Received: 8 October 2021 | Accepted: 22 October 2021

DOI: 10.1002/joa3.12652

Journal of Arrhythmia Open Access WILEY

GUIDELINES

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

Tze-Fan Chao MD, PhD[1,2] | Boyoung Joung MD, PhD[3] | Yoshihide Takahashi MD, PhD[4] | Toon Wei Lim MD, PhD[5] | Eue-Keun Choi MD, PhD[6] | Yi-Hsin Chan MD[7,8,9] | Yutao Guo MD[10] | Charn Sriratanasathavorn MD[11] | Seil Oh MD, PhD[6] | Ken Okumura MD, PhD[12] | Gregory Y. H. Lip MD[13,14]

[1]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

[2]Institute of Clinical Medicine, and Cardiovascular Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

[3]Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

[4]The Department of Advanced Arrhythmia Research, Tokyo Medical and Dental University, Tokyo, Japan

[5]National University Heart Centre, National University Hospital, Singapore, Singapore

[6]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

[7]Microscopy Core Laboratory, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan

[8]College of Medicine, Chang Gung University, Taoyuan, Taiwan

[9]Microscopy Core Laboratory, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan

[10]Pulmonary Vessel and Thrombotic Disease, Chinese PLA General Hospital, Beijing, China

[11]Her Majesty Cardiac Center, Siriraj, Thailand

[12]Division of Cardiology, Saiseikai Kumamoto Hospital, Kumamoto, Japan

[13]Liverpool Centre for Cardiovascular Science, University of Liverpool & Liverpool Heart and Chest Hospital, Liverpool, UK

[14]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Correspondence
Tze-Fan Chao, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan.
Email: eyckeyck@gmail.com

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

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 reprented by CHA_2DS_2-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 CHA_2DS_2-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 signifcantly 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]

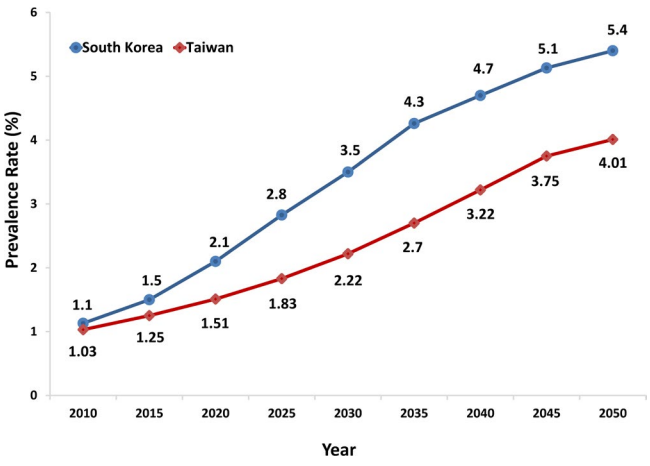


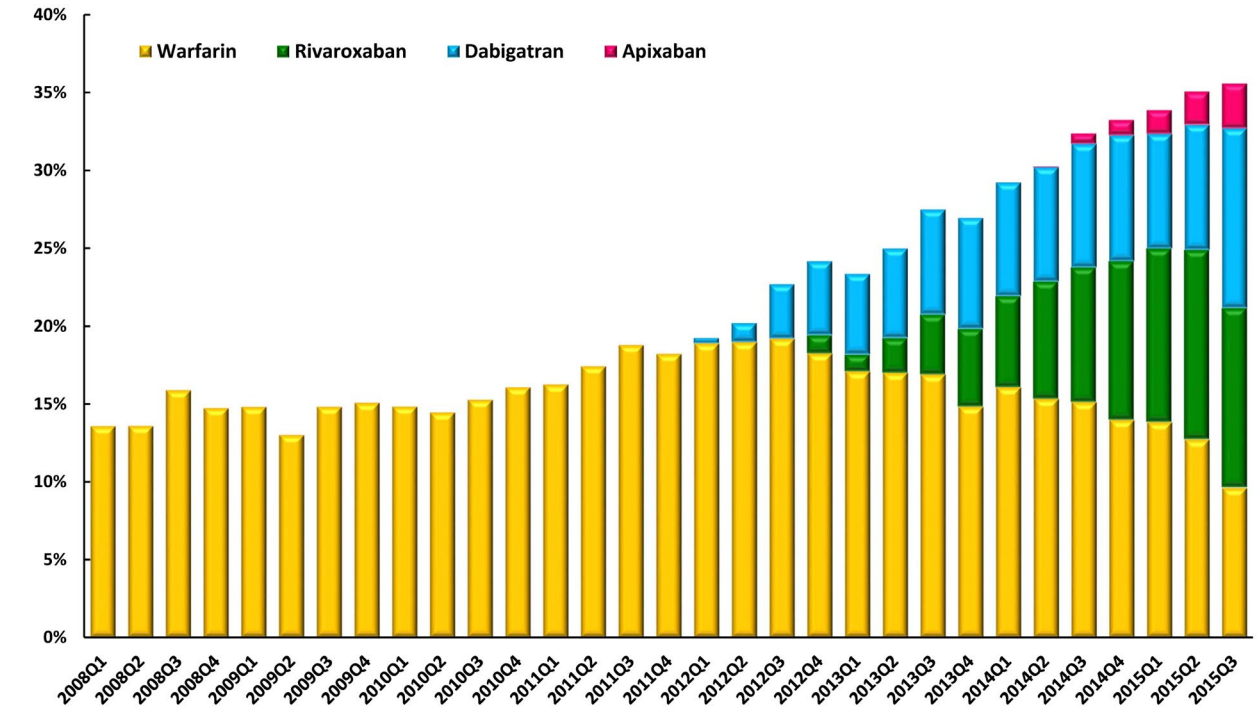
FIGURE 1 Projected prevalence of AF in Taiwan and South Korea. AF, atrial fibrillation. Data used in the figure were adapted from the papers by Chao et al. and Kim et al[3,4]

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.

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 al[5]

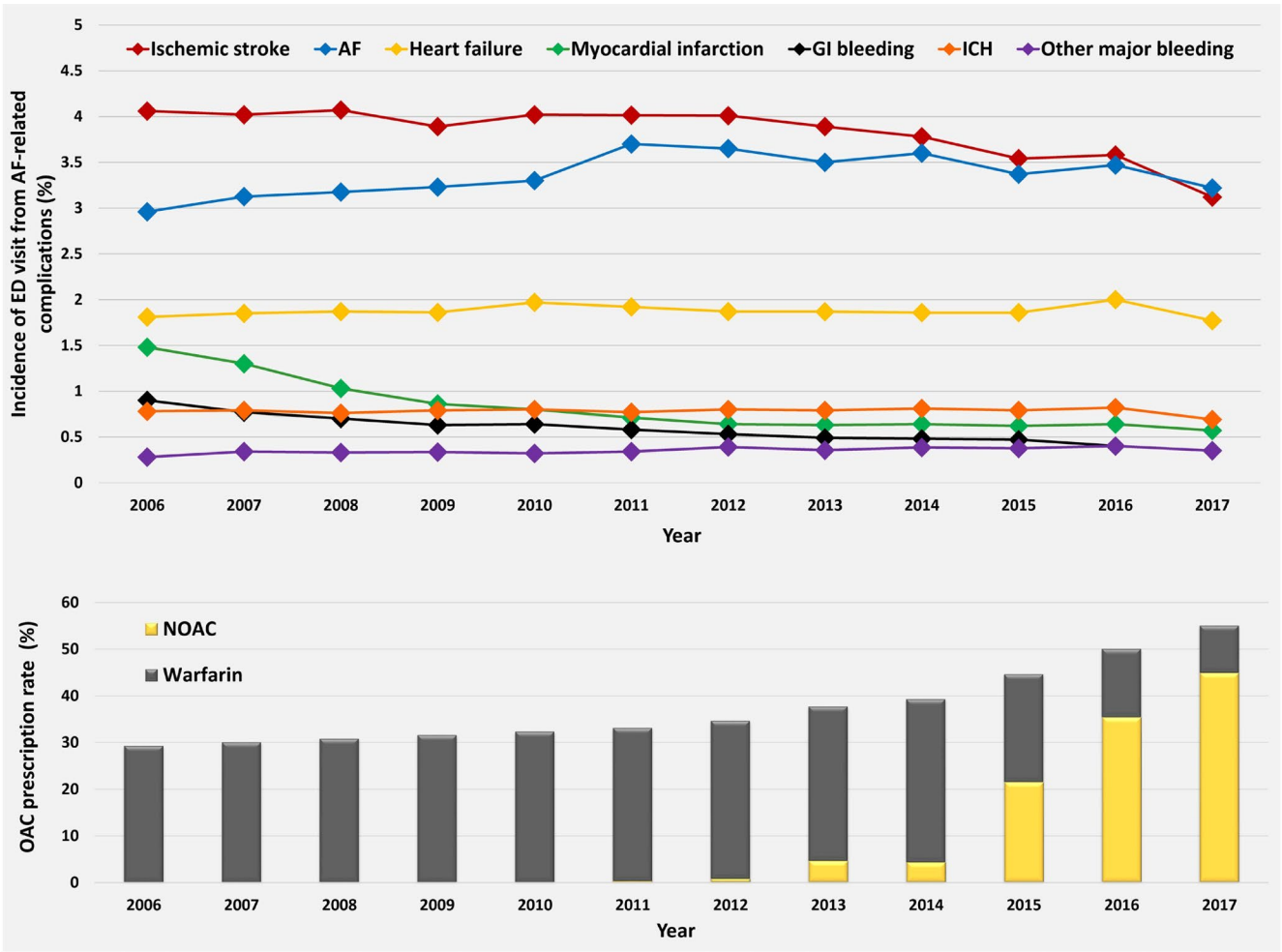


FIGURE 3 Temporal trends of incidence of ED visits from AF-related complications and OAC prescription rate. The figure was redraw and modified from the paper by Lee et al[7]
AF, atrial fibrillation; ED, emergency department; GI, gastrointestinal; ICH, intracranial hemorrhage; NOAC, non-vitamin K antagonist 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%;

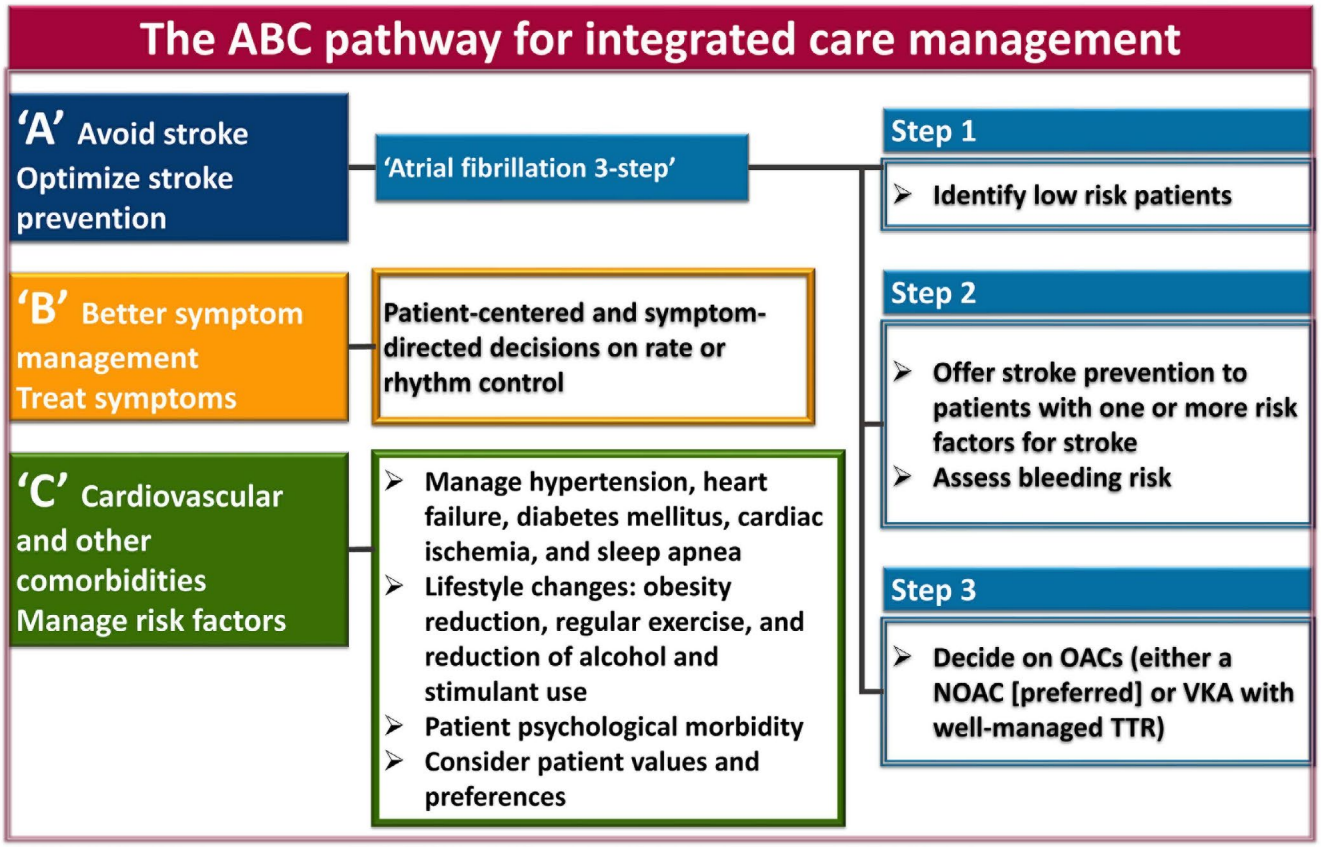
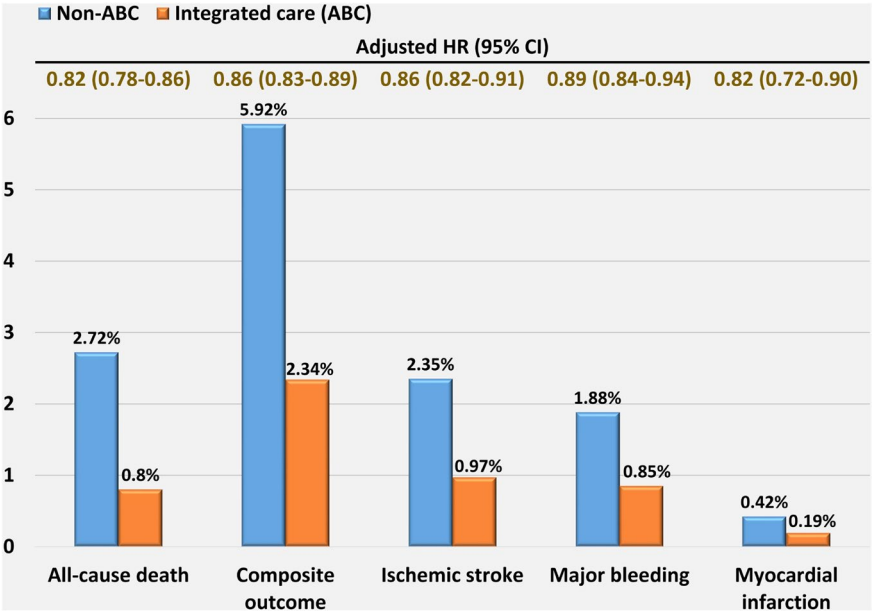


