in recent clinical trials of hospitalized COVID-19 patients but showed conflicting results.^{312–316} For example, in noncritically ill patients with COVID-19, the ATTACC, ACTIV-4a, and REMAP-CAP investigators found that an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis.³¹³ However, in patients hospitalized with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical

outcomes and increased bleeding compared with prophylactic anticoagulation in ACTION trial.³¹⁶ Besides, these studies did not specifically enroll patients with AF, and therefore, data about the optimal dosage of LMWH for hospitalized AF COVID-19 patients were very limited.

COVID-19 vaccines are usually administered by intramuscular injection and are an important part of our pandemic response.³¹⁷ An opportunity to screen for AF amongst attendees for vaccination has been promoted.³¹⁸ In patients with AF treated with NOACs, it is advisable to follow the scheme for “minor risk” interventions, and therefore, it is not necessary to withhold any NOAC dosage before and after the injection procedure.³¹⁹ However, it is recommended to use a fine-gauge needle for injection, and apply firm pressure for 5–10 min after the injection. If the scheduled NOAC dosage is close to the injection time before, the scheduled NOAC dosage may be postponed until after the injection if no progression of local hematoma noted.

17.1 | Recommendations

1. For outpatients with AF during the COVID-19 pandemic, NOAC therapy in replacement of VKA (unless contraindicated) may be considered.
2. For patients with AF already treated with NOACs or VKA infected with COVID-19 and particularly in case of severe infection requiring hospitalization or critical care, conversion from NOAC or VKA into LMWH during the hospitalization course of COVID-19 infection may be considered.
3. In patients with AF taking NOACs planned to receive COVID-19 vaccine injection, it is advisable to follow the scheme for “minor risk” interventions, and therefore, it is not necessary to withhold any NOAC dosage before and after the injection procedure.

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