FIGURE 4 The ABC pathway of integrated care management. ABC, Atrial fibrillation Better Care; NOAC, non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; TTR, time in therapeutic range; VKA, vitamin K antagonist. The figure was redraw and modified from the paper by Lip et al[12]

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 al[17]



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 mAFA 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]

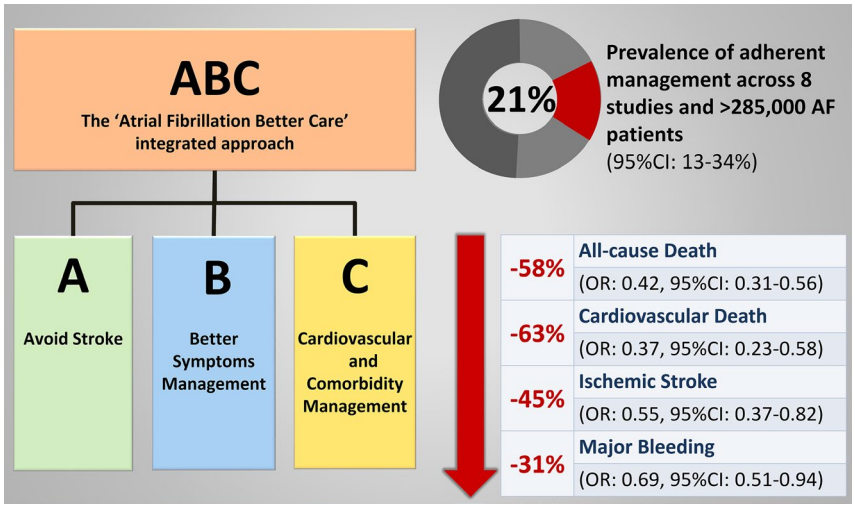


FIGURE 6 Impacts of adherence to the ABC pathway on clinical outcomes in patients with AF. ABC, Atrial fibrillation Better Care; CI, confidence interval; OR, odds ratio. The figure was redraw and modified from the paper by Romiti et al[20]

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 CHA_2DS_2-VASc score for stroke risk assessment for Asian patients with AF.[29]

In this focused update, we still recommend the use of the CHA_2DS_2-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 CHA_2DS_2-VASc score.

The impact of individual stroke risk factors is not uniform, and for a single CHA_2DS_2-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

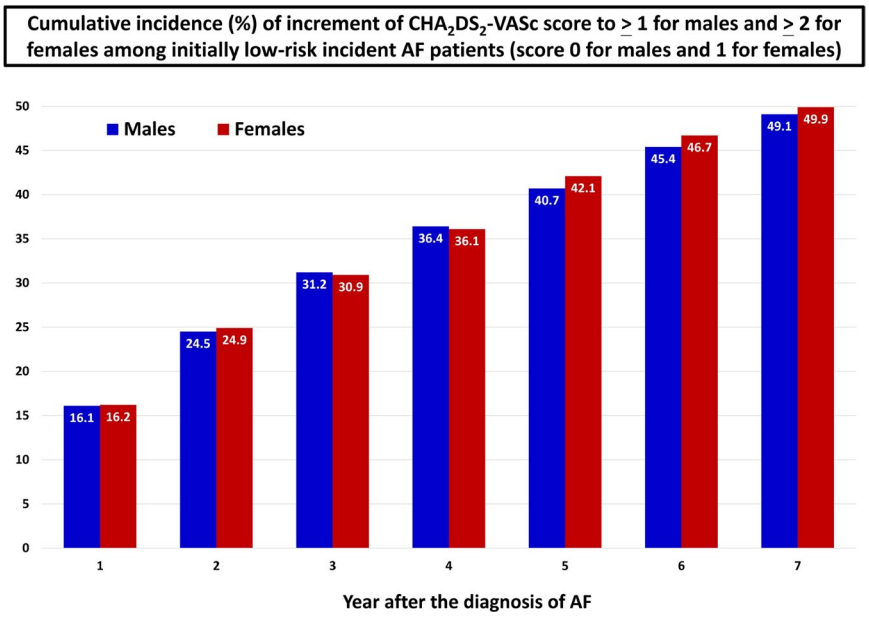


FIGURE 7 Cumulative incidences of increment of CHA_2DS_2-VASc score to ≥1 (males) or ≥2 (females). AF, atrial fibrillation. The figure was redraw, and data were adapted from the papers by Chang et al. and Chao et al[47,49]

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 CHA_2DS_2-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 CHA_2DS_2-VASc scores.[47] For example, in a study from Taiwan which enrolled 31,039 patients with AF without comorbidities of the CHA_2DS_2-VASc score except for age and gender at baseline, the mean CHA_2DS_2-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 CHA_2DS_2-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 CHA_2DS_2-VASc score and change in stroke risk ("delta-CHA_2DS_2-VASc" score, i.e., the difference between the baseline and follow-up scores) had betteer predictive value for ischaemic stroke compared with the baseline CHA_2DS_2-VASc score.[48,51] Almost 90% of initailly low-risk patients with AF had a delta CHA_2DS_2-VASc score ≥1 before the occurrence of ischemic stroke.[48] For initially low-risk (CHA_2DS_2-VASc score 0 for males or 1 for females) nonanticogulated patients with AF, the use of OACs once their CHA_2DS_2-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 CHA_2DS_2-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 CHA_2DS_2-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 (CHA_2DS_2-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 CHA_2DS_2-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 CHA_2DS_2-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 (CHA_2DS_2-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 scoress 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.

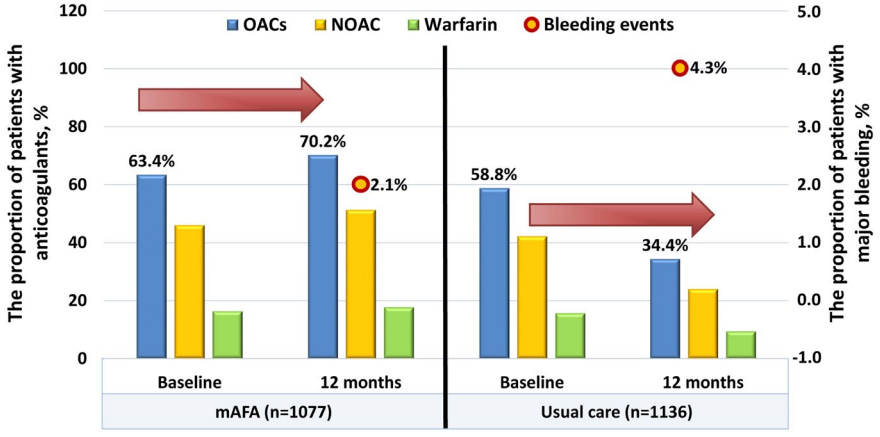


FIGURE 8 Use of OACs and risk of bleeding among patients received integrated care approach and usual care. AF, atrial fibrillation; NOAC, non–vitamin K antagonist oral anticoagulant; OACs, oral anticoagulants. The figure was redraw and modified from the paper by Guo et al[21]

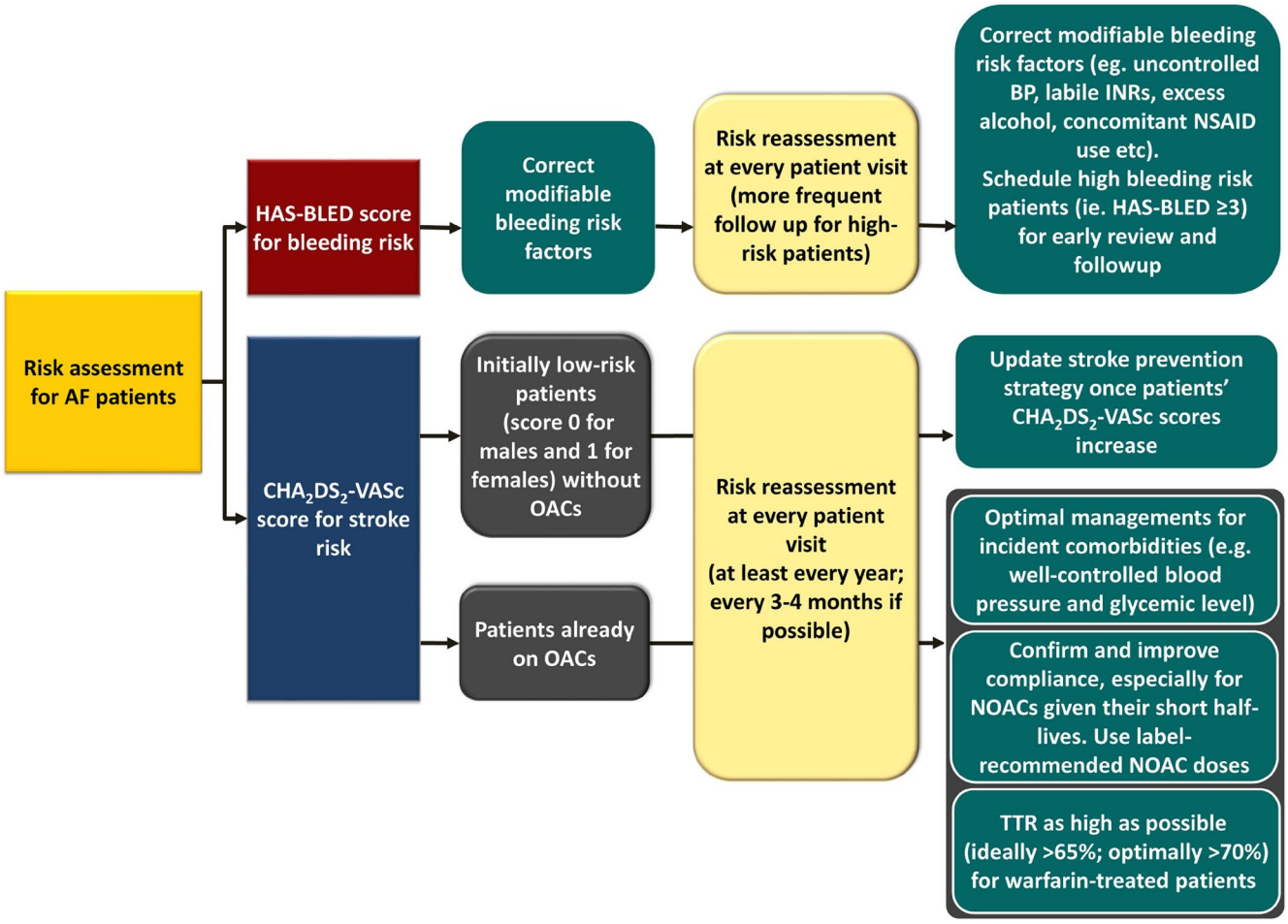


FIGURE 9 Stroke and bleeding risk assessment in AF. AF, atrial fibrillation; BP, blood pressure; INR, international normalized ratio; NOAC, non–vitamin K antagonist oral anticoagulant; NSAIDs, nonsteroidal anti-inflammatory drugs; OACs, oral anticoagulants; TTR, time in therapeutic range. The figure was redraw and modified from the paper by Chang et al[47]

3. 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 CHA_2DS_2-VASc and HAS-BLED scores and highly emphasize the clinical importance of risk reassessement. The recommended clinical practice about stroke and bleeding risk assessement 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 CHA_2DS_2VASc 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 (CHA_2DS_2VASc 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., CHA_2DS_2VASc 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

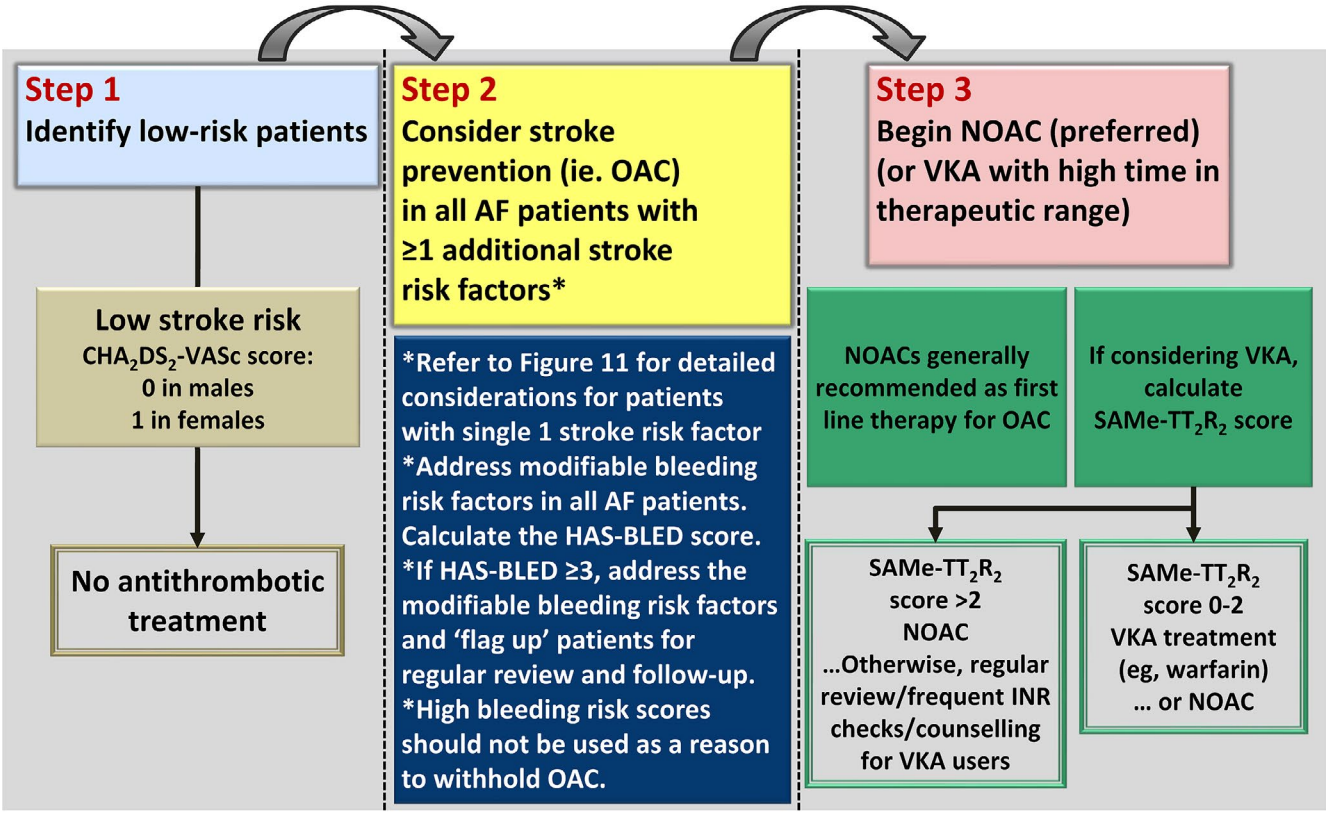


FIGURE 10 Three-step approach for the use of OACs for stroke prevention in AF. AF, atrial fibrillation; INR, international normalized ratio; NOAC, non–vitamin K antagonist oral anticoagulant; OACs, oral anticoagulants; VKA, vitamin K antagonist. The flowchart was redraw and modified from the paper by Lip et al[26]

delicate approach for these patients is required.[65] Because the risk of stroke of each CHA_2DS_2-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-TT_2R_2 scores. A high SAMe-TT_2R_2 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,

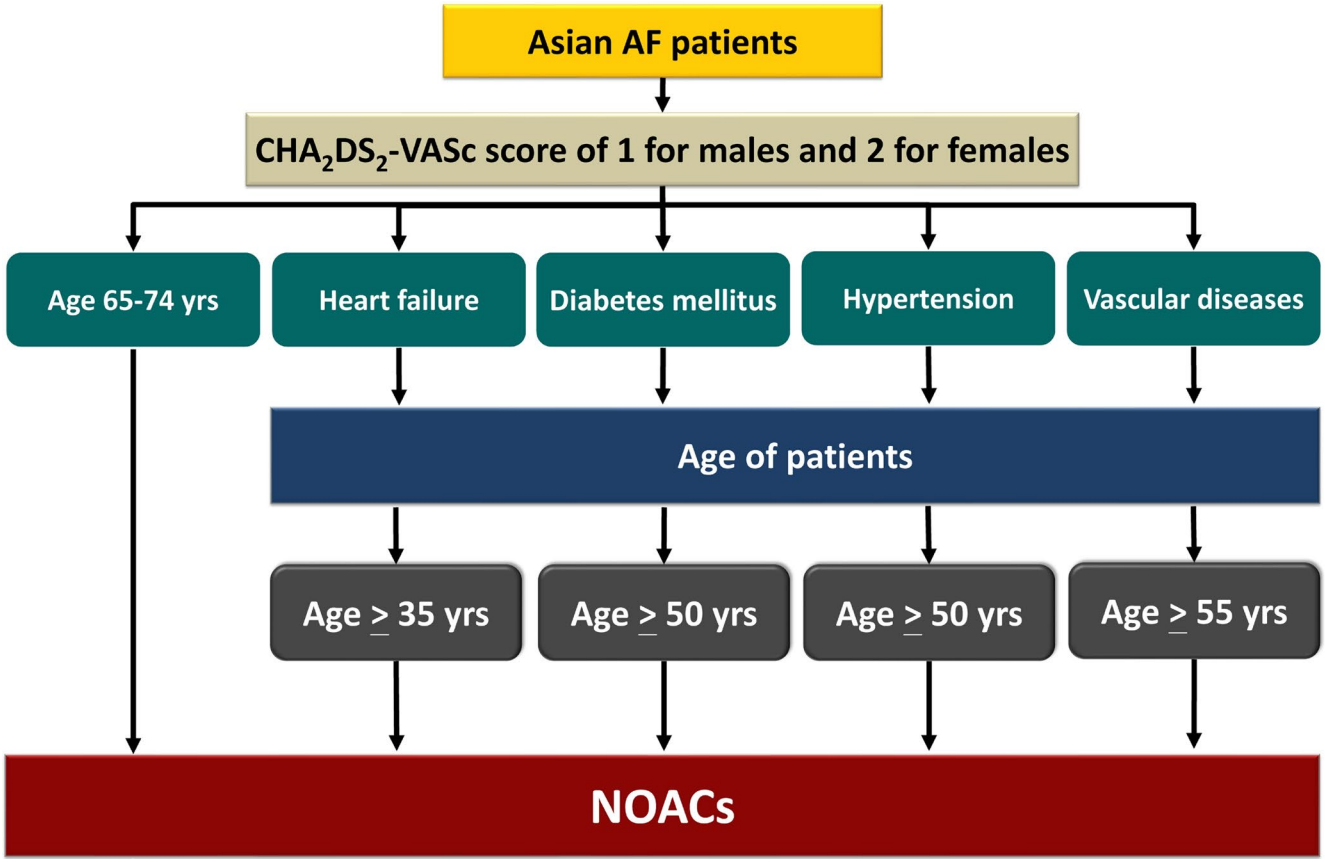


FIGURE 11 Considerations about the use of NOACs for Asian patients with AF with a CHA_2DS_2-VASc score of 1 (males) or 2 (females). AF, atrial fibrillation; NOAC, non–vitamin K antagonist oral anticoagulant

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 CHA_2DS_2-VASc stroke risk score to initially identify patients at "low stroke risk" (CHA_2DS_2-VASc = 0 in men or 1 in women) who should not be offered antithrombotic therapy.
5. In patients with AF with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women, OAC is recommended for stroke prevention.
6. In patients with AF with a CHA_2DS_2-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 ≥65% (ideally ≥70%)
   - A high SAMe-TT_2R_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 ≥65% (or even 70%) in Asian patients.[91] We should ensure TTR is ≥65% (optimal ≥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 ≥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 ($p_{int} = 0.063$ 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 Cockroft–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

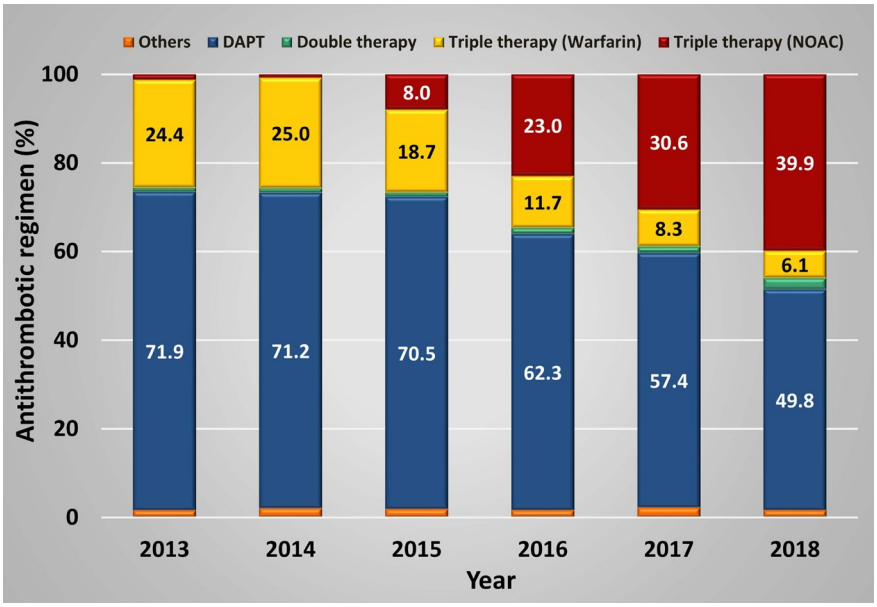


FIGURE 12 Increasing use of OACs (especially NOACs) and combination therapy with antiplatelet agents among patients with AF undergoing percutaneous coronary intervention. AF, atrial fibrillation; DAPT, dual antiplatelet therapy; NOAC, non–vitamin K antagonist oral anticoagulant. The figure was redraw, and data were adapted from the paper by Kwon et al[114]

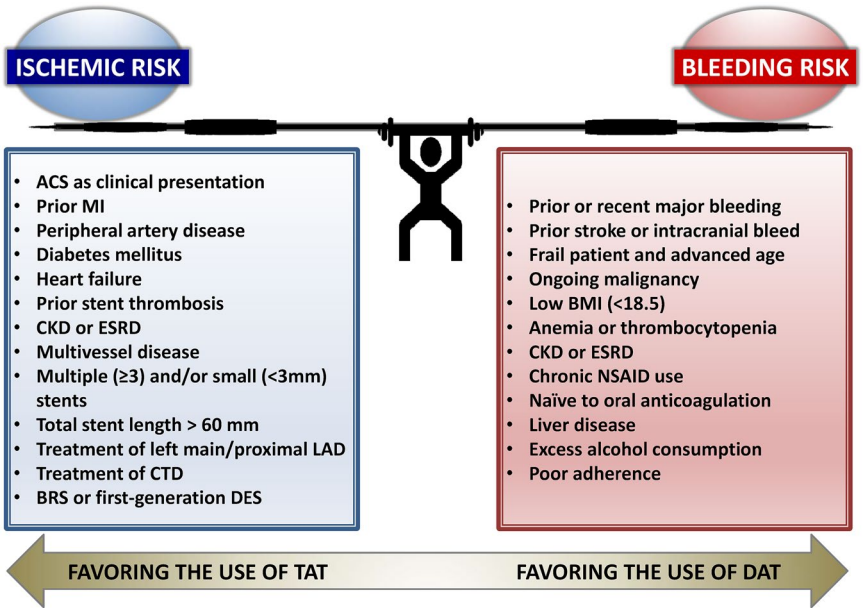


FIGURE 13 Factors tipping the balance between ischemic and bleeding risk in patients with AF presenting with ACS and/or undergoing PCI. ACS, acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; BRS, bioresorbable scaffold; CKD, chronic kidney disease; CTO, chronic total ccclusion; 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 al[115]

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 ≥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	• Rivaroxaban 15 mg + a P2Y12 inhibitor (group 1) • Rivaroxaban 2.5 mg + DAPT (group 2) • VKA + DAPT (group 3)	• 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 • Apixaban 5 mg versus VKA • Aspirin versus placebo	• 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.

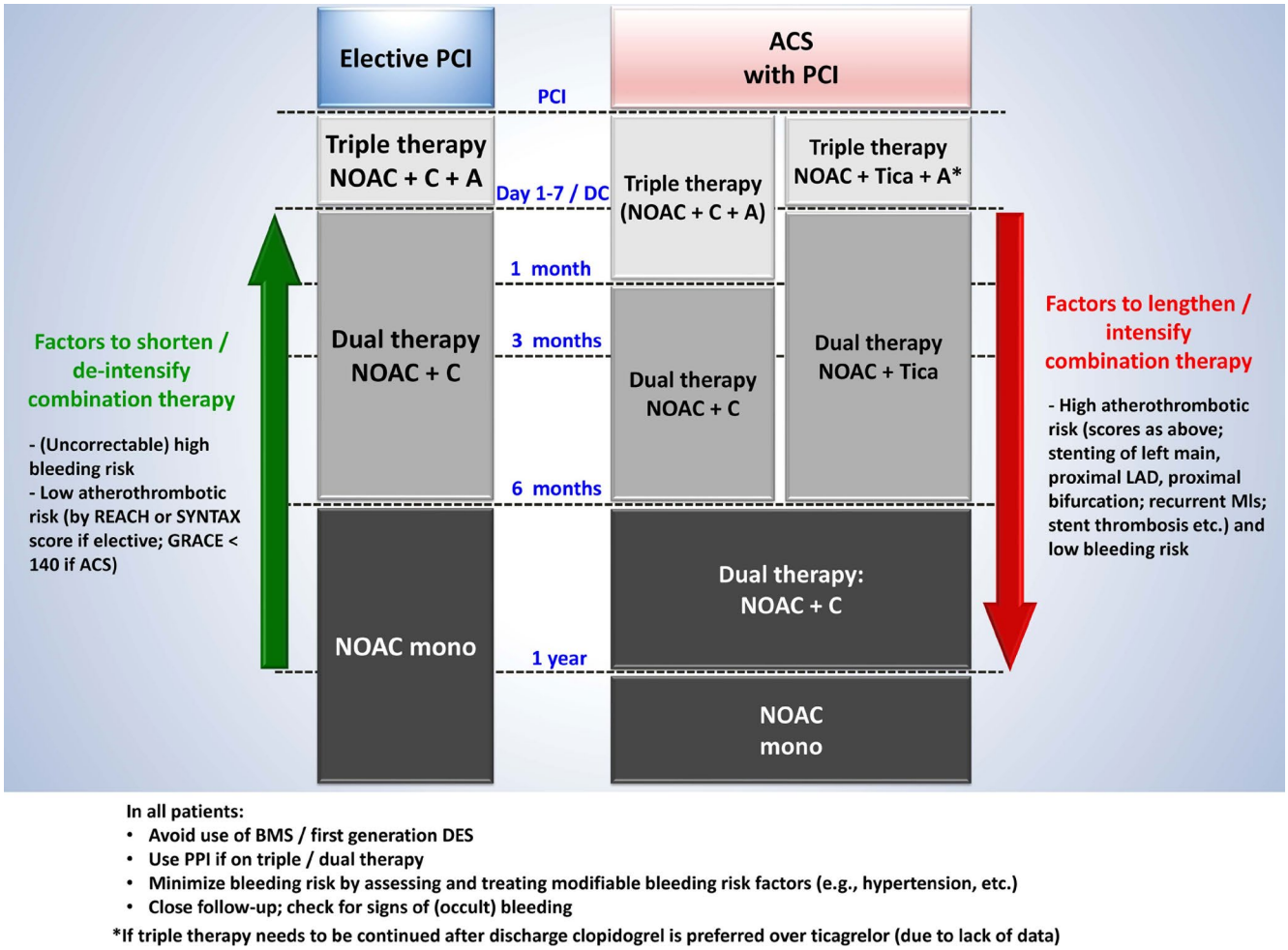


FIGURE 14 Anticoagulation therapy after elective PCI or ACS in patients with AF. A = aspirin 75–100 mg QD; C = clopidogrel 75 mg QD; Tica = Ticagrelor 90 mg BID. AF, atrial fibrillation; ACS, acute coronary syndrome; BID, twice daily; BMS, bare metal stent; DES, drug-eluting stent; LAD, left anterior 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 al[123]

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.

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 | 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.

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_2DS_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.
[a]Dose 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.

2. 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

1. 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.
2. 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 prothromboembolic 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 VKA[130]; RE-CIRCUIT study for dabigatran versus VKA[131]; AXAFA-AFNET 5 study for apixaban versus VKA[132]; 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-AF[133] 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 studies[134] 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 Japan[136] 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 Korea[137] 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 study[138] 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 study[139] ($n = 513$) 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 CHA_2DS_2-VASc stroke risk factors rather than the rhythm status.

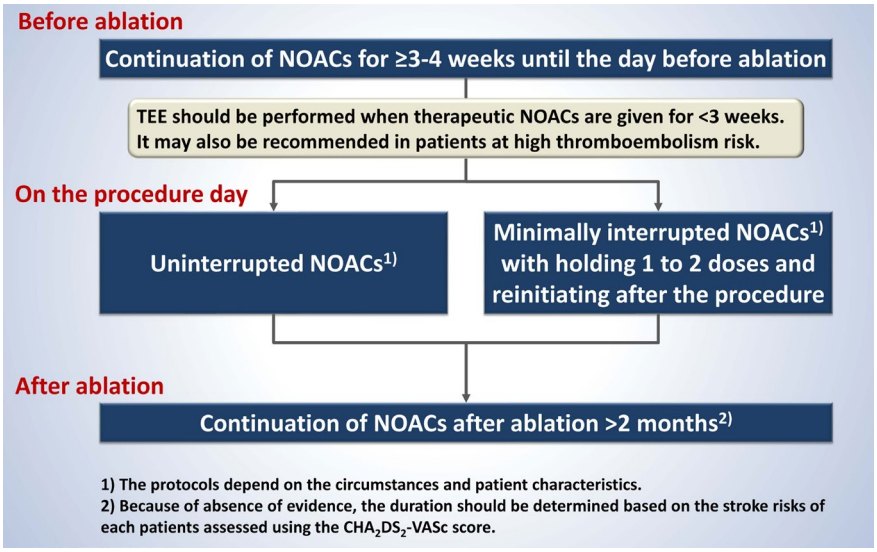


FIGURE 15 A flowchart about the general recommendation for NOACs in the periprocedural period of catheter ablation. NOACs, non–vitamin K antagonist oral anticoagulants; TEE, transeshophageal echocardiography

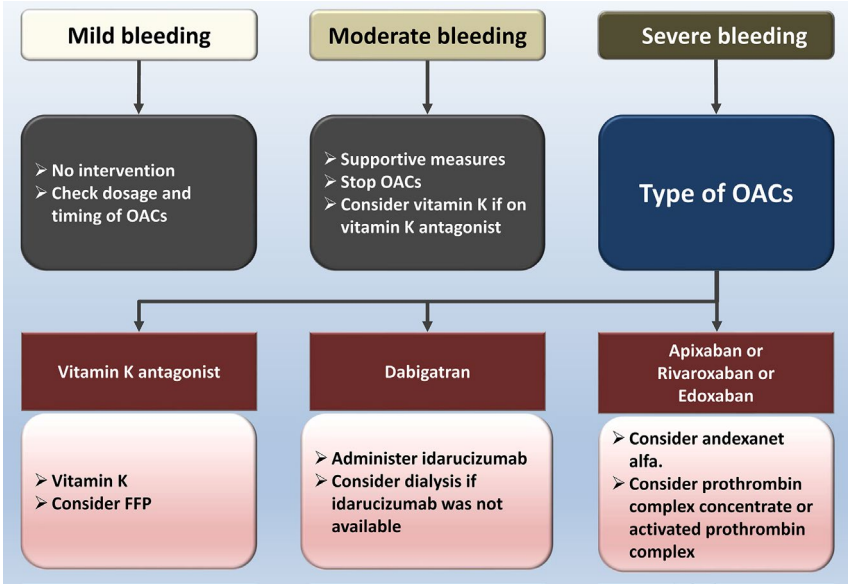


FIGURE 16 General principles of managements of bleeding for anticoagulated patients with AF. AF, atrial fibrillation; FFP, fresh frozen plasma; NOACs, non–vitamin K antagonist oral anticoagulants; OACs, oral anticoagulants

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)
p 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)
p 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)
p 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 ElderR 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/m^2 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

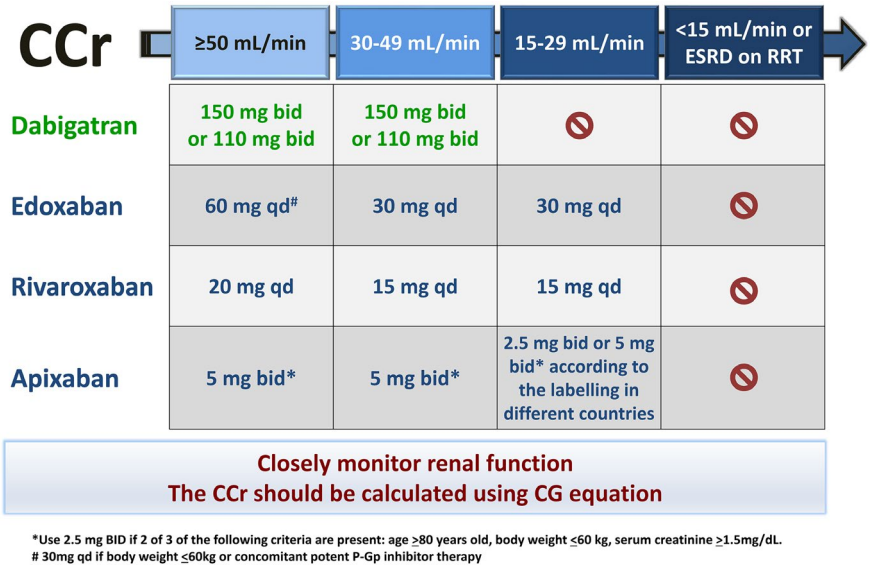


FIGURE 17 Recommendations about the dosing of NOACs according to renal function. bid, twice daily; CCr, creatinine clearance; qd, once daily; ESRD, end-stage renal disease; NOACs, non–vitamin K antagonist oral anticoagulants; RRT, renal replacement therapy

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 CHA_2DS_2-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 vital 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 VHDs[193] 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 valves[200] 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 group[201] 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 CHA_2DS_2-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 CHA_2DS_2-VASc stroke risk factors was similar to that of those patients without hypertrophic cardiomyopathy with CHA_2DS_2-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

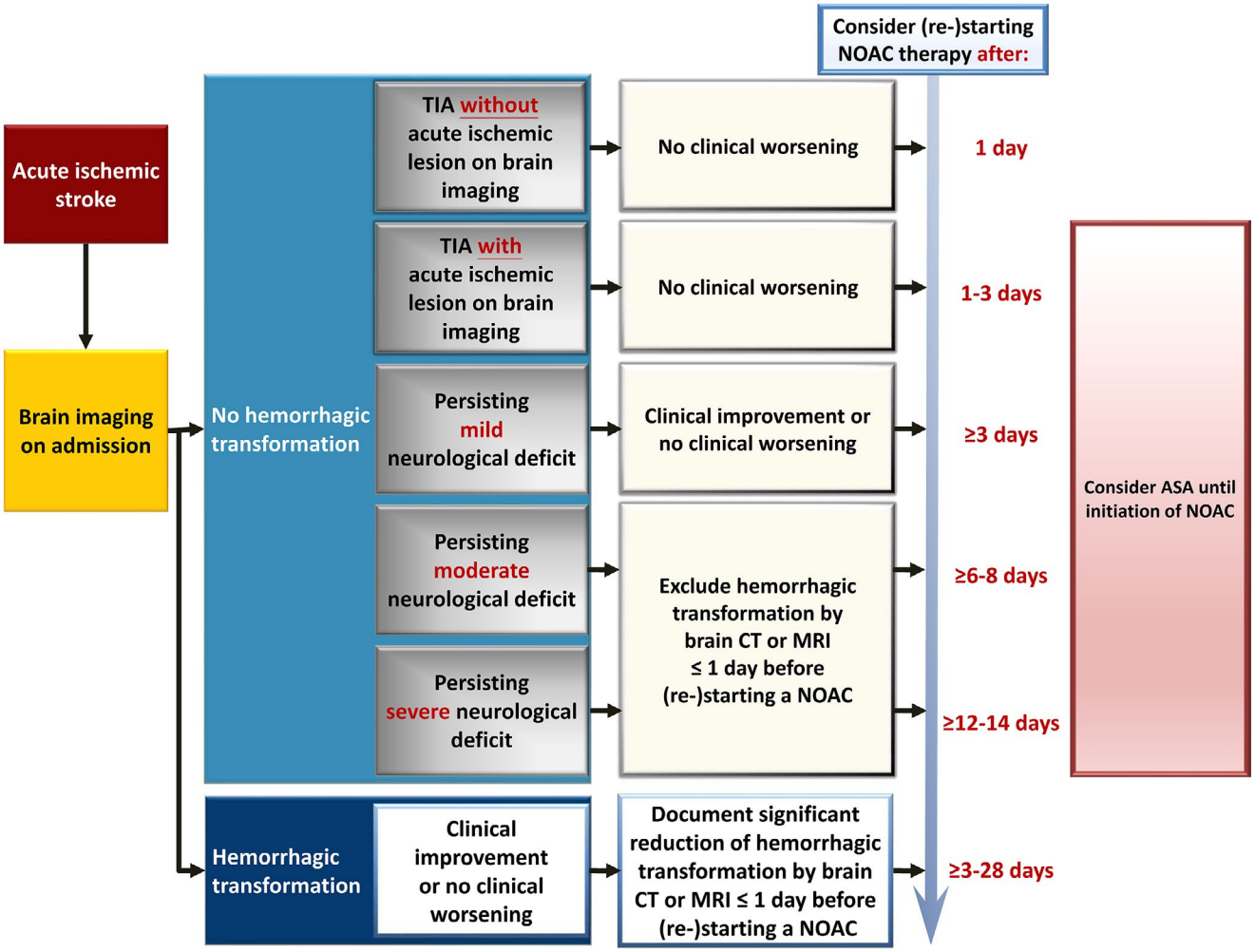


FIGURE 18 Use of OACs after acute ischemic stroke or transient ischemic attack. CT, computed tomography; MRI, magnetic resonance imaging; NOAC, non–vitamin K antagonist oral anticoagulant; TIA, transient ischaemic attack. The figure was redraw and modified from the 2021 European Heart Rhythm Association Practical Guide on the use of NOACs in patients with AF by Steffel et al[123]

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 CHA_2DS_2-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] ≥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 ≥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 (CHA_2DS_2-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 trial[240] 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 year[254] as well as high annual rates of mortality (7.4%), ischemic strokes (4.3%), and major hemorrhages (4.5%).[255] The EUROC-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 registry[249] 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 CHA_2DS_2-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 CHA_2DS_2-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 (PM_{10}) in aerodynamic diameter are consistently associated with adverse cardiac events. In the Asian general population, long-term exposure of PM2.5 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 CHA_2DS_2-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.

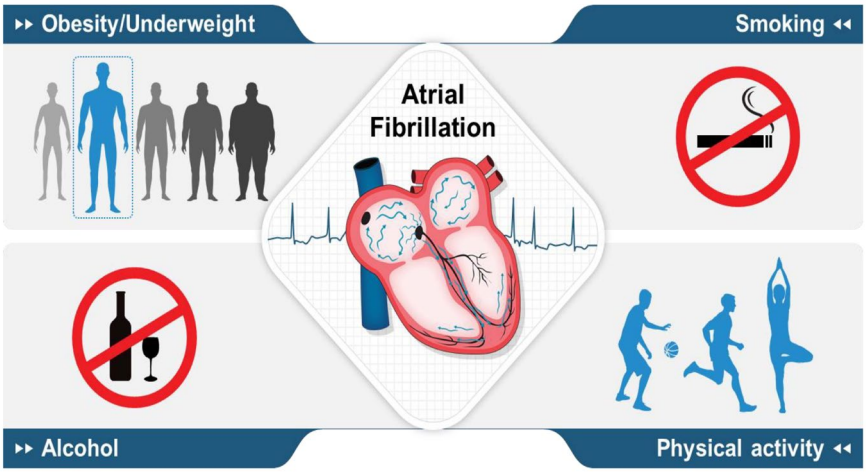


FIGURE 19 The integration of lifestyle management in patients with AF. AF, atrial fibrillation

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.

DISCLOSURE

Tze-Fan Chao: None. Boyoung Joung: Boyoung Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and received research funds from Samjin, Medtronic and Abbott. No fees have been received directly or personally. Yoshihide Takahashi: Research grants from Medtronic Japan, Boston Scientific, Japan Lifeline, WIN International, Abbott and Biosense-Webster, and speaker honoraria from Abbott and Biosense-Webster. Toon-Wei Lim: None. Eue-Keun Choi: None. Yi-Hsin Chan: None. Yutao Guo: None. Charn Sriratanasathavorn: None. Seil Oh: None. Ken Okumura: None. Gregory Lip: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

ORCID

Tze-Fan Chao https://orcid.org/0000-0002-6587-3094
Boyoung Joung https://orcid.org/0000-0001-9036-7225
Eue-Keun Choi https://orcid.org/0000-0002-0411-6372
Yutao Guo https://orcid.org/0000-0002-7626-7751
Gregory Y. H. Lip https://orcid.org/0000-0002-7566-1626

REFERENCES

1. Zhang J, Johnsen SP, Guo Y, Lip GYH. Epidemiology of atrial fibrillation: geographic/ecological risk factors, age, sex, genetics. Card Electrophysiol Clin. 2021;13:1–23.
2. Bai Y, Wang YL, Shantsila A, Lip GYH. The global burden of atrial fibrillation and stroke: a systematic review of the clinical epidemiology of atrial fibrillation in Asia. Chest. 2017;152:810–20.
3. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, et al. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan nationwide AF cohort study. Chest. 2018;153:453–66.
4. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. Am Heart J. 2018;202:20–6.
5. Chao TF, Chiang CE, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Evolving changes of the use of oral anticoagulants and outcomes in patients with newly diagnosed atrial fibrillation in Taiwan. Circulation. 2018;138:1485–7.
6. Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. PLoS One. 2017;12:e0189495.
7. Lee S-R, Choi E-K, Lee S-Y, Lee E, Han K-D, Cha M-J, et al. Temporal trends of emergency department visits of patients with atrial fibrillation: a nationwide population-based study. J Clin Med. 2020;9.
8. Bai Y, Guo SD, Shantsila A, Lip GYH. Modelling projections for the risks related with atrial fibrillation in East Asia: a focus on ischaemic stroke and death. Europace. 2018;20:1584–90.
9. Burdett P, Lip GYH. Atrial fibrillation in the United Kingdom: predicting costs of an emerging epidemic recognising and forecasting the cost drivers of atrial fibrillation-related costs. Eur Heart J Qual Care Clin Outcomes. 2020.
10. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015. Heart. 2018;104:2010–7.
11. Ogawa H, An Y, Nishi H, Fukuda S, Ishigami K, Ikeda S, et al. Characteristics and clinical outcomes in atrial fibrillation patients classified using cluster analysis: the Fushimi AF Registry. Europace. 2021;23(9):1369–79.
12. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017;14:627–8.
13. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (atrial fibrillation better care) pathway. Am J Med. 2018;131(1359–1366):e1356.
14. Proietti M, Vitolo M, Lip GYH. Integrated care and outcomes in patients with atrial fibrillation and comorbidities. Eur J Clin Invest. 2021;51:e13498.
15. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated care management of patients with atrial fibrillation and risk of cardiovascular events: the ABC (atrial fibrillation better care) pathway in the ATHERO-AF study cohort. Mayo Clin Proc. 2019;94:1261–7.
16. Proietti M, Lip GYH, Laroche C, Fauchier L, Marin F, Nabauer M, et al. Relation of outcomes to ABC (Atrial Fibrillation Better Care) pathway adherent care in European patients with atrial fibrillation: an analysis from the ESC-EHRA EORP Atrial Fibrillation General Long-Term (AFGen LT) Registry. Europace. 2021;23:174–83.
17. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple ABC (atrial fibrillation better care) pathway for integrated care management: a nationwide cohort study. Thromb Haemost. 2019;119:1695–703.
18. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, et al. Mobile health technology to improve care for patients with atrial fibrillation. J Am Coll Cardiol. 2020;75:1523–34.
19. Stevens D, Harrison SL, Kolamunnage-Dona R, Lip GYH, Lane DA. The Atrial Fibrillation Better Care pathway for managing atrial fibrillation: a review. Europace. 2021;23(10):1511–27.
20. Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the 'Atrial Fibrillation Better Care' pathway in patients with atrial fibrillation: impact on clinical outcomes—a systematic review and meta-analysis of 285,000 patients. Thromb Haemost. 2021.
21. Guo Y, Lane DA, Chen Y, Lip GYH. Regular bleeding risk assessment associated with reduction in bleeding outcomes: the mAFA-II Randomized Trial. Am J Med. 2020;133:1195–1202.e1192.
22. Guo Y, Guo J, Shi X, Yao Y, Sun Y, Xia Y, et al. Mobile health technology-supported atrial fibrillation screening and integrated care: a report from the mAFA-II trial Long-term Extension Cohort. Eur J Intern Med. 2020;82:105–11.
23. Pastori D, Farcomeni A, Pignatelli P, Violi F, Lip GY. ABC (Atrial fibrillation Better Care) pathway and healthcare costs in atrial fibrillation: the ATHERO-AF study. Am J Med. 2019;132:856–61.
24. Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Uhm JS, et al. The effect of integrated care management on dementia in atrial fibrillation. J Clin Med. 2020;9.
25. Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Lip GYH, et al. Application of the simple atrial fibrillation better care pathway for integrated care management in frail patients with atrial fibrillation: a nationwide cohort study. J Arrhythmia. 2020;36:668–77.
26. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018;154:1121–201.
27. Joung B, Lee JM, Lee KH, Kim TH, Choi EK, Lim WH, et al. 2018 Korean guideline of atrial fibrillation management. Korean Circ J. 2018;48:1033–80.
28. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al; Group ESCSD. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2020;2021(42):373–498.
29. Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T, et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythmia. 2017;33:345–67.
30. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, et al. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. J Am Coll Cardiol. 2014;64:1658–65.
31. Xiong Q, Chen S, Senoo K, Proietti M, Hong K, Lip GY. The CHADS2 and CHA2DS2-VASc scores for predicting ischemic stroke among East Asian patients with atrial fibrillation: a systemic review and meta-analysis. Int J Cardiol. 2015;195:237–42.
32. Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, et al. Comparisons of CHADS2 and CHA2DS2-VASc scores for stroke risk stratification in atrial fibrillation: which scoring system should be used for Asians? Heart Rhythm. 2016;13:46–53.
33. Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ, et al. Risk of ischemic stroke in patients with non-valvular atrial fibrillation not receiving oral anticoagulants—Korean nationwide population-based study. Circulation J. 2017;81:1158–64.
34. Kim TH, Yang PS, Uhm JS, Kim JY, Pak HN, Lee MH, et al. CHA(2)DS(2)-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65–74, female) for stroke in

Asian patients with atrial fibrillation: a Korean nationwide sample cohort study. Stroke. 2017;48:1524–30.
35. Kim TH, Yang PS, Kim D, Yu HT, Uhm JS, Kim JY, et al. CHA(2)DS(2)-VASc score for identifying truly low-risk atrial fibrillation for stroke: a Korean nationwide cohort study. Stroke. 2017;48:2984–90.
36. Proietti M, Rivera-Caravaca JM, Esteve-Pastor MA, Marín F, Lip GYH. Stroke and thromboembolism in warfarin-treated patients with atrial fibrillation: comparing the CHA2DS2-VASc and GARFIELD-AF risk scores. Thromb Haemost. 2021;121:1107–14.
37. Lip GYH, Tran G, Genaidy A, Marroquin P, Estes C, Landsheftl J. Improving dynamic stroke risk prediction in non-anticoagulated patients with and without atrial fibrillation: comparing common clinical risk scores and machine learning algorithms. Eur Heart J Qual Care Clin Outcomes. 2021.
38. Boriani G, Vitolo M, Lane DA, Potpara TS, Lip GY. Beyond the 2020 guidelines on atrial fibrillation of the European society of cardiology. Eur J Intern Med. 2021;86:1–11.
39. Lane DA, Lip GYH. Stroke and bleeding risk stratification in atrial fibrillation: a critical appraisal. Eur Heart J Suppl. 2020;22:O14–O27.
40. Camelo-Castillo A, Rivera-Caravaca JM, Marín F, Vicente V, Lip GYH, Roldán V. Predicting adverse events beyond stroke and bleeding with the ABC-stroke and ABC-bleeding scores in patients with atrial fibrillation: the Murcia AF project. Thromb Haemost. 2020;120:1200–7.
41. Esteve-Pastor MA, Roldán V, Rivera-Caravaca JM, Ramírez-Macías I, Lip GYH, Marín F. The use of biomarkers in clinical management guidelines: a critical appraisal. Thromb Haemost. 2019;119:1901–19.
42. Noubiap JJ, Feteh VF, Middeldorp ME, Fitzgerald JL, Thomas G, Kleinig T, et al. A meta-analysis of clinical risk factors for stroke in anticoagulant-naïve patients with atrial fibrillation. Europace. 2021;23(10):1528–38.
43. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Age threshold for the use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation: insights into the optimal assessment of age and incident comorbidities. Eur Heart J. 2019;40:1504–14.
44. Kim TH, Yang PS, Yu HT, Jang E, Uhm JS, Kim JY, et al. Age threshold for ischemic stroke risk in atrial fibrillation. Stroke. 2018;49:1872–9.
45. Nielsen PB, Larsen TB, Skjøth F, Overvad TF, Lip GY. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: a nationwide cohort study. Sci Rep. 2016;6:27410.
46. Nielsen PB, Overvad TF. Female sex as a risk modifier for stroke risk in atrial fibrillation: using CHA2DS2-VASc versus CHA2DS2-VA for stroke risk stratification in atrial fibrillation: a note of caution. Thromb Haemost. 2020;120:894–8.
47. Chang TY, Lip GYH, Chen SA, Chao TF. Importance of risk reassessment in patients with atrial fibrillation in guidelines: assessing risk as a dynamic process. Can J Cardiol. 2019;35:611–8.
48. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. J Am Coll Cardiol. 2018;71:122–32.
49. Chao TF, Chiang CE, Chen TJ, Lip GYH, Chen SA. Reassessment of risk for stroke during follow-up of patients with atrial fibrillation. Ann Intern Med. 2019;170:663–4.
50. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Dynamic changes of CHA2DS2-VASc score and the risk of ischaemic stroke in Asian patients with atrial fibrillation: a nationwide cohort Study. Thromb Haemost. 2018;118:1296–304.
51. Fauchier L, Bodin A, Bisson A, Herbert J, Spiesser P, Clementy N, et al. Incident comorbidities, aging and the risk of stroke in 608,108 patients with atrial fibrillation: a nationwide analysis. J Clin Med. 2020;9.
52. Chao TF, Liao JN, Tuan TC, Lin YJ, Chang SL, Lo LW, et al. Incident co-morbidities in patients with atrial fibrillation initially with a CHA2DS2-VASc score of 0 (males) or 1 (females): implications for reassessment of stroke risk in initially 'low-risk' patients. Thromb Haemost. 2019;119:1162–70.
53. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. Thromb Haemost. 2018;118:2171–87.
54. Proietti M, Romiti GF, Vitolo M, Potpara TS, Boriani G, Lip GYH. Comparison of HAS-BLED and ORBIT bleeding risk scores in AF patients treated with NOACs: a report from the ESC-EHRA EORP-AF general long-term registry. Eur Heart J Qual Care Clin Outcomes. 2021.
55. Zulkifly H, Lip GYH, Lane DA. Bleeding risk scores in atrial fibrillation and venous thromboembolism. Am J Cardiol. 2017;120:1139–45.
56. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY, et al. Ideal blood pressure in patients with atrial fibrillation. J Am Coll Cardiol. 2018;72:1233–45.
57. Guo Y, Zhu H, Chen Y, Lip GYH. Comparing bleeding risk assessment focused on modifiable risk factors only versus validated bleeding risk scores in atrial fibrillation. Am J Med. 2018;131:185–92.
58. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. Thromb Haemost. 2018;118:768–77.
59. Chao TF, Chan YH, Chiang CE, Tuan TC, Liao JN, Chen TJ, et al. Continuation or discontinuation of oral anticoagulants after HAS-BLED scores increase in patients with atrial fibrillation. Clin Res Cardiol. 2021.
60. Chao TF, Chan YH, Tuan TC, Liao JN, Chen TJ, Lip GYH, et al. Should oral anticoagulants still be prescribed to patients with atrial fibrillation with a single stroke risk factor but at high bleeding risk? A nationwide cohort study. Eur Heart J Qual Care Clin Outcomes. 2021.
61. Lip GYH, Collet JP, de Caterina R, Fauchier L, Lane DA, Larsen TB, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: executive summary of a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC working group on valvular heart disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Thromb Haemost. 2017;117:2215–36.
62. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367:1903–12.
63. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. New Engl J Med. 2009;361:1139–51.
64. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. New Engl J Med. 2011;364:806–17.
65. Chao TF, Chen SA, Lip GYH. Recommendations on stroke prevention for patients having a CHA(2)DS(2)-VASc score of 1 (males) or 2 (females) in 2019 atrial fibrillation guidelines. Trends Cardiovasc Med. 2019;29:427–8.
66. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, et al. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? J Am Coll Cardiol. 2015;65:635–42.

67. Chao TF, Wang KL, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Age threshold for increased stroke risk among patients with atrial fibrillation: a nationwide cohort study from Taiwan. J Am Coll Cardiol. 2015;66:1339–47.
68. Chao TF, Chiang CE, Liao JN, Chen TJ, Lip GYH, Chen SA. Comparing the effectiveness and safety of nonvitamin K antagonist oral anticoagulants and warfarin in elderly Asian patients with atrial fibrillation: a nationwide cohort study. Chest. 2020;157:1266–77.
69. Kuo L, Chan YH, Liao JN, Chen SA, Chao TF. Stroke and bleeding risk assessment in atrial fibrillation: where are we now? Korean Circ J. 2021;51:668–80.
70. Lee SR, Lee YS, Park JS, Cha MJ, Kim TH, Park J, et al. Label adherence for non-vitamin K antagonist oral anticoagulants in a prospective cohort of Asian patients with atrial fibrillation. Yonsei Med J. 2019;60:277–84.
71. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Optimal rivaroxaban dose in Asian patients with atrial fibrillation and normal or mildly impaired renal function. Stroke. 2019;50:1140–8.
72. Cheng WH, Chao TF, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Low-dose rivaroxaban and risks of adverse events in patients with atrial fibrillation. Stroke. 2019;50:2574–7.
73. Chan YH, Chao TF, Chen SW, Lee HF, Yeh YH, Huang YC, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and clinical outcomes in Asian patients with atrial fibrillation. Heart Rhythm. 2020;17:2102–10.
74. Yu HT, Yang PS, Jang E, Kim TH, Uhm JS, Kim JY, et al. Label adherence of direct oral anticoagulants dosing and clinical outcomes in patients with atrial fibrillation. J Am Heart Assoc. 2020;9:e014177.
75. Lee SR, Choi EK, Park SH, Jung JH, Han KD, Oh S, et al. Off-label underdosed apixaban use in Asian patients with non-valvular atrial fibrillation. Eur Heart J Cardiovasc Pharmacother. 2021;7:415–23.
76. Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. The optimal drug adherence to maximize the efficacy and safety of non-vitamin K antagonist oral anticoagulant in real-world atrial fibrillation patients. Europace. 2020;22:547–57.
77. Kim H, Lee YS, Kim TH, Cha MJ, Lee JM, Park J, et al. A prospective survey of the persistence of warfarin or NOAC in nonvalvular atrial fibrillation: a COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF). Korean J Intern Med. 2020;35:99–108.
78. Guo Y, Kotalczyk A, Imberti JF, Wang Y, Lip GYH. Quality indicators in the management of elderly Chinese patients with atrial fibrillation: a report from the Optimal Thromboprophylaxis in Elderly Chinese Patients with Atrial Fibrillation (ChiOTEAF) registry. Eur Heart J Qual Care Clin Outcomes. 2021.
79. Pandey AK, Xu K, Zhang L, Gupta S, Eikelboom J, Cook O, et al. Lower versus standard INR targets in atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. Thromb Haemost. 2020;120:484–94.
80. Berwaerts J, Dijkhuizen RS, Robb OJ, Webster J. Prediction of functional outcome and in-hospital mortality after admission with oral anticoagulant-related intracerebral hemorrhage. Stroke. 2000;31:2558–62.
81. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008;1:84–91.
82. Proietti M, Lane DA, Lip GY. Relation of the SAMe-TT2R2 score to quality of anticoagulation control and thromboembolic events in atrial fibrillation patients: observations from the SPORTIF trials. Int J Cardiol. 2016;216:168–72.
83. Chan PH, Hai JJ, Chan EW, Li WH, Tse HF, Wong IC, et al. Use of the SAMe-TT2R2 score to predict good anticoagulation control with warfarin in chinese patients with atrial fibrillation: relationship to ischemic stroke incidence. PLoS One. 2016;11:e0150674.
84. Roldán V, Cancio S, Gálvez J, Valdés M, Vicente V, Marín F, et al. The SAMe-TT2R2 score predicts poor anticoagulation control in AF patients: a prospective 'real-world' inception cohort study. Am J Med. 2015;128:1237–43.
85. Gallego P, Roldán V, Marin F, Gálvez J, Valdés M, Vicente V, et al. SAMe-TT2R2 score, time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. Am J Med. 2014;127:1083–8.
86. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. Chest. 2013;144:1555–63.
87. Wang KL, Lip GY, Lin SJ, Chiang CE. Non-vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. Stroke. 2015;46:2555–61.
88. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circulation J. 2014;78:1997–2021.
89. Dalal J, Bhave A, Oomman A, Vora A, Saxena A, Kahali D, et al. The Indian consensus guidance on stroke prevention in atrial fibrillation: an emphasis on practical use of nonvitamin K oral anticoagulants. Indian Heart J. 2015;67(Suppl 2):S13–34.
90. Chiang CE, Wu TJ, Ueng KC, Chao TF, Chang KC, Wang CC et al. 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. J Formosan Med Assoc. 2016;115(11):893–952.
91. Chao TF, Guo Y. Should we adopt a standard international normalized ratio range of 2.0 to 3.0 for Asian patients with atrial fibrillation? An appeal for evidence-based management, not eminence-based recommendations. Thromb Haemost. 2020;120:366–8.
92. Liu T, Hui J, Hou YY, Zou Y, Jiang WP, Yang XJ, et al. Meta-analysis of efficacy and safety of low-intensity warfarin therapy for east Asian patients with nonvalvular atrial fibrillation. Am J Cardiol. 2017;120:1562–7.
93. Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T. Target intensity of anticoagulation with warfarin in Japanese patients with valvular atrial fibrillation—subanalysis of the J-RHYTHM Registry. Circulation J. 2015;79:325–30.
94. Pritchett RV, Bem D, Turner GM, Thomas GN, Clarke JL, Fellows R, et al. Improving the prescription of oral anticoagulants in atrial fibrillation: a systematic review. Thromb Haemost. 2019;119:294–307.
95. Hwang J, Han S, Bae HJ, Jun SW, Choi SW, Lee CH, et al. NOAC adherence of patients with atrial fibrillation in the real world: dosing frequency matters? Thromb Haemost. 2020;120:306–13.
96. Jones NR, Crawford W, Yang Y, Hobbs FDR, Taylor CJ, Petrou S. A systematic review of economic aspects of service interventions to increase anticoagulation use in atrial fibrillation. Thromb Haemost. 2021.
97. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–62.
98. Chao TF, Chen SA, Ruff CT, Hamershock RA, Mercuri MF, Antman EM, et al. Clinical outcomes, edoxaban concentration, and anti-factor Xa activity of Asian patients with atrial fibrillation compared with non-Asians in the ENGAGE AF-TIMI 48 trial. Eur Heart J. 2019;40:1518–27.
99. Chan YH, Lee HF, Chao TF, Wu CT, Chang SH, Yeh YH, et al. Real-world comparisons of direct oral anticoagulants for stroke prevention in Asian patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. Cardiovasc Drugs Ther. 2019;33:701–10.
100. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. Circulation. 2018;138:37–47.
101. Lee SR, Choi EK, Park CS, Han KD, Jung JH, Oh S, et al. Direct oral anticoagulants in patients with nonvalvular atrial fibrillation and low body weight. J Am Coll Cardiol. 2019;73:919–31.

102. Lee SR, Lee HJ, Choi EK, Han KD, Jung JH, Cha MJ, et al. Direct oral anticoagulants in patients with atrial fibrillation and liver disease. J Am Coll Cardiol. 2019;73:3295–308.
103. Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? J Am Heart Assoc. 2017;6.
104. Kwon S, Lee SR, Choi EK, Choe WS, Lee E, Jung JH, et al. Non-vitamin K antagonist oral anticoagulants in very elderly east Asians with atrial fibrillation: a nationwide population-based study. Am Heart J. 2020;229:81–91.
105. Tsai CT, Liao JN, Chen SJ, Jiang YR, Chen TJ, Chao TF. Non-vitamin K antagonist oral anticoagulants versus warfarin in AF patients ≥85 years. Eur J Clin Invest. 2021;51:e13488.
106. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol. 2017;69:2779–90.
107. Pokorney SD, Peterson ED, Piccini JP. When less is not more. J Am Coll Cardiol. 2017;69(23):2791–3.
108. Wang KL, Lopes RD, Patel MR, Büller HR, Tan DS, Chiang CE, et al. Efficacy and safety of reduced-dose non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. Eur Heart J. 2019;40:1492–500.
109. Cheng WH, Chan YH, Liao JN, Kuo L, Chen SA, Chao TF. Optimal management of anticoagulation therapy in Asian patients with atrial fibrillation. Circ J. 2021;85:1245–53.
110. Chan YH, Chao TF, Lee HF, Yeh YH, Yeh CH, Huang YC, et al. Impacts of different renal function estimation formulas on dosing of DOACs and clinical outcomes. J Am Coll Cardiol. 2020;76:1808–10.
111. Chan YH, Lee HF, Wang CL, Chang SH, Yeh CH, Chao TF, et al. Comparisons of rivaroxaban following different dosage criteria (ROCKET AF or J-ROCKET AF Trials) in Asian patients with atrial fibrillation. J Am Heart Assoc. 2019;8:e013053.
112. Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, et al. Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: a north American perspective-2016 update. Circ Cardiovasc Interv. 2016;9.
113. Park J, Choi EK, Han KD, Choi YJ, Lee E, Choe W, et al. Temporal trends in prevalence and antithrombotic treatment among Asians with atrial fibrillation undergoing percutaneous coronary intervention: a nationwide Korean population-based study. PLoS One. 2019;14:e0209593.
114. Kwon S, Jung JH, Choi EK, Lee SW, Park J, Lee SR, et al. Impact of non-vitamin K antagonist oral anticoagulants on the change of antithrombotic regimens in patients with atrial fibrillation undergoing percutaneous coronary intervention. Korean Circ J. 2021;51:409–22.
115. Vitolo M, Javed S, Capodanno D, Rubboli A, Boriani G, Lip GYH. Antithrombotic treatment in atrial fibrillation patients undergoing percutaneous coronary interventions: focus on stent thrombosis. Expert Rev Cardiovasc Ther. 2020;18:587–600.
116. Kim HK, Tantry US, Smith SC Jr, Jeong MH, Park SJ, Kim MH, et al. The east Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. Thromb Haemost. 2021;121:422–32.
117. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381:1107–15.
118. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. New Engl J Med. 2016;375:2423–34.
119. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. New Engl J Med. 2017;377:1513–24.
120. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. New Engl J Med. 2019;380:1509–24.
121. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet. 2019;394:1335–43.
122. Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, et al. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. Eur Heart J. 2019;40:1553–62.
123. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace. 2021.
124. Lee SR, Rhee TM, Kang DY, Choi EK, Oh S, Lip GYH. Meta-analysis of oral anticoagulant monotherapy as an antithrombotic strategy in patients with stable coronary artery disease and nonvalvular atrial fibrillation. Am J Cardiol. 2019;124:879–85.
125. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. New Engl J Med. 2019;381:1103–13.
126. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation. 2014;129:2638–44.
127. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2017;14:e275–e444.
128. Murakawa Y, Yamane T, Goya M, Inoue K, Naito S, Kumagai K, et al. Influence of substrate modification in catheter ablation of atrial fibrillation on the incidence of acute complications: analysis of 10 795 procedures in J-CARAF Study 2011–2016. J Arrhythmia. 2018;34:435–40.
129. Hohnloser SH, Camm AJ. Safety and efficacy of dabigatran etexilate during catheter ablation of atrial fibrillation: a meta-analysis of the literature. Europace. 2013;15:1407–11.
130. Cappato R, Marchlinski FE, Hohnloser SH, Naccarelli GV, Xiang J, Wilber DJ, et al. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. Eur Heart J. 2015;36:1805–11.
131. Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. New Engl J Med. 2017;376:1627–36.
132. Kirchhof P, Haeusler KG, Blank B, De Bono J, Callans D, Elvan A, et al. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. Eur Heart J. 2018;39:2942–55.
133. Hohnloser SH, Camm J, Cappato R, Diener HC, Heidbüchel H, Mont L, et al. Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation: the ELIMINATE-AF trial. Eur Heart J. 2019;40:3013–21.
134. Zhao Y, Lu Y, Qin Y. A meta-analysis of randomized controlled trials of uninterrupted periprocedural anticoagulation strategy in patients undergoing atrial fibrillation catheter ablation. Int J Cardiol. 2018;270:167–71.

135. Cardoso R, Knijnik L, Bhonsale A, Miller J, Nasi G, Rivera M, et al. An updated meta-analysis of novel oral anticoagulants versus vitamin K antagonists for uninterrupted anticoagulation in atrial fibrillation catheter ablation. Heart Rhythm. 2018;15:107–15.
136. Nakamura K, Naito S, Sasaki T, Take Y, Minami K, Kitagawa Y, et al. Uninterrupted vs. interrupted periprocedural direct oral anticoagulants for catheter ablation of atrial fibrillation: a prospective randomized single-centre study on post-ablation thrombo-embolic and haemorrhagic events. Europace. 2019;21:259–67.
137. Yu HT, Shim J, Park J, Kim TH, Uhm JS, Kim JY, et al. When is it appropriate to stop non-vitamin K antagonist oral anticoagulants before catheter ablation of atrial fibrillation? A multicentre prospective randomized study. Eur Heart J. 2019;40:1531–7.
138. Nogami A, Harada T, Sekiguchi Y, Otani R, Yoshida Y, Yoshida K, et al. Safety and efficacy of minimally interrupted dabigatran vs uninterrupted warfarin therapy in adults undergoing atrial fibrillation catheter ablation: a randomized clinical trial. JAMA Netw Open. 2019;2:e191994.
139. Takahashi N, Mukai Y, Kimura T, Yamaguchi K, Matsumoto T, Origasa H, et al. Efficacy and safety of uninterrupted periprocedural edoxaban in patients undergoing catheter ablation for atrial fibrillation—the prospective KYU-RABLE study. Circulation J. 2019;83:2017–24.
140. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, et al. A specific antidote for dabigatran: functional and structural characterization. Blood. 2013;121:3554–62.
141. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. New Engl J Med. 2015;373:511–20.
142. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for dabigatran reversal—full cohort analysis. New Engl J Med. 2017;377:431–41.
143. Eikelboom JW, van Ryn J, Reilly P, Hylek EM, Elsaesser A, Glund S, et al. Dabigatran reversal with idarucizumab in patients with renal impairment. J Am Coll Cardiol. 2019;74:1760–8.
144. Fanikos J, Murwin D, Gruenenfelder F, Tartakovsky I, França LR, Reilly PA, et al. Global use of idarucizumab in clinical practice: outcomes of the RE-VECTO surveillance program. Thromb Haemost. 2020;120:27–35.
145. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013;19:446–51.
146. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. New Engl J Med. 2015;373:2413–24.
147. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with Factor Xa inhibitors. New Engl J Med. 2019;380:1326–35.
148. Chang TY, Chan YH, Chiang CE, Lin YJ, Chang SL, Lo LW, et al. Risks and outcomes of gastrointestinal malignancies in anticoagulated atrial fibrillation patients experiencing gastrointestinal bleeding: a nationwide cohort study. Heart Rhythm. 2020;17:1745–51.
149. Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, et al. Clinical significance of hematuria in atrial fibrillation with oral anticoagulation therapy. Circulation J. 2017;81:158–64.
150. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285:2370–5.
151. Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA(2)DS(2)-VASc score in the entire Korean population. Int J Cardiol. 2017;236:226–31.
152. Cheng WH, Chiang CE, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Non-vitamin K antagonist oral anticoagulants in elderly (≥85 years) patients with newly diagnosed atrial fibrillation: changing clinical practice and outcomes for stroke prevention in a nationwide cohort study. Mayo Clin Proc. 2021;96:52–65.
153. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New Engl J Med. 2011;365:883–91.
154. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 2011;365:981–92.
155. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 2013;369:2093–104.
156. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123:2363–72.
157. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). Circulation. 2014;130:138–46.
158. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J. 2014;35:1864–72.
159. Kato ET, Giugliano RP, Ruff CT, Koretsune Y, Yamashita T, Kiss RG, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc. 2016;5.
160. Chao TF, Chiang CE, Chan YH, Liao JN, Chen TJ, Lip GYH, et al. Oral anticoagulants in extremely-high-risk, very elderly (>90 years) patients with atrial fibrillation. Heart Rhythm. 2021;18:871–7.
161. Okumura K, Lip GYH, Akao M, Tanizawa K, Fukuzawa M, Abe K, et al. Edoxaban for the management of elderly Japanese patients with atrial fibrillation ineligible for standard oral anticoagulant therapies: rationale and design of the ELDERCARE-AF study. Am Heart J. 2017;194:99–106.
162. Okumura K, Akao M, Yoshida T, Kawata M, Okazaki O, Akashi S, et al. Low-dose edoxaban in very elderly patients with atrial fibrillation. New Engl J Med. 2020;383:1735–45.
163. De Caterina R, Lip GYH. The non-vitamin K antagonist oral anticoagulants (NOACs) and extremes of body weight-a systematic literature review. Clin Res Cardiol. 2017;106:565–72.
164. Park CS, Choi EK, Kim HM, Lee SR, Cha MJ, Oh S. Increased risk of major bleeding in underweight patients with atrial fibrillation who were prescribed non-vitamin K antagonist oral anticoagulants. Heart Rhythm. 2017;14:501–7.
165. Hohnloser SH, Fudim M, Alexander JH, Wojdyla DM, Ezekowitz JA, Hanna M, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and extremes in body weight. Circulation. 2019;139:2292–300.
166. Boriani G, Ruff CT, Kuder JF, Shi M, Lanz HJ, Rutman H, et al. Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. Eur Heart J. 2019;40:1541–50.
167. Boriani G, Ruff CT, Kuder JF, Shi M, Lanz HJ, Antman EM, et al. Edoxaban versus warfarin in patients with atrial fibrillation at the extremes of body weight: an analysis from the ENGAGE AF-TIMI 48 trial. Thromb Haemost. 2021;121:140–9.

168. Zeng WT, Sun XT, Tang K, Mei WY, Liu LJ, Xu Q, et al. Risk of thromboembolic events in atrial fibrillation with chronic kidney disease. Stroke. 2015;46:157–63.
169. Sardar P, Chatterjee S, Herzog E, Nairooz R, Mukherjee D, Halperin JL. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. Can J Cardiol. 2014;30: 888–97.
170. Nielsen PB, Lane DA, Rasmussen LH, Lip GY, Larsen TB. Renal function and non-vitamin K oral anticoagulants in comparison with warfarin on safety and efficacy outcomes in atrial fibrillation patients: a systemic review and meta-regression analysis. Clin Res Cardiol. 2015;104:418–29.
171. Andò G, Capranzano P. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with chronic kidney disease: a systematic review and network meta-analysis. Int J Cardiol. 2017;231:162–9.
172. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, et al. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. Heart Rhythm. 2014;11:1752–9.
173. Yoon CY, Noh J, Jhee JH, Chang TI, Kang EW, Kee YK, et al. Warfarin use in patients with atrial fibrillation undergoing hemodialysis: a nationwide population-based study. Stroke. 2017;48:2472–9.
174. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation. 2018;138:1519–29.
175. Chokesuwattanaskul R, Thongprayoon C, Tanawuttiwat T, Kaewput W, Pachariyanon P, Cheungpasitporn W. Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: meta-analysis. Pacing Clin Electrophysiol. 2018;41:627–34.
176. Coleman CI, Kreutz R, Sood NA, Bunz TJ, Eriksson D, Meinecke AK, et al. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. Am J Med. 2019;132:1078–83.
177. De Vriese AS, Caluwé R, Van Der Meersch H, De Boeck K, De Bacquer D. Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter randomized controlled trial. J Am Soc Nephrol. 2021;32:1474–83.
178. Kuno T, Takagi H, Ando T, Sugiyama T, Miyashita S, Valentin N, et al. Oral anticoagulation for patients with atrial fibrillation on long-term hemodialysis. J Am Coll Cardiol. 2020;75:273–85.
179. See LC, Lee HF, Chao TF, Li PR, Liu JR, Wu LS, et al. Effectiveness and safety of direct oral anticoagulants in an Asian population with atrial fibrillation undergoing dialysis: a population-based cohort study and meta-analysis. Cardiovasc Drugs Ther. 2021;35:975–86.
180. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. New Engl J Med. 2011;365:147–56.
181. Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. Hepatology. 2006;44:1039–46.
182. Khoury T, Ayman AR, Cohen J, Daher S, Shmuel C, Mizrahi M. The complex role of anticoagulation in cirrhosis: an updated review of where we are and where we are going. Digestion. 2016;93:149–59.
183. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral anticoagulation in patients with liver disease. J Am Coll Cardiol. 2018;71:2162–75.
184. Lauschke VM, Ingelman-Sundberg M. The importance of patient-specific factors for hepatic drug response and toxicity. Int J Mol Sci. 2016;17.
185. Efird LM, Mishkin DS, Berlowitz DR, Ash AS, Hylek EM, Ozonoff A, et al. Stratifying the risks of oral anticoagulation in patients with liver disease. Circ Cardiovasc Qual Outcomes. 2014;7:461–7.
186. Douros A, Azoulay L, Yin H, Suissa S, Renoux C. Non-vitamin K antagonist oral anticoagulants and risk of serious liver injury. J Am Coll Cardiol. 2018;71:1105–13.
187. Wang CL, Wu VC, Kuo CF, Chu PH, Tseng HJ, Wen MS, et al. Efficacy and safety of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with impaired liver function: a retrospective cohort study. J Am Heart Assoc. 2018;7:e009263.
188. Qamar A, Antman EM, Ruff CT, Nordio F, Murphy SA, Grip LT, et al. Edoxaban versus warfarin in patients with atrial fibrillation and history of liver disease. J Am Coll Cardiol. 2019;74:179–89.
189. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330–93.
190. Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. Eur J Haematol. 2017;98:393–7.
191. Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, et al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci. 2016;61:1721–7.
192. Kubitza D, Roth A, Becka M, Alatrach A, Halabi A, Hinrichsen H, et al. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol. 2013;76:89–98.
193. Lip GYH, Collet JP, Caterina R, Fauchier L, Lane DA, Larsen TB, et al.; Group ESCSD. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Europace. 2017;19:1757–8.
194. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. European Heart J. 2014;35:3328–35.
195. Melgaard L, Overvad TF, Jensen M, Lip GYH, Larsen TB, Nielsen PB. Thromboembolism and bleeding complications in anticoagulated patients with atrial fibrillation and native aortic or mitral valvular heart disease: a descriptive nationwide cohort study. Eur Heart J Cardiovasc Pharmacother. 2021;7:f101–f110.
196. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial (randomized evaluation of long-term anticoagulant therapy). Circulation. 2016;134:589–98.
197. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. Circulation. 2015;132:624–32.
198. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR, et al. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J. 2014;35:3377–85.
199. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF, et al. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol. 2017;69:1372–82.
200. Carnicelli AP, De Caterina R, Halperin JL, Renda G, Ruff CT, Trevisan M, et al. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. Circulation. 2017;135:1273–5.

201. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. J Am Coll Cardiol. 2017;69:1363–71.
202. Moon I, Lee SR, Choi EK, Lee E, Jung JH, Han KD, et al. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. J Clin Med. 2019;8.
203. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. New Engl J Med. 2013;369:1206–14.
204. Kim JY, Kim SH, Myong JP, Kim YR, Kim TS, Kim JH, et al. Outcomes of direct oral anticoagulants in patients with mitral stenosis. J Am Coll Cardiol. 2019;73:1123–31.
205. Zhou M, Chan EW, Hai JJ, Wong CK, Lau YM, Huang D, et al. Protocol, rationale and design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS): a randomised, open-label study. BMJ Open. 2020;10:e038194.
206. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart. 2014;100:465–72.
207. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517–24.
208. Lee SE, Park JK, Uhm JS, Kim JY, Pak HN, Lee MH, et al. Impact of atrial fibrillation on the clinical course of apical hypertrophic cardiomyopathy. Heart. 2017;103:1496–501.
209. Choi YJ, Choi EK, Han KD, Jung JH, Park J, Lee E, et al. Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among Asian patients with hypertrophic cardiomyopathy: a nationwide population-based study. Int J Cardiol. 2018;273:130–5.
210. Jung H, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, et al. Hypertrophic cardiomyopathy in patients with atrial fibrillation: prevalence and associated stroke risks in a nationwide cohort study. Thromb Haemost. 2019;119:285–93.
211. Jung H, Sung JH, Yang PS, Jang E, Yu HT, Kim TH, et al. Stroke risk stratification for atrial fibrillation patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2018;72:2409–11.
212. Lee HJ, Kim HK, Jung JH, Han KD, Lee H, Park JB, et al. Novel oral anticoagulants for primary stroke prevention in hypertrophic cardiomyopathy patients with atrial fibrillation. Stroke. 2019;50:2582–6.
213. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. Chest. 2019;155:354–63.
214. Arch Intern Med Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. 1994;154:1449–57.
215. Hankey GJ, Stevens SR, Piccini JP, Lokhnygina Y, Mahaffey KW, Halperin JL, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke. 2014;45:1304–12.
216. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. Stroke. 2012;43:1511–7.
217. Rost NS, Giugliano RP, Ruff CT, Murphy SA, Crompton AE, Norden AD, et al. Outcomes with edoxaban versus warfarin in patients with previous cerebrovascular events: findings from ENGAGE AF-TIMI 48 (effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48). Stroke. 2016;47:2075–82.
218. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012;11:503–11.
219. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012;11:315–22.
220. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010;9:1157–63.
221. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: an updated systematic review and meta-analysis of randomized controlled trials. Int J Stroke. 2017;12:589–96.
222. Park J, Lee SR, Choi EK, Kwon S, Jung JH, Han KD, et al. Effectiveness and safety of direct oral anticoagulant for secondary prevention in Asians with atrial fibrillation. J Clin Med. 2019;8.
223. Chao TF, Liu CJ, Liao JN, Wang KL, Lin YJ, Chang SL, et al. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. Circulation. 2016;133:1540–7.
224. Nielsen PB, Larsen TB, Skjøth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: a nationwide cohort study. Circulation. 2015;132:517–25.
225. Nielsen PB, Larsen TB, Skjøth F, Lip GY. Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation. JAMA Intern Med. 2017;177:563–70.
226. Ottosen TP, Grijota M, Hansen ML, Brandes A, Damgaard D, Husted SE, et al. Use of antithrombotic therapy and long-term clinical outcome among patients surviving intracerebral hemorrhage. Stroke. 2016;47:1837–43.
227. Murthy SB, Gupta A, Merkler AE, Navi BB, Mandava P, Iadecola C, et al. Restarting anticoagulant therapy after intracranial hemorrhage: a systematic review and meta-analysis. Stroke. 2017;48:1594–600.
228. Tsai CT, Liao JN, Chiang CE, Lin YJ, Chang SL, Lo LW, et al. Association of ischemic stroke, major bleeding, and other adverse events with warfarin use vs non-vitamin K antagonist oral anticoagulant use in patients with atrial fibrillation with a history of intracranial hemorrhage. JAMA Netw Open. 2020;3:e206424.
229. Lee SR, Choi EK, Kwon S, Jung JH, Han KD, Cha MJ, et al. Oral anticoagulation in asian patients with atrial fibrillation and a history of intracranial hemorrhage. Stroke. 2020;51:416–23.
230. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
231. Raparelli V, Proietti M, Cangemi R, Lip GY, Lane DA, Basili S. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. Thromb Haemost. 2017;117:209–18.
232. Shore S, Carey EP, Turakhia MP, Jackevicius CA, Cunningham F, Pilote L, et al. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. Am Heart J. 2014;167:810–7.
233. Gorst-Rasmussen A, Skjøth F, Larsen TB, Rasmussen LH, Lip GY, Lane DA. Dabigatran adherence in atrial fibrillation patients during

the first year after diagnosis: a nationwide cohort study. J Thromb Haemost. 2015;13:495–504.
234. Yao X, Abraham NS, Alexander GC, Crown W, Montori VM, Sangaralingham LR, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. J Am Heart Assoc. 2016;5.
235. Borne RT, O'Donnell C, Turakhia MP, Varosy PD, Jackevicius CA, Marzec LN, et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. BMC Cardiovasc Disord. 2017;17:236.
236. Schulman S, Shortt B, Robinson M, Eikelboom JW. Adherence to anticoagulant treatment with dabigatran in a real-world setting. J Thromb Haemost. 2013;11:1295–9.
237. Desteghe L, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Dendale P, et al. Telemonitoring-based feedback improves adherence to non-vitamin K antagonist oral anticoagulants intake in patients with atrial fibrillation. Eur Heart J. 2018;39:1394–403.
238. Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion—an update. Europace. 2020;22(2):184–4.
239. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. New Engl J Med. 2021;384:2081–91.
240. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009;374:534–42.
241. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014;64:1–12.
242. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation. 2011;123:417–24.
243. Holmes DR Jr, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. J Am Coll Cardiol. 2015;65:2614–23.
244. Osmancik P, Tousek P, Herman D, Neuzil P, Hala P, Stasek J, et al. Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study). Am Heart J. 2017;183:108–14.
245. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. J Am Coll Cardiol. 2020;75:3122–35.
246. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. Heart Rhythm. 2017;14:1302–8.
247. Mazzone P, D'Angelo G, Regazzoli D, Molon G, Senatore G, Saccà S, et al. Percutaneous Left Atrial Appendage Closure with WATCHMAN™ device: peri-procedural and mid-term outcomes from the TRAPS Registry. J Intervent Cardiac Electrophysiol. 2018;52:47–52.
248. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. Circulation Arrhythmia Electrophysiol. 2019;12:e006841.
249. Phillips KP, Santoso T, Sanders P, Alison J, Chan JLK, Pak HN, et al. Left atrial appendage closure with WATCHMAN in Asian patients: 2 year outcomes from the WASP registry. Int J Cardiol Heart Vasc. 2019;23:100358.
250. Aonuma K, Yamasaki H, Nakamura M, Ootomo T, Takayama M, Ando K, et al. Percutaneous WATCHMAN left atrial appendage closure for Japanese patients with nonvalvular atrial fibrillation at increased risk of thromboembolism—first results from the SALUTE Trial. Circulation J. 2018;82:2946–53.
251. Bajaj NS, Parashar A, Agarwal S, Sodhi N, Poddar KL, Garg A, et al. Percutaneous left atrial appendage occlusion for stroke prophylaxis in nonvalvular atrial fibrillation: a systematic review and analysis of observational studies. JACC Cardiovasc Interv. 2014;7:296–304.
252. Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, Hoosien M, et al. Utilization and adverse outcomes of percutaneous left atrial appendage closure for stroke prevention in atrial fibrillation in the United States: influence of hospital volume. Circulation Arrhythmia Electrophysiol. 2015;8:42–8.
253. Lempereur M, Aminian A, Freixa X, Gafoor S, Kefer J, Tzikas A, et al. Device-associated thrombus formation after left atrial appendage occlusion: a systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. Catheter Cardiovasc Interv. 2017;90:E111–21.
254. Fauchier L, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. J Am Coll Cardiol. 2018;71:1528–36.
255. Fauchier L, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Gras D, et al. Major adverse events with percutaneous left atrial appendage closure in patients with atrial fibrillation. J Am Coll Cardiol. 2019;73:2638–40.
256. Sedaghat A, Vij V, Al-Kassou B, Gloekler S, Galea R, Fürholz M, et al. Device-related thrombus after left atrial appendage closure: data on thrombus characteristics, treatment strategies, and clinical outcomes from the EUROC-DRT-registry. Circ Cardiovasc Interv. 2021;14:e010195.
257. Holmes DR, Reddy VY, Buchbinder M, Stein K, Elletson M, Bergmann MW, et al. The assessment of the watchman device in patients unsuitable for oral anticoagulation (ASAP-TOO) trial. Am Heart J. 2017;189:68–74.
258. Reddy VY, Akehurst RL, Gavaghan MB, Amorosi SL, Holmes DR Jr. Cost-effectiveness of left atrial appendage closure for stroke reduction in atrial fibrillation: analysis of pooled, 5-year, long-term data. J Am Heart Assoc. 2019;8:e011577.
259. Reddy VY, Akehurst RL, Armstrong SO, Amorosi SL, Beard SM, Holmes DR Jr. Time to cost-effectiveness following stroke reduction strategies in AF: warfarin versus NOACs versus LAA closure. J Am Coll Cardiol. 2015;66:2728–39.
260. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol. 2015;65:2159–69.
261. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. J Am Coll Cardiol. 2015;66:985–96.
262. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol. 2014;64:2222–31.

263. Joung B. Risk Factor Management for Atrial Fibrillation. Korean Circ J. 2019;49:794–807.
264. Lim C, Kim TH, Yu HT, Lee SR, Cha MJ, Lee JM, et al. Effect of alcohol consumption on the risk of adverse events in atrial fibrillation: from the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) registry. Europace. 2021;23:548–56.
265. Kim TH, Yang PS, Yu HT, Jang E, Shin H, Kim HY, et al. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. Eur Heart J. 2019;40:809–19.
266. Lee SS, Ae Kong K, Kim D, Lim YM, Yang PS, Yi JE, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. Eur Heart J. 2017;38:2599–607.
267. Lee SR, Choi EK, Ahn HJ, Han KD, Oh S, Lip GYH. Association between clustering of unhealthy lifestyle factors and risk of new-onset atrial fibrillation: a nationwide population-based study. Sci Rep. 2020;10:19224.
268. Lee JH, Yang PS, Yu HT, Kim TH, Jang E, Uhm JS, et al. Association of cardiovascular health and incident atrial fibrillation in elderly population. Heart. 2021;107(15):1206–12.
269. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA. 2004;292:2471–7.
270. Baek YS, Yang PS, Kim TH, Uhm JS, Park J, Pak HN, et al. Associations of abdominal obesity and new-onset atrial fibrillation in the general population. J Am Heart Assoc. 2017;6.
271. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA. 2013;310:2050–60.
272. Lim YM, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Body mass index variability and long-term risk of new-onset atrial fibrillation in the general population: a Korean nationwide cohort study. Mayo Clin Proc. 2019;94:225–35.
273. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R, et al. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. Europace. 2018;20:1929–35.
274. Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ, et al. Underweight is a risk factor for atrial fibrillation: a nationwide population-based study. Int J Cardiol. 2016;215:449–56.
275. Lee HJ, Choi EK, Han KD, Lee E, Moon I, Lee SR, et al. Bodyweight fluctuation is associated with increased risk of incident atrial fibrillation. Heart Rhythm. 2020;17:365–71.
276. Overvad TF, Rasmussen LH, Skjøth F, Overvad K, Lip GY, Larsen TB. Body mass index and adverse events in patients with incident atrial fibrillation. Am J Med. 2013;126(640):e649–e617.
277. Proietti M, Guiducci E, Cheli P, Lip GY. Is there an obesity paradox for outcomes in atrial fibrillation? A systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant trials. Stroke. 2017;48:857–66.
278. Lee SR, Choi EK, Jung JH, Park SH, Han KD, Oh S, et al. Body mass index and clinical outcomes in Asian patients with atrial fibrillation receiving oral anticoagulation. Stroke. 2021;52:521–30.
279. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. J Am Coll Cardiol. 2014;64:281–9.
280. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093–100.
281. Overvad TF, Rasmussen LH, Skjøth F, Overvad K, Albertsen IE, Lane DA, et al. Alcohol intake and prognosis of atrial fibrillation. Heart. 2013;99:1093–9.
282. Lee SR, Choi EK, Jung JH, Han KD, Oh S, Lip GYH. Lower risk of stroke after alcohol abstinence in patients with incident atrial fibrillation: a nationwide population-based cohort study. Eur Heart J. 2021.
283. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, et al. Alcohol abstinence in drinkers with atrial fibrillation. New Engl J Med. 2020;382:20–8.
284. Choi YJ, Han KD, Choi EK, Jung JH, Lee SR, Oh S, et al. Alcohol abstinence and the risk of atrial fibrillation in patients with newly diagnosed type 2 diabetes mellitus: a nationwide population-based study. Diabetes Care. 2021;44:1393–401.
285. Chamberlain AM, Agarwal SK, Folsom AR, Duval S, Soliman EZ, Ambrose M, et al. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. Heart Rhythm. 2011;8:1160–6.
286. Zhu W, Yuan P, Shen Y, Wan R, Hong K. Association of smoking with the risk of incident atrial fibrillation: a meta-analysis of prospective studies. Int J Cardiol. 2016;218:259–66.
287. Kwon S, Kim TJ, Choi EK, Ahn HJ, Lee E, Lee SR, et al. Predictors of ischemic stroke for low-risk patients with atrial fibrillation: a matched case-control study. Heart Rhythm. 2021;18:702–8.
288. Lee SR, Choi EK, Jung JH, Han KD, Oh S, Lip GYH. Smoking cessation after diagnosis of new-onset atrial fibrillation and the risk of stroke and death. J Clin Med. 2021;10.
289. Kim IS, Yang PS, Lee J, Yu HT, Kim TH, Uhm JS, et al. Long-term exposure of fine particulate matter air pollution and incident atrial fibrillation in the general population: a nationwide cohort study. Int J Cardiol. 2019;283:178–83.
290. Kim IS, Yang PS, Jang E, Jung H, You SC, Yu HT, et al. Long-term PM(2.5) exposure and the clinical application of machine learning for predicting incident atrial fibrillation. Sci Rep. 2020;10:16324.
291. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. Circulation. 2008;118:800–7.
292. Hegbom F, Stavem K, Sire S, Heldal M, Orning OM, Gjesdal K. Effects of short-term exercise training on symptoms and quality of life in patients with chronic atrial fibrillation. Int J Cardiol. 2007;116:86–92.
293. Osbak PS, Mourier M, Kjaer A, Henriksen JH, Kofoed KF, Jensen GB. A randomized study of the effects of exercise training on patients with atrial fibrillation. Am Heart J. 2011;162:1080–7.
294. Faselis C, Kokkinos P, Tsimploulis A, Pittaras A, Myers J, Lavie CJ, et al. Exercise capacity and atrial fibrillation risk in veterans: a cohort study. Mayo Clin Proc. 2016;91:558–66.
295. Jin MN, Yang PS, Song C, Yu HT, Kim TH, Uhm JS, et al. Physical activity and risk of atrial fibrillation: a nationwide cohort study in general population. Sci Rep. 2019;9:13270.
296. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. Europace. 2009;11:1156–9.
297. Ahn HJ, Lee SR, Choi EK, Han KD, Jung JH, Lim JH, et al. Association between exercise habits and stroke, heart failure, and mortality in Korean patients with incident atrial fibrillation: a nationwide population-based cohort study. PLoS Medicine. 2021;18:e1003659.
298. Lim J, Lee SR, Choi EK, Han KD, Jung JH, Ahn HJ, et al. Exercise and the risk of dementia in patients with newly diagnosed atrial fibrillation: a nationwide population-based study. J Clin Med. 2021;10.
299. Elias P, Poterucha TJ, Jain SS, Sayer G, Raikhelkar J, Fried J, et al. The prognostic value of electrocardiogram at presentation to emergency department in patients with COVID-19. Mayo Clin Proc. 2020;95:2099–109.

300. Musikantow DR, Turagam MK, Sartori S, Chu E, Kawamura I, Shivamurthy P, et al. Atrial fibrillation in patients hospitalized with COVID-19: incidence, predictors, outcomes, and comparison to influenza. JACC Clinical Electrophysiology. 2021;7:1120–30.
301. Lip GYH, Genaidy A, Tran G, Marroquin P, Estes C. Incident atrial fibrillation and its risk prediction in patients developing COVID-19: a machine learning based algorithm approach. Eur J Intern Med. 2021;91:53–8.
302. Romiti GF, Corica B, Lip GYH, Proietti M. Prevalence and impact of atrial fibrillation in hospitalized patients with COVID-19: a systematic review and meta-analysis. J Clin Med. 2021;10.
303. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75:2950–73.
304. Emren ZY, Şenöz O, Erseçgin A, Emren SV. Evaluation of bleeding rate and time in therapeutic range in patients using warfarin before and during the COVID-19 pandemic-warfarin treatment in COVID-19. Clin Appl Thromb Hemost. 2021;27:10760296211021495.
305. Papakonstantinou PE, Borovac JA, Gąsecka A, Bongiovanni D, Ehrlinder H, Giustozzi M, et al. Anticoagulation therapy in nonvalvular atrial fibrillation in the COVID-19 era: is it time to reconsider our therapeutic strategy? Eur J Prev Cardiol. 2021.
306. Li X, Zuo C, Lu W, Zou Y, Xu Q, Li X, et al. Evaluation of remote pharmacist-led outpatient service for geriatric patients on rivaroxaban for nonvalvular atrial fibrillation during the COVID-19 pandemic. Front Pharmacol. 2020;11:1275.
307. Bikdeli B, Madhavan MV, Gupta A, Jimenez D, Burton JR, Der Nigoghossian C, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. Thromb Haemost. 2020;120:1004–24.
308. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol. 2020;76:1815–26.
309. Denas G, Gennaro N, Ferroni E, Fedeli U, Lorenzoni G, Gregori D, et al. Reduction in all-cause mortality in COVID-19 patients on chronic oral anticoagulation: a population-based propensity score matched study. Int J Cardiol. 2021;329:266–9.
310. Rivera-Caravaca JM, Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Marín F, et al. Direct-acting oral anticoagulants use prior to COVID-19 diagnosis and associations with 30-day clinical outcomes. Thromb Res. 2021;205:1–7.
311. Fumagalli S, Trevisan C, Del Signore S, Pelagalli G, Volpato S, Gareri P, et al. COVID-19 and atrial fibrillation in older patients: does oral anticoagulant therapy provide a survival benefit?—an insight from the GeroCovid registry. Thromb Haemost. 2021.
312. Talasaz AH, Sadeghipour P, Kakavand H, Aghakouchakzadeh M, Kordzadeh-Kermani E, Van Tassell BW, et al. Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC state-of-the-art review. J Am Coll Cardiol. 2021;77:1903–21.
313. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. New Engl J Med. 2021;385:790–802.
314. Bikdeli B, Talasaz AH, Rashidi F, Bakhshandeh H, Rafiee F, Rezaeifar P, et al. Intermediate-dose versus standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the intensive care unit: 90-day results from the INSPIRATION randomized trial. Thromb Haemost. 2021.
315. Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA. 2021;325:1620–30.
316. Lopes RD, de Barros ESPGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet. 2021;397:2253–63.
317. Gerotziafas GT, Catalano M, Theodorou Y, Dreden PV, Marechal V, Spyropoulos AC, et al. The COVID-19 pandemic and the need for an integrated and equitable approach: an international expert consensus paper. Thromb Haemost. 2021;121:992–1007.
318. Ford GA, Hargroves D, Lowe D, Hicks N, Lip GYH, Rooney G, et al. Targeted atrial fibrillation (AF) detection in COVID-19 vaccination clinics. Eur Heart J Qual Care Clin Outcomes. 2021.
319. Elalamy I, Gerotziafas G, Alamowitch S, Laroche JP, Van Dreden P, Ageno W, et al. SARS-CoV-2 vaccine and thrombosis: an expert consensus on vaccine-induced immune thrombotic thrombocytopenia. Thromb Haemost. 2021;121:982–91.

How to cite this article: Chao T-F, Joung B, Takahashi Y, Lim TW, Choi E-K, Chan Y-H, et al. 2021 Focused update of the 2017 consensus guidelines of the Asia Pacific Heart Rhythm Society (APHRS) on stroke prevention in atrial fibrillation. J Arrhythmia. 2021;37:1389–1426. https://doi.org/10.1002/joa3.12